Myeloma in adults: diagnosis and management

Appendix G: Evidence review

Developed for NICE by the National Collaborating Centre for Cancer

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Chapter 1 Communication and support

The specific information and support needs of patients with myeloma and their families and carers at diagnosis and treatment planning, and during and after treatment (including end of life care).

Review Question

What are the specific information and support needs of patients with myeloma and their families and carers?

Question in PICO format

PICO Table		
Population	**Themes**	**Outcomes**
Adults) with myeloma and their carers: • At diagnosis and treatment planning • During treatment • During follow up • During end of life care	Information and support needs of patients with myeloma and their families and carers, e.g., • Patient and carer perceived support and information needs • Perceived problems with the number of specialists/sites involved in care • Education • Pregnancy prevention/fertility issues • Involvement of clinical nurse specialists in all aspects of patient/carer support • Advance care planning • Use of online resources	• Patient and/or carer satisfaction (with communication, information support and treatment received) • Health-related quality of life • Holistic needs assessment • Achievement of advance care planning • Understanding/knowledge of disease and treatment • Psychological factors (e.g. depression, distress, coping) • Referral to support groups/networks
Additional comments on PICO		
All information and support needs identified in the literature will be reviewed and presented - it will not be limited to those examples in the PICO.		

Evidence statements

Information and support needs of myeloma patients

The evidence suggests that the unmet information needs of myeloma patients are low, and patients are generally satisfied with the information they receive. The most common unmet information needs surrounded the need for patients to know more about their future prognosis and include the cause and course of disease as well as side effects and long-term effects of treatment. A common theme throughout the evidence was that patients are interested in experiential information (information from other myeloma patients' experiences). Many patients who had access to such information found it helpful and those who didn't have access to such information would have liked it. However there were some patients who found experiential information unhelpful or even harmful. Evidence from one study on palliative care demonstrated that information on palliative care was not easily available and most patients who were aware of palliative care gained their information from personal experiences they had in the past. There was a contrast between some participants wanting early discussions on palliative care and some only wanting information when needed.

With regards to support needs the evidence suggests that the majority of the unmet support needs of myeloma patients are emotional and psychosocial. In the identified studies many patients were anxious (8-27%) or depressed (5-25%) and many patients desired psychosocial interventions. The most common preferences were relaxation and counseling. Other common support needs include continuity of care, seeing the person in the patient, more time with healthcare professionals and support to manage ongoing symptoms such as fatigue, pain and mobility.

Information and support needs of carers

Evidence concerning carers determined that carers information needs were in relation to understanding myeloma symptoms better and what is normal, financial advice and information around prognosis.

While the most frequently reported unmet supportive care needs of the carers were the same as the patients the partners had their own additional needs that were not reported by patients. Additional partner needs were mostly around the practical and informational aspects of the patients care: the need for help to manage ongoing side effects and/or complications experienced by patients as a result of their treatment, provision of up-to-date information, local health-care services that are available when the patient requires them, help in dealing with changes that myeloma has caused to the patient, emotional support to themselves, information to be provided in a way that they can understand.

Anxiety and depression were common in carers with anxiety being higher in partners than in patients.

Quality of evidence

Evidence about the information and support needs of patients with myeloma and carers was identified from 14 studies (Table 1.1) (Boland et al 2014, Kelly & Dowling 2011, Lamers et al., 2013, Maher & De Vries, 2001, McGrath et al 2013, Molassiotis et al., 2011a, Molassiotis et al., 2011b, Oerlemans et al., 2012, Osborne et al, 2014, Rini et al., 2007, Spencer et al 2014, Tariman et al, 2014, Vlossak & Fitch 2008 and Myeloma UK survey 2014), which were either qualitative interview (n=9) or questionnaire studies (n=5). All 14 studies addressed the needs of patients whilst 3 studies also examined carer needs. The studies are limited by the small numbers of participants which were recruited from single cancer centers/hospitals. Also, people who participate in these questionnaire/interview studies may have information and support needs that are not

representative of other myeloma patients/carers. Furthermore, recall bias may have been present in some studies where participants were asked to retrospectively recall the information and support that was provided.

Eight studies (Kelly & Dowling 2011, Lamers et al., 2013, McGrath et al 2013, Oerlemans et al., 2012, Rini et al., 2007, Spencer et al 2014, Tariman et al, 2014 and Vlossak & Fitch 2008) were conducted in countries other than the UK, so their relevance to current UK practice may be limited.

1 ***Table 1.1: Summary of included studies – quality assessment***

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Boland et al 2014	questionnaire	Well reported	Well reported	Well reported	population from UK	• Cross-sectional • Small sample (n=32) • Not representative of all myeloma patients (patients in the study were younger and more intensively treated)
Kelly & Dowling 2011	interview	Well reported	Well reported	Well reported	population from Ireland	• Findings apply to the context and point in time for the participants • Small sample (n=11) • Phenomenological interpretation – no clear end-point to interpretation. May be open to re-interpretation
Lamers et al., 2013	questionnaire	Well reported	Well reported	Well reported	population from Germany	• Cross-sectional • The study applied a predefined checklist with intervention alternatives which may not have represented the entire spectrum of intervention forms
Maher & De Vries, 2001	interview	Well reported	Well reported	Well reported	population from UK	• findings apply to the context and point in time for the participants • Small sample (n=8)
McGrath et al 2013	interview	Well reported	Well reported	Well reported	population from Australia	• Small sample (n=15)
Molassiotis et al., 2011a	questionnaire	Well reported	Well reported	Well reported	population from UK	• Cross-sectional • Not representative of all myeloma patients (results reflect those in remission and who have survived longer) • Low response rate from partners (50%). The non-responders partners may constitute a group of caregivers with more needs and problems than those reported by the respondents.
Molassiotis et al., 2011b	interview	Well reported	Well reported	Well reported	population from UK	• Findings apply to the context and point in time for the participants (long term survivors in remission) • Small sample (patients n=20, carers n=16) • Selection bias – participants purposely selected on their responses to a questionnaire.
Oerlemans et al., 2012	questionnaire	Well reported	Well reported	Well reported	population from Netherlands	• Cross-sectional
Osborne et al, 2014	interview	Well reported	Well reported	Well reported	population from UK	

Study	Study type	Population	Methods	Analysis	Relevance to guideline population	Other comments
Rini et al., 2007	interview	Adequately reported. Mixed sample of haematological cancers (n=30). Paper does not specify how many myeloma patients (although specific quotes from myeloma patients are provided in the results)	Poorly reported – limited information about interview procedure	Adequately reported	population from USA	• Mainly patients with good outcomes who were commenting retrospectively
Spencer et al 2014	interview	Adequately reported	Well reported	Well reported	population from Australia	small sample (n=21 patients)
Tariman et al, 2014	interview	Well reported	Well reported	Well reported	population from USA	
Vlossak & Fitch 2008	interview	Adequately reported	Well reported	Well reported	population from Canada	• Findings apply to the context and point in time for the participants • Small sample (n=20)
Myeloma UK survey. March 2014.	questionnaire	Adequately reported	Adequately reported – details of questionnaire methods given but no details on how the results were analysed.	Well reported	population from UK	• Cross-sectional • The responses do not consist of a representative sample of patients who have undergone high-dose therapy and stem cell transplantation and were not adjusted for geographical spread, age of patients, length of time since their treatment, or any other factor.

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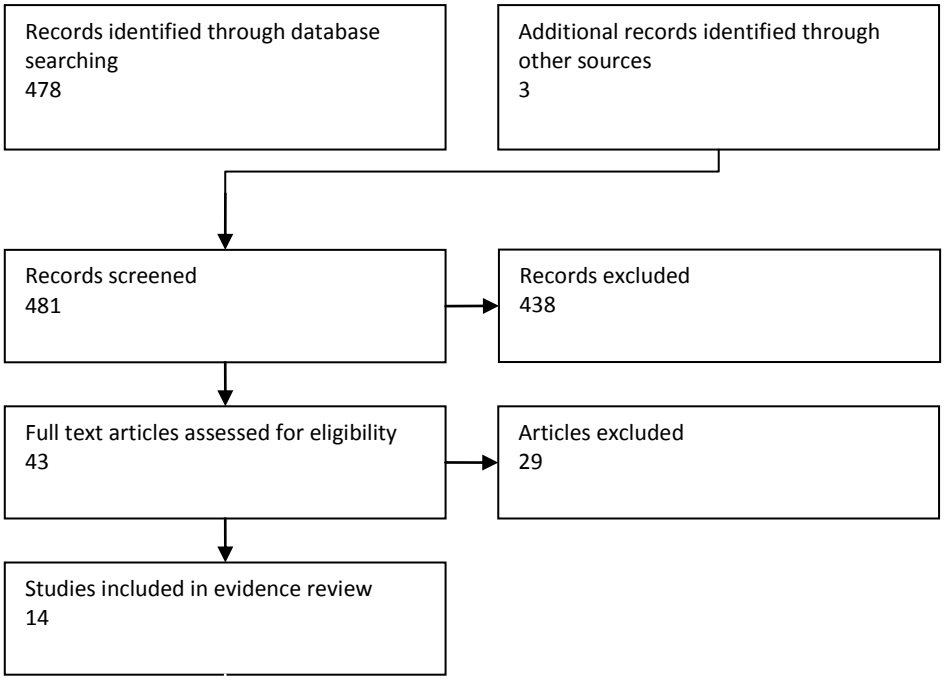
Search Results

Figure 1.1: Search and screening results



References of included studies

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12. Tariman, J. D. (2014). Patient, physician and contextual factors are influential in the treatment decision making of older adults newly diagnosed with symptomatic myeloma. *Cancer Treatment Communications*, 2, 34-47.
13. Vlossak, D. & Fitch, M. I. (2008) Multiple myeloma: the patient's perspective. Canadian Oncology Nursing Journal, 18: 141-151
14. Myeloma UK survey. March 2014. Understanding patient experience of high-dose therapy and stem cell transplantation in myeloma.

Evidence tables

Reference	Boland et al 2014
Study type	Cross-sectional questionnaire study
Country	UK
Research question(s)	Aim: to characterise previously unidentified holistic needs in patients with advanced, intensively treated but otherwise stable myeloma
Theoretical approach	n/a
Data collection	Patient's holistic needs were assessed using the self reporting tool, Sheffield Profile for Assessment and Referral for Care (SPARC).
Method and process of analysis	Quantitative data were analysed using Predictive Analytics SoftWare (PASW) version 20. Non-parametric tests were used for descriptive statistics.
Population and sample collection	Patients were enrolled upon fulfilling the eligibility criteria for symptomatic myeloma by the International Working Group criteria and who had undergone haematopoietic stem cell transplantation and subsequent treatment for at least one episode of progressive disease but were in stable plateau phase (defined as a ≤25 % change in serum or urine M-protein or, in patients with low serum M-proteins (≤5 g/L), no evidence of progressive disease (i.e. a rise in M-protein ≥5 g/L) and either off of active cytotoxic treatment or on maintenance treatment for at least 3 months). 32 Caucasian patients (17males and 15 females) were recruited with a median age of 60 years (range 41–71) at assessment and at a median of 5.5 years from diagnosis (range 2–12).
Key themes	30 patients (94 %) felt well supported by their family and did not feel they needed more help than their family could give. 29 patients (91 %) did not feel anxious or depressed, and none of the 32 patients felt that life was not worth living. With regards to personal issues, 30 patients (94 %) did not need any help with their personal affairs and nor did they feel the need to talk to another professional about their condition or treatment.
Additional comments/ Limitations	**Limitations :** Cross-sectional study. Relatively small numbers. Study enrolled patients who were more intensively treated (all of whom had at least one HSCT procedure) and younger, compared to the average patient with myeloma. Therefore, it is unlikely to be representative of all patients, especially older patients with myeloma who receive less intensive treatments.

Reference	Kelly & Dowling 2011
Study type	Qualitative study - interviews
Country	Ireland
Research question(s)	Aim: to explore patients lived experience of being diagnosed with myeloma
Theoretical	Hermeneutic phenomenology

approach	
Data collection	Qualitative interviews focusing on the experience of living with myeloma
Method and process of analysis	Significant statements and phrases pertaining to living with a diagnosis of myeloma were identified and 4 main themes emerged. Each transcript was then read again with the 4 main themes in mind and sub-themes were subsequently identified.
Population and sample collection	11 patients diagnosed with myeloma mean age 63 (range: 42–83) 7 male, 4 female Time since diagnosis 1.5–4 years
Key themes	1. Lived body: a changed body Alopecia, fatigue All participants commented on changes in their bodily functions and physical appearance. For most, changes in appearance resulted in a negative view of self, while acting as a constant reminder of their illness. Moreover, concerns about how others viewed them and the realisation that they could no longer conceal their cancer had a major psychosocial effect. 2. Lived space: living in limbo Living with an 'unknown' cancer, stigma of cancer, loss, feeling 'lucky' The unfamiliar identity of myeloma was multidimensional encompassing lack of personal and public knowledge of the condition. Only one participant had heard of myeloma before diagnosis and three participants had not associated myeloma with cancer. 3. Lived time: time is precious Fear or recurrence, limited time with healthcare professional A major concern for participants was the limited time spent with healthcare professionals. Participants perceived nurses and doctors were too busy. As a result they refrained from talking about important issues and questions remained unanswered. 4. Lived relations: significance of support Family support, protecting others Participants spoke about the benefits of talking to other patients who had myeloma. This support usually began informally, in the clinic waiting rooms. However, for the majority of participants, the opportunity to talk to others with myeloma patients had not arisen.
Additional comments/ Limitations	Limitations: The findings of this study only apply to the context and point in time for the participants. Participants may feel differently later when, for example, their disease relapses. With phenomenological interpretation, there is no clear end-point to interpretation, which is always open to re-interpretation.

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Reference	Lamers et al., 2013
Study type	Cross-sectional questionnaire study
Country	Germany

Research question(s)	Aim: to identify psychosocial intervention desires of myeloma patients at time of diagnosis
Theoretical approach	n/a
Data collection	Patients completed questionnaires that included a checklist on desired psychosocial interventions and the Patient Health Questionnaire 9-item (PHQ-9) depression and Generalized Anxiety Disorder 7-item scale (GAD-7) anxiety scales. The questionnaires were completed at home and given to a staff member at the first appointment in the clinic. Medical data were extracted from the patients' electronic records.
Method and process of analysis	Sociodemographic and medical variables as well as patients' intervention desires and comorbidity are presented descriptively as mean with standard deviation, median with range, or number and percentage, depending on the scale level. A non-responder analysis and comparisons of distressed and non-distressed patients were conducted using X^2 tests or Fisher's exact tests if expected cell counts were less than five.
Population and sample collection	Patients with newly diagnosed multiple myeloma were recruited from the outpatient myeloma unit at the Heidelberg University Hospital. Of the 294 patients scheduled with suspected multiple myeloma, 104 were excluded because diagnosis could not be confirmed, and 60 patients were excluded because they had received chemotherapy. Of all included patients, 16 did not complete the questionnaires or declined participation, corresponding to a participation rate of 87. 7%. The study ultimately included 114 myeloma patients. The mean age of the 114 participating patients was 62 years (SD = 10.6; range = 32–84). 52 patients (45.6%) were 60 years or younger. Men (51.8%) and women (48.2%) were represented equally. The mean time since diagnosis was 1.65 months (SD= 2.74, range = 0–12 months).
Key themes	The study indicates that already at the time of diagnosis, myeloma patients have a high level of psychosocial intervention desires. Half of the patients (51%) in the study desired psychosocial interventions. The most common preferences were relaxation techniques and psychosocial counseling. Approximately 24% of the patients reported symptoms of depression, and 8% reported symptoms of anxiety. All of these patients scoring high for anxiety also screened positive for depressive symptoms. Because of the high overlap between anxiety and depression for comparative analyses, all patients with either an elevated score for depression or anxiety were summarized as 'emotionally distressed'.
Additional comments/ Limitations	**Limitations :** The results are developed from a tertiary cancer centre at a single phase of disease, and it is known that both the distress and quality of life of myeloma patients change over time. This situation may reduce the study's generalizability to other settings and patients. The study applied a predefined checklist with intervention alternatives; these, however, may not have represented the entire spectrum of intervention forms. Combining depression and anxiety into one group of 'emotionally distressed' (although it is stated that all analyses were recalculated for depressive and anxious patients separately and the results did not differ significantly).

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Reference	Maher & De Vries, 2001
Study type	Qualitative study - interviews
Country	UK
Research question(s)	Aim: to explore how the experience of living with relapsed myeloma had affected the quality of the lives of these individuals.
Theoretical approach	Hermeneutic phenomenology (enables the use of language to lead to undiscovered meanings)
Data collection	Audiotaped unstructured qualitative interviews conducted in a conversational manner to elicit narrative data
Method and process of analysis	Data were analysed from transcribed interview transcripts using a method of thematic content
Population and sample collection	8 people living with relapsed myeloma Age range, 48–74 5 male, 3 female.
Key themes	Key themes: 1. Living with uncertainty (cited as the dominant overarching theme) Affect of uncertainty on future and daily routine, uncertainty due to both disease and treatment, apprehension and worry about test results, re-evaluation of life and priorities, not being able to plan for the future 2. Intuitive knowing Alongside uncertainty about the future was knowledge (certainty) that the illness had relapsed before being told by a clinician 3. Maintenance of normality Living a normal life vital to coping with uncertainty, acceptance that family and friends avoided discussing the illness, reluctance to share true feelings to maintain normality 4. Adjustment to illness Recognising limitations, importance of support from family, disintegration of some and friend unable to provide support, physical and psychological stress, impact on activities of daily living, anxiety and depression leading to social isolation 5. Hope Coping with uncertainty, importance of spiritual beliefs, and importance of potential new treatments giving an 'illusion or safety' 6. Effects of treatment Toxicity of treatment – infection, neuropathy, pain, nausea, fatigue 7. Trusting healthcare professionals Importance of information in reducing uncertainty, feeling valued if concerns listened to, importance of confidence in the team 8. Fighting spirit An important coping mechanism – to remain 'strong' and 'brave' Overall, the patients in this study placed importance on the emotional aspect of their experience. Hope, intuitive knowing, a fighting spirit and trusting healthcare professionals were expressed as

	required positive elements that enabled living with relapsed myeloma. These assisted in maintaining normality, coping with bad news and in adjusting to the illness. Pervading through these themes was the need to control uncertainty and having strong support from significant others provided something to live for and the necessary social support required to promote a new orientation to life.
Additional comments/ Limitations	Limitations: - the recruitment from one organisation only - time constraints which meant only one interview was conducted with each participant

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Reference	McGrath et al 2013
Study type	Qualitative study - interviews
Country	Australia
Research question(s)	Aim: to explore the perceptions and experiences about end-of-life care for individuals with a hematological malignancy
Theoretical approach	n/a
Data collection	open-ended interviews and one focus group
Method and process of analysis	The interviews and focus group were recorded, transcribed verbatim, coded, and thematically analyzed
Population and sample collection	Fifty participants (n = 26 male; n = 24 female) were interviewed representing the major hematological diagnostic groups. 15 myeloma patients
Key themes	The findings indicated that those fortunate enough to know about the benefits of palliative care are more likely to access palliative care during end-of-life care. However, for many patients there are still problems with timely referrals to the palliative system. **Comments from myeloma patients:** Many individuals indicated that they already knew about palliative care due to a range of reasons including from personal experiences with family members and friends dying or from work as or with health professionals. Some did not know about palliative care and when informed, many indicated that they would like more information. *"Oh, could you send me out anything on that (information on palliative care and hospice)?"* It was noted that information on palliative care was not easily available. *"Like it's not sort of advertised so to speak a lot … because when you're going through something like that you just don't know what's out there*" The individuals' preference for the timing of discussions about palliative care was explored. Some individuals indicated that they did want information on palliative care before it was needed so that they would be in a better state of mind to think about the issues and plan for their family: *''I think to know while you were in a better state of mind that information might be better now than you know, 6 months down the track so you can start to plan and you can start to feel sure that your loved ones are taken care of''*

	However, there was a group of participants who clearly indicated that they preferred the "need-to-know" approach of only talking about palliative care during the final stages of care. Only one person indicated that they did not want to know about the possibility of death and dying at all: *''I just want to deal with my own space and even when they use the word "hospice," I don't like that word. I don't like that word … leave me alone, I'm alive, I'm getting on with it. Now they don't even use that life expectancy, they don't use that word now which is good''* With the contrast between some participants wanting early discussions on palliative care and most only wanting information when needed, significance was placed on the doctor in having the skills and sensitivity to know the individual's preference: *''Well, I suppose you know it depends on the person. I know it's very hard but I think doctors are pretty smart. They're the ones that should know when to sort of approach people on those subjects you know. You should be quite selective. I'd rather it that way anyway.''*
Additional comments/ Limitations	

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Reference	Molassiotis et al., 2011a
Study type	Cross-sectional questionnaire study
Country	UK
Research question(s)	Aim: to identify unmet supportive care needs of both patients living with myeloma and their partners
Theoretical approach	n/a
Data collection	Patients completed a questionnaire exploring their Supportive Care Needs (Cancer Survivors' Unmet Needs measure (CaSUN)), the Hospital Anxiety and Depression Scale (HADS) and the EORTC QOL scale with its Myeloma module. The partners completed the partners' version of the Supportive Care Needs scale and HADS. The questionnaires were completed at home and returned to the researchers in pre-paid envelopes.
Method and process of analysis	Using SPSS (v.13) descriptive statistics were calculated to summarise the data and identify subgroups of patients with great number of needs.
Population and sample collection	Patients and their partners were recruited from 4 hospitals in the UK The inclusion criteria for patients were: (a) diagnosed with multiple myeloma; (b) being more than 1 year post-initial diagnosis; (c) having received chemotherapy with or without immunomodulatory drugs, marrow or blood stem cell transplantation for their myeloma. Patients receiving maintenance treatments were also included and (d) willing to participate in the study and able to complete the study's questionnaires. Patients less than 1 year post-diagnosis were excluded from the study because the focus of the study was longer term needs in myeloma survivors. Patients with advanced/progressing disease were also excluded.

The patients' partners were also recruited, and they were included in patient– partner dyads if they were in a relationship with the patient, living together and/or were the primary caregiver of the patient.

The study recruited 132 patients and 93 of their partners.

The mean age of the patients was 62 years (SD58.8, range535–83)
The mean age of the partners was 58.9 years (SD512.6; range525–80).
Fifty patients (37.9%) were less than 60 years old.
Mean time post-diagnosis of 5 years.

Key themes

26.5% of survivors and 29% of partners reported at least 1 unmet need. Most were described as weak or moderate.
Most common unmet needs for both patients and their partners were accessibility of hospital car parking, obtaining life and/or travel insurance and managing concerns about cancer recurrence.

Unmet supportive care needs in myeloma patients and their partners

Statement of need	% of total sample of patients[a]	% of total sample of partners[a]
I need more accessible hospital parking	10.6 (1)*	15.0 (1)*
Due to myeloma, I need help getting life or travel insurance	10.4 (2)	12.5 (2)
I need help to manage my concerns about myeloma coming back	7.9 (3)	11.5 (3)
I need an ongoing case manager to whom I can go to find about services whenever they are needed	7.4 (4)	10.8 (4)
I need help to reduce stress in my life	6.6 (5)	9.0 (8)
I need help to try to make decisions about my life in the context of uncertainty	6.4 (6)	8.2 (11)
I need to know that all my doctors talk to each other to coordinate my care	6.4 (6)	9.8 (6)
My family and/or partner needs information relevant to them	6.3 (7)	8.3 (10)
I need to talk to others who have experience myeloma	6.2 (8)	6.7 (16)
I need help to deal with my own and/or others expectations of me as a myeloma survivor	6.2 (8)	n/a
I need help to adjust to changes in my QOL as a result of my myeloma	5.6 (9)	n/a
I need help to find out about financial support and/or state benefits to which I am entitled	5.6 (9)	9.1 (7)
I need help to know how to support my partner and/or family	5.5 (10)	6.4 (19)
I need help to cope with others not acknowledging the impact that myeloma had on my life	5.5 (10)	6.9 (15)
I need help to adjust to changes to the way I (my partner) feel(s) about my (his/her) body.	5.5 (10)	3.7 (28)

[a] *These percentages represent needs in up to 40% of patients and up to 52% of partners who communicated at least one need.*
**Numbers in brackets indicate the rank of patient/partner need*

Additional partner needs

While the most frequently reported unmet supportive care needs were the same in both patients and partners, the partners had their own additional needs that were not reported by patients. Additional partner' needs were mostly around the practical and informational aspects of the patients' care.

Additional partner needs	***% of those who expressed a need***	***% of total sample***
the need for help to manage ongoing side effects and/or complications experienced by patients as a result of their treatment	34.4	10
provision of up-to-date	30.5	9
local health-care services that are available when the patient requires them	27.6	8
help in dealing with changes that myeloma has caused to the patient	26.2	7.6
emotional support to themselves	26.2	7.6
information to be provided in a way that they can understand	24.6	7.1

Depression and anxiety

	% of patients	***% of partners***	***Patients score mean (SD)***	***Partners score mean (SD)***
anxiety	27.4	48.8	5.64 (3.83)	7.72 (4.31)
depression	25.2	13.6	5.18 (3.37)	4.57(3.63)

Patients with an anxiety score of 8 or more had significantly greater number of unmet needs reported (45.7% vs
19.4%, P=0.002). Similarly, those with signs of depression had double the amount of unmet needs reported than those with no signs of depression (43.8% vs 21.1%, P=0.012).

Anxiety was significantly higher in the partners than the patients (P<0.05).

Additional comments/ Limitations

Limitations:

It was noted in the paper that many patients commented that had they completed this scale during treatment and soon after, their responses would have been very different and with more needs, suggesting that supportive care needs may be higher in this population during active treatment times.

There was a lower than expected response rate from the partners (50.3%).
The non-respondent partners may constitute a group of caregivers with more needs and problems than those reported by the respondents. The most common reason that partners alluded to for not participating was that they did not want to be reminded of their partners' disease.

The results reflect the views of those in remission and who have survived for longer.

Almost all (but 6) patients were of white origin, and hence findings cannot be applied in other ethnic groups.

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eference	Molassiotis et al., 2011b
Study type	Qualitative – Interviews
Country	UK
Research question(s)	Aim: to provide a more in depth and personal insight into the key issues identified in the quantitative part of the study
Theoretical approach	While no specific qualitative paradigm was followed, the principles of grounded theory were maintained, including studying the participants in naturally occurring settings (their homes), using open-ended and flexible questions in that these questions could be modified as the research progressed and new information was revealed, and identifying themes and coding frames without predefined ideas or coding categories.
Data collection	Semi-structured interviews with patients and carers to talk about the effects of myeloma on their lives, issues and concerns, their supportive care needs and how they were coping in everyday life. All interviews took place in the participants' home.
Method and process of analysis	Interviews were tape recorded and later professionally transcribed verbatim. A 'bottom-up' approach was taken in identifying themes within the data utilising content analysis, developing coding frames (conceptual labels) and analysing the data.
Population and sample collection	Subset of patients and carers from study above (Moassiotis et al 2011 *Psycho-Oncology,* 20: 88-97). Purposefully selected based on their responses to the questionnaire. Participants were selected to represent both positive views and concerns with their living with myeloma. 20 myeloma patients 12 female and 8 male Mean age 61.8 years. Married = 16; single = 2; separated = 1; widowed = 1 All were of white British origin. None of the participants were currently receiving any active treatment, although five had relapsed and were either awaiting treatment (n=2) or were on a treatment break at the time of interview (n=3). Mean time post-diagnosis was 5 years (range 1–11.5). 16 informal caregivers. 9 female and 7 male Mean age 61.4 years 14 were the patients' partners and two were the daughters of the patients. All partners were living with the patients in the same house, while the two daughters did not live with the patient.
Key themes	**Information needs of patients:** While some patients were eager to gather knowledge around myeloma and the management of their illness, several others avoided any knowledge (avoidance coping). Knowledge avoidance was split between patients who saw it as a positive way of coping, with statements such as '…helps me remain blasé about the treatment', '…happy to bury my head' and '…purposely I don't take an interest in the disease as it's generally bad news', to those patients who were in a dilemma between wanting to know more about their illness but not wanting bad news. Information needs were generally low, and patients were satisfied with the information they had received. Unmet information needs usually surrounded the need to know more about their future prognosis, although patients understood that often it was difficult to put a time frame on their illness.

	Support groups were not popular, with only one patient having attended a group. The vast majority did not have a desire to attend support groups, and as one caregiver put it: 'he wouldn't want to go to a support group…doesn't want to go to a 'commiseraters' club'. **Information needs of carers:** No caregivers recalled having been given specific information (e.g. leaflets) designed specifically for caregivers of patients with myeloma. However, only one saw this as a problem, and most never thought of this until mentioned by the interviewer. They had low expectations of what help or information is available to them, most mentioned 'just getting on with it'. The few participants who mentioned unmet information needs reported needs in relation to understanding myeloma symptoms better and what is normal, financial advice and information around prognosis. **Support needs of patients:** 9 of 20 patients said that they had no needs. However, during discussions and through probing questions, needs might then be elicited from the same people. There seemed to be a general lack of expectation about what help can be accessed. Typical comments were 'I don't know what help is available' or 'I don't know how to go about finding that help'. Patients felt that once they had received the initial treatment and were in remission they were then 'forgotten' by the specialists; they were now not seen by the consultant and saw a different doctor each time they visited the hospital. One patient said '…might say I've lost that personal touch-leaves a bit of an empty hole'. 4 patients expressed that they would like help to manage their ongoing symptoms (lack of energy, bowel problems, back pain and mobility were mentioned). **Support needs of carers:** Because none of the patients were currently receiving any antineoplastic treatment, most informal caregivers felt they had already been through the most difficult period. Few unmet needs were verbalised. Some participants felt that they did not know who to turn to when there were problems, e.g. '…I don't know who to ask for help or what help is out there'. The vast majority of caregivers felt they did not need help from outside agencies and that at times when patients had been ill, they had relied on family for extra support. 3 caregivers mentioned that outside help had not been pursued because they perceived that the patient would not allow it; one participant described '…[the patient said] I don't want no Macmillan nurses [specialist community palliative care nurses] calling here, no way – I felt the same', alluding to a connotation between specialist palliative care support and death. 3 caregivers highlighted the problem of not having anyone to talk to. Some participants found it difficult to speak to the doctors and felt they were interested more about the disease, proposing to 'seeing the person in the patient'.
Additional comments/ Limitations	Cross-sectional design. Selection bias. Participants purposefully selected based on their responses to questionnaire. Not randomly selected.

	(Participants were selected to represent both positive views and concerns with their living with myeloma) Most patients who participated were considered long-term survivors and were in remission; hence, experiences of those with advanced progressing disease and those on-treatments may be substantially different. Participants were about 5 years younger than the average myeloma population. All participants were Caucasian. Informal caregivers were identified through the patients, and this may have introduced selection biases. Caregiver experiences were reflecting more stable families, as the vast majority were spouses.

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Reference	Oerlemans et al., 2012
Study type	Cross-sectional questionnaire study
Country	Netherlands
Research question(s)	Aim: to evaluate the current perceived level of and satisfaction with information received
Theoretical approach	n/a
Data collection	The Dutch version of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-INFO25 questionnaire was used to evaluate the perceived level of and satisfaction with information
Method and process of analysis	After linear transformation, all scales and items range in scores from 0 to 100, with higher scores indicating better perceived information provision.
Population and sample collection	The population-based Eindhoven Cancer Registry (records data on all patients who are newly diagnosed with cancer in the southern part of the Netherlands) was used to select all patients diagnosed with NHL, HL and MM from 1999 to 2009. In total, 1,448 survivors received a questionnaire, and 1,135 of them responded (78.4 %). 153 myeloma patients Female: 69, male: 83 Mean age at time of survey 66.1 years (SD 10 years) Mean years since diagnosis 2.4 (SD 2.3 years)
Key themes	29% of myeloma patients would have liked to receive more information. (only 1% wanted less information) Most frequently mentioned topics to receive more information about were: cause and course of disease (54%), late effects of treatment (30%) and psychosocial aftercare (30%). ***Mean EORTC QLQ-INFO25 subscale scores (±SD)***

EORTC QLQ-INFO25	**Mean (SD)**
Information about disease	51 (22)
Information about medical tests	65 (23)
Information about treatment	47 (24)
Information about other services	22 (21)
Satisfaction with information	61 (28)

	Usefulness of information: 62 (25) *EORTC-QLQ INFO25 scales 0–100: a higher score reflects better perceived information received* Myeloma patients under active surveillance reported lower perceived levels of information about treatment (β=−0.45; p<0.05) compared to patients who were actively treated. Myeloma patients who had been diagnosed more recently had higher perceived levels of information provision, which possibly indicates that information provision has improved with time. However, it is also possible that recall bias influenced these findings, for those diagnosed more recently, the information received is still fresh in their memory.
Additional comments/ Limitations	**Limitations:** Cross-sectional design. It remains unknown why non-respondents declined to participate in the study.

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Reference	Osborne, 2014
Study type	Qualitative study – structured interviews
Country	UK
Research question(s)	Aim: to explore the issues important to QOL from the perspective of people with myeloma (and also to explore the views of patients and staff about existing QOL measures – but this aspect is not appraised here).
Theoretical approach	n/a
Data collection	Semi-structured interviews – all conducted by the same researcher, designed to probe the QOL issues of importance to the patient.
Method and process of analysis	The interview recordings were transcribed verbatim, imported into NVivo software and analysed using thematic analysis.
Population and sample collection	Participants were 20 patients with myeloma – a purposive sample intended to maximise variation across gender, age and disease stage.
Key themes	The themes most closely related to QOL were emotional status, activity & participation and support factors.
Additional comments/ Limitations	The main focus of the study was to develop a theoretical model of QOL in myeloma to be used in the clinical care of such patients.

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Reference	Rini 2007
Study type	Qualitative - interviews
Country	USA
Research question(s)	What are the effects of experiential information on cancer patients?
Theoretical approach	n/a
Data collection	Interview questions
Method and process of analysis	Content analysis of the responses to interview questions

Population and sample collection	Participants consisted of 20 men and 10 women completing a screening protocol for a multisite trial testing a psychological intervention for hematopoietic stem-cell transplant (HSCT) survivors. All patients had undergone HSCT 1 to 3 years earlier to treat hematologic malignancies such as myeloma, lymphoma, and leukemia. Study does not specific how many myeloma patients. They were, on average, 54 years old, married (n=25), white (n=25), and well-educated (22 had college or graduate degrees).
Key themes	**Preparatory coping: knowing what to expect and how to cope with it** Patients most often described how learning about fellow patients' experiences helped them prepare for transplantation. Patients specifically discussed learning about people's day-to-day experiences on the transplant unit, physical and emotional effects of transplantation, treatment decisions, and coping strategies. Many patients who did not have access to this information wished they had. Comments from myeloma patients: *"At the very beginning, I was frightened and I was confused, and we didn't know what course to take. . . . If I had more knowledge of what the disease was or what other people had experienced, it would have been very helpful. . . . To know what route or what choices. . . were there for me,. . . and to know that really I personally didn't have to be afraid."* *"I did talk to someone who had it—a friend of my husband's who worked with him. . . . I would tell him how I'm feeling. He would say, 'Yeah, you're going to feel this way and then you're going to get better. It goes away. You're going to eat this. You're not going to feel like eating that.' I spoke with him, and that helped a lot."* *"My daughter gave me the name of a doctor that was diagnosed 2 years previously with multiple myeloma. So I got in touch with the doctor and his wife over the phone, and he gave me someone else's name, and I got in touch with that person. And then someone at work gave me the name of someone else, and I got in touch with that person. When we went to the conference last year [held by the Multiple Myeloma Foundation], I met other patients, and I've been in contact with them to find out what their experiences were and how they're dealing, and what their protocol is now."* **Social comparisons: knowing where you stand in relation to others** Patients described using experiential information as a basis for social comparisons. Comments from myeloma patients: *''As much as I have gone through, I always see somebody that has had it worse than I have."* *"If I sit in the doctor's office and I see somebody who says, 'I have been Coming back and forth for 10 years with this,' they think they're discouraging me. But what they're really doing is making me feel good. I'm saying, 'They lived 10 years after this. That's great!'"* **Negative effects of experiential information: what can go wrong?** Substantial minority of patients (23%) mentioned situations in which learning about experiences of fellow patients was unhelpful or even harmful, highlighting potential pitfalls of experiential information. Patients who thought it was unhelpful usually commented that others' experiences would differ

	from their own and thus be uninformative. Harmful effects fell into two categories: stories that were distressing or stories that communicated what patients felt was harmful information. For instance, several patients reported distress after hearing about enduring negative adverse effects In this study, patients who reacted negatively to experiential information also appeared to restrict their exposure to medical information, consistent with reports that some cancer patients prefer limited information about their situation, in general. **Accessing experiential information** Patients who spoke with fellow patients most often found them through informal networking with friends, family, or acquaintances. It appeared that these contacts were strongly desired, but not readily available through formal channels
Additional comments/ Limitations	Mainly patients with good outcomes who were commenting retrospectively.

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Reference	Stephens, 2014
Study type	Qualitative study – structured interviews
Country	Australia
Research question(s)	Aim: to report findings from a qualitative study of the experiences of patients with multiple myeloma following first relapse in the era of novel agents.
Theoretical approach	Grounded theory approach
Data collection	Semi-structured interviews
Method and process of analysis	Interviews were recorded and transcribed verbatim. Inductive analysis used to identify themes of particular interest
Population and sample collection	A convenience sample of 11 patients with myeloma and 10 carers. Recruitment stopped when no new insights were generated.
Key themes	To adapt to the effects of myeloma and its treatments required great effort which the reviewers termed “illness work”. This was typically effort required to mitigate the risks to the well being of the patient and carer. For example modifications to diet, avoidance of infection and skeletal injury. Emotion work was also required to manage the feelings of self and others during the cycles of treatment and relapse.
Additional comments/ Limitations	

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Reference	Tariman, 2014
Study type	Qualitative, descriptive cross sectional study
Country	USA
Research question(s)	To examine patient perspectives on factors relevant to treatment decision making in myeloma
Theoretical	n/a

approach	
Data collection	Semi-structured interviews
Method and process of analysis	Interviews were recorded and transcribed verbatim. Directed content analysis was used to extract the major themes
Population and sample collection	N=20. Age ≥ 60 years, with newly diagnosed symptomatic myeloma. Patients were recruited from University and community based practices to maximise the diversity of the participants.
Key themes	*Trust in the physician, healthcare team and/or institution:* Participants expressed their trust in physician, healthcare team and/or institution as influential in treatment decisions. *Participants have many sources of information related to myeloma:* Participants described the different sources of myeloma-related information including: the internet, physicians, family and friends who help to research myeloma-related material, physician visits, books, pamphlets, nurses, other patients and support groups. *Participants have various decisional role preferences:* Patients described their role preferences or any changes in role preferences as being either active (patient making their own treatment decision with or without consideration of the physician's opinion), shared (between patient and physician) or delegated (to the physician). *Patient specific factors influence treatment decisions:* these factors include the patients' experience of myeloma therapies, age, beliefs and values, spiritual faith, opinions of others and past experience of non-myeloma treatments. *Negative perceptions of treatment decision making*: some described negative perceptions of treatment decision making – including lack of discussion of treatment options, long waiting times, inability to reach a healthcare team member, and wanting to have more information about the disease, prognosis, treatment and side effects. *Decisions driven by the benefits of being cancer free, in remission or longer life:* patients described the benefits of their therapy. *Contextual factors:* these included health insurance, financial status, availability of free medicine, geographical considerations, social support, housing, retirement planning and significant family events. *Initial shock at time of diagnosis*: participants described being in a state of shock, feeling very overwhelmed and not in the right frame of mind to process what was heard from the physicians during the visit – feeling paralyzed from participating in decision making.
Additional comments/ Limitations	

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Reference	Vlossak & Fitch 2008
Study type	Qualitative study - interviews
Country	Canada
Research question(s)	Aim: to To explore in a qualitative manner the impact of a diagnosis of myeloma on the patient and family'
Theoretical	n/a

approach	
Data collection	Qualitative telephone interviews focusing on experiences specific to living with myeloma. Participants were asked open-ended questions to allow them to discuss what was important t them.
Method and process of analysis	Interviews were transcribed verbatim. The transcripts were subjected to a standard content and theme analysis.
Population and sample collection	20 myeloma patients age range 44–88 13 male, 6 female. Time from diagnosis 6 months–6 years
Key themes	1. Shock of diagnosis 2. Few options for treatment 3. Worry about family 4. Treatment is difficult, long, complex 5. Fatigue is overwhelming 6. Loss of independence 7. Change in self concept/self image 8. Obsession about how and when the end will come 9. Fear of recurrence 10. Rationalisation of changes in hopes for the future The study indicated that the patients were satisfied with the physical care they receive. However their responses demonstrated that their primary needs are emotional and psychosocial. When the patients were questioned about sharing these feelings with their physicians and nurses almost all were reluctant to approach the medical team with concerns surrounding their emotional health. *''I have my monthly meeting and they're so busy…you're sort of in and out. I just think because they're so busy I don't feel comfortable doing it right now…you go there and my God, there are a hundred people waiting. So you hate to, you're waiting two and three hours to see them. You don't want to do that to somebody else.''* *''Well, like I say they (medical team) look so busy. And you go in and you see these poor people that are desperately ill and you think, well I don't know what I am complaining about because I can do this and that the other. So almost, what am I doing here?''*
Additional comments/ Limitations	Limitations: - the recruitment from one organisation only - time constraints which meant only one interview was conducted with each participant

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Reference	Myeloma UK survey. March 2014.
Study type	Cross-sectional questionnaire study
Country	UK

Research question(s)	Aim: to capture the experiences of patients who have had high-dose therapy and stem cell transplantation to better understand the issues that most impact on their experience
Theoretical approach	n/a
Data collection	Online survey - mixture of qualitative and quantitative questions, with space for free text in many of the questions to allow patients to expand on their answers and explain their experience in more detail.
Method and process of analysis	Not reported
Population and sample collection	Myeloma UK undertook an online survey which was promoted through the Myeloma UK website, particularly via the online discussion forum and myeloma patients who had undergone a high-dose therapy and stem cell transplantation within the last few years were invited to participate and share their experience. The survey was live on the Myeloma UK website during June and July 2013. In total, 162 responses to the survey were collected.
Key themes	87.1% of patients who responded to the survey were 'very satisfied' or 'satisfied' with the amount and quality of information that they received. The most significant findings: 1. Many patients surveyed would have liked the opportunity to speak to another patient who has already undergone high-dose therapy and stem cell transplantation, before deciding whether to undergo the treatment themselves. Only 17% of respondents were given the option to speak to another patient who had already undergone high-dose therapy and stem cell transplantation. Of those who were not given the option, 48% would have liked the chance to speak to another patient so they could learn more about what to expect from the treatment. 2. Information about the emotional impact of receiving high-dose therapy and a stem cell transplant is often not provided. 27% of respondents were given no information on the potential emotional impact that this treatment might have on them. 3. Stem cell mobilisation and collection is a source of worry amongst some patients. 21% of patients were given no information on what would happen if not enough stem cells were collected, yet 69% of respondents were anxious, about whether they would produce enough stem cells in order to proceed with high-dose therapy and stem cell transplantation. 4. Patient experience is enhanced with the addition of a named nurse or transplant coordinator acting as their main point of contact. 73% of patients had a named nurse or transplant coordinator who acted as their main point of contact during their stay in hospital. 68% of those with a named nurse rated their care in hospital as excellent. 37% of those who did not have a named nurse rated their care in hospital as excellent.

	5. anxiety can be a significant factor for patients throughout the treatment journey – from making a decision about whether to undergo the treatment, through to stem cell mobilisation and collection, the high-dose therapy, transplant and returning home. 23.3% of respondents answered that they were 'anxious' and 5.3% stated they were 'depressed' when asked about their predominant emotion while they were in hospital. Providing high quality and appropriate information at critical times should help reduce patient anxiety and worry. However, only 25% of respondents stated that they felt less worried or anxious about having the treatment after receiving information, while 20% of respondents said that information had in fact made them feel more anxious.
Additional comments/ Limitations	The responses do not consist of a representative sample of patients who have undergone high-dose therapy and stem cell transplantation and were not adjusted for geographical spread, age of patients, length of time since their treatment, or any other factor.

1 ***Excluded papers (after checking full text)***

Paper	Reasons for exclusion
1. Bertolotti, P., Bilotti, E., Colson, K., Curran, K., Doss, D., Faiman, B., Gavino, M., Jenkins, B., Lilleby, K., Love, G., Mangan, P. A., McCullagh, E., Miceli, T., Miller, K., Rogers, K., Rome, S., Sandifer, S., Smith, L. C., Tariman, J. D. & Westphal, J. (2008) Management of side effects of novel therapies for multiple myeloma: consensus statements developed by the International Myeloma Foundation's Nurse Leadership Board. *Clinical Journal of Oncology Nursing,* 12: 9-12.	Not relevant for review question. Not a study to identify what are the information and support needs. Paper reports on the development of consensus statements by the International Myeloma Foundation's Nurse Leadership Board.
2. Bilotti, E., Faiman, B. M., Richards, T. A., Tariman, J. D., Miceli, T. S., Rome, S. I. & International Myeloma Foundation Nurse Leadership Board. (2011) Survivorship care guidelines for patients living with multiple myeloma: consensus statements of the International Myeloma Foundation Nurse Leadership Board. *Clinical Journal of Oncology Nursing,* 15 Suppl: 5-8.	Editorial article. Not relevant for review question. Overview of Survivorship care guidelines for patients living with multiple myeloma. Most significant patient needs determined based on a survey of Nurse Leadership Board members. Bone health, health maintenance, mobility and safety, sexual dysfunction and renal health.
3. Chhabra, K. R. (2013) Physician communication styles in initial consultations for hematological cancer. *Patient Education and Counseling,* 93: 573-578.	Not specific to myeloma. Haematological cancers. 30% myeloma. Not relevant for review question. Study does not aim to identify the specific information and support needs of patients. Study to investigate physician communication styles in consultations.
4. Clarke, H. (2010) A randomised controlled trial of an educational booklet for multiple myeloma patients with peripheral neuropathy. *Haematologica,* Conference: 588-589.	Conference abstract. Therefore limited information/details of the study
5. David, N. (2013) Internet-based program for coping with cancer: A randomized controlled trial with hematologic cancer patients. *Psycho-Oncology,* 22: 1064-1072.	Not specific to myeloma. Haematological cancers. 4% myeloma. Not relevant for review question. Study does not aim to identify the specific information and support needs of patients Objective of study was to develop and conduct a field experimental assessment of an internet based cognitive behavioral program to support coping with illness in haematological cancer.

6. El, T. A., Abel, G. A., Roland, M. & Lyratzopoulos, G. (2013) Variation in reported experience of involvement in cancer treatment decision making: evidence from the National Cancer Patient Experience Survey. *British Journal of Cancer,* 109: 780-787.	Not relevant for review question. Data from the 2010 English National Cancer Patient Experience Survey. Responses from 41,411 patients (myeloma n=1,873) were analysed with regards to a single question examining patient experience of involvement in treatment decision making and how this varied between patients of different age, gender, ethnicity, socioeconomic deprivation and cancer diagnosis.
7. Hall, A. (2013) Supportive care needs of hematological cancer survivors: A critical review of the literature. *Critical Reviews in Oncology/Hematology,* 88: 102-116.	Review to determine perceived supportive care needs of haematological cancer survivors. Myeloma not looked at separately. But included studies on myeloma are included in evidence review separately.
8. Hayes, L. & Cooney, M. (2013) Identifying and Addressing the Supportive Care Needs of the 'Complex' Patient with Multiple Myeloma Within A Nurse Practitioner Led Service. *Asia-Pacific Journal of Clinical Oncology,* 9: 121.	Conference abstract. Therefore limited information/details of the study
9. Heras, P. (2010) Education and psychosocial adaptation of multiple myeloma patients. *European Journal of Cancer, Supplement,* Conference: 4.	Conference abstract. Therefore limited information/details of the study
10. Hoff, L., Tidefelt, U., Thaning, L. & Hermeren, G. (2007) In the shadow of bad news - views of patients with acute leukaemia, myeloma or lung cancer about information, from diagnosis to cure or death. *BMC Palliative Care,* 6: 1.	Not specific to myeloma. The study consists of recurrent interviews with 12 cancer patients: 7 with haematological cancer. Not stated how many myeloma patients.
11. Husson, O. (2013) Satisfaction with information is associated with baseline and follow-up quality of life among lymphoma and multiple myeloma survivors: Results from the profiles registry. *Supportive Care in Cancer,* Conference: S37-S38.	Conference abstract. Therefore limited information/details of the study
12. Husson, O., Thong, M. S., Mols, F., Oerlemans, S., Kaptein, A. A. & van de Poll-Franse LV. (2013) Illness perceptions in cancer survivors: what is the role of information provision? *Psycho-Oncology,* 22: 490-498.	Study is relevant but myeloma data from this paper is already included in Oerlemans et al 2012 as the 2 reports are by the same group so would be repeating the data if this paper was to be included also.
13. King, T. (2012) 'For the first month I was telling everyone i had myeloma: Addressing the information needs of myeloma patients. *Supportive Care in Cancer,* Conference: S211.	Conference abstract. Therefore limited information/details of the study
14. King, T. (2012) "The Devil's Tic Tac's"-Understanding the adverse events of steroid therapy associated with the treatment of multiple myeloma. *Bone Marrow Transplantation,* Conference: S467-S468.	Conference abstract. Therefore limited information/details of the study
15. Kurtin, S., Lilleby, K. & Spong, J. (2013) Caregivers of Multiple Myeloma Survivors. *Clinical Journal of Oncology Nursing,* 17: 25-30.	Expert/narrative review
16. Low E., M. (2012) UK patient perspectives of bisphosphonate treatment highlight a lack of knowledge on therapeutic benefits and strong preferences for choice and location of treatment. *Blood,* Conference: 21.	Conference abstract. Therefore limited information/details of the study

17. Meehan, K. R. (2006) The financial requirements and time commitments of caregivers for autologous stem cell transplant recipients. *Journal of Supportive Oncology,* 4: 187-190.	Caregivers for autologous stem cell transplant recipients. 40 patients of which 18 were myeloma patients. Study looks at time commitments and financial requirements . USA study.
18. Osborne, T. R., Ramsenthaler, C., Siegert, R. J., Edmonds, P. M., Schey, S. A. & Higginson, I. J. (2012) What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. [Review]. *European Journal of Haematology,* 89: 437-457.	Not relevant for review question - systematic review of the literature to identify and evaluate all existing HRQOL tools developed or validated for use in myeloma. There is a small section regarding studies that have identified issues important to HRQOL from the patients perspective. Studies relevant for information and support needs will be assessed in the evidence review separately.
19. Osby, E. & Reizenstein, P. (1989) Quality of life and care in leukemia, myeloma and non-malignant disease. Opinions of patients and relatives, and effects of geography and time. *Medical Oncology & Tumor Pharmacotherapy,* 6: 133-141.	Questionnaire study Interviewed in 1980: 20 myeloma patients Interviewed in 1986: 15 myeloma patients Study looks at how satisfaction with information has improved over time and also compares against satisfaction in other cancers. Study does not look at what are the specific information and support needs of myeloma patients.
20. Pelagalli, M. F. (2010) Physician-patient relationship: Intervention opportunities for multiple myeloma patients' needs. *Blood,* Conference: 21.	Conference abstract. Therefore limited information/details of the study
21. Rathwell, J. & Lee, D. (2002) The information needs of patients with multiple myeloma and their usage of the Internet. *Blood,* 100: 873A.	Conference abstract. Therefore limited information/details of the study
22. Sherman, R. S. (2005) Dialogue among survivors of hematopoietic cell transplantation: Support-group themes. *Journal of Psychosocial Oncology,* 23: 1-24.	Hematopoietic cell transplantation survivors who attend a monthly support group. Paper describes issues discussed in the support group. Average attendance 6-8 participants. Mix of hematologiocal cancers including myeloma but paper doesn't specify how many with myeloma.
23. Stephens, M. (2005) The lived experience post-autologous haematopoietic stem cell transplant (HSCT): a phenomenological study. *European Journal of Oncology Nursing,* 9: 204-215.	Small sample size. Five adult patients who had previously undergone autologous transplantation for a haematological malignancy (myeloma n=1) were interviewed to explore their experiences, concerns and the impact that transplantation had on their lives.
24. Tariman, J. D. (2013) Treatment, prognosis and self-care are top information priorities of older adults newly diagnosed with active myeloma. *Clinical Lymphoma, Myeloma and Leukemia,* Conference: S206.	Conference abstract. Therefore limited information/details of the study
25. Tariman JD, Doorenbos A, Schepp KG, Singhal S, Berry DL. Information Needs Priorities in Patients Diagnosed With	Not specific to myeloma

Cancer: A Systematic Review. J Adv Pract Oncol. 2014;2014(5):115-122.	
26. Tarzian, A. J. (1999) Autologous bone marrow transplantation: The patient's perspective of information needs. *Cancer Nursing,* 22: 103-110.	Interviews to explore patient experiences. 20 patients who had undergone an autologous bone marrow transplant (myeloma n=2).
27. Thong, M. (2011) Illness perceptions in cancer survivors: What is the role of information provision? *Psycho-Oncology,* Conference: 35-36.	Conference abstract. Therefore limited information/details of the study
28. Tripathy, D., Durie, B. G., Mautner, B., Ferenz, K. S. & Moul, J. W. (2014) Awareness, concern, and communication between physicians and patients on bone health in cancer. *Supportive Care in Cancer,* 22: 1601-1610.	Mixed cancer sample – breast, prostate and myeloma (831 myeloma patients). Not relevant for review question to asses specific information and support needs. Study aims to explore physician–patient communications about bone metastases and cancer treatment induced bone loss.
29. Ulla Diez S., A. (2001) Needs and resources of hemato-oncologic patients admitted to a general hospital. *Oncologia,* 24: 37-48.	Foreign language paper

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Chapter 2: Laboratory investigations

Laboratory investigations for people with suspected myeloma

Review question:
What is the optimal laboratory testing strategy for suspected myeloma?

PICO

Population	Index tests	Reference standard	Outcomes
People referred to secondary care with suspected myeloma, including those with MGUS	• Bone marrow trephine biopsy and immunochemistry • Bone marrow aspirate biopsy • Bone marrow immunophenotyping • Protein electrophoresis • Immunofixation • Urinary Bence Jones protein/urinary free light chains • Serum free light chains •Different sequences of the above tests	Note what reported by studies	• Diagnostic accuracy • Rate of confirmed diagnosis • Delay in diagnosis • Test related adverse events • Patient awareness of diagnosis • Cost effectiveness

Evidence statements

Diagnostic accuracy of laboratory tests for suspected plasma cell disorders (see Figure 2.1 and Table 2.1)

Serum protein electrophoresis (SPE)
Evidence from 4 studies including 4888 patients (McTaggart et al 2013, Hill et al 2006, Piehler et al 2008 and Vermeersch et al 2008) suggests serum protein electrophoresis has sensitivity 85% [95%C.I. 75% – 92%] and specificity of 95% [95%C.I. 85% – 98%] for the diagnosis of plasma cell disorders.

Serum free light chain (sFLC) analysis
Evidence from of 4 studies including 4888 patients (McTaggart et al 2013, Hill et al 2006, Piehler et al 2008 and Vermeersch et al 2008) suggests serum free light chain ratio outside the normal range has sensitivity of 47% [33% – 60%] and specificity of 95% [85% – 99%] for the diagnosis of plasma cell disorders.

Combined SPE and sFLC
Evidence from 3 studies including 4054 patients (McTaggart et al 2013, Hill et al 2006, Piehler et al 2008) suggests that combining serum free light chain analysis with serum protein electrophoresis, improves sensitivity for the diagnosis of plasma cell disorders with a pooled estimate of 94% [72% – 99%]. In this strategy patients with a negative serum protein electrophoresis test would go on to have a serum free light chain test.

Other tests for plasma cell disorders

Three studies were identified which aimed to determine the most clinically effective diagnostic testing strategy for plasma cell disorders. In one UK study, 2,799 patients with suspected plasma cell dyscrasias were tested with serum protein electrophoresis with either urine protein electrophoresis (UPE) or serum free light chain analysis (McTaggart et al., 2013). The combination of sFLC and SPE had the greatest sensitivity (100% (95% CI 97 to 100), detecting all 124 patients with plasma cell disorders, and had specificity of 97% (95% CI 96 to 97). This was greater than the diagnostic accuracy of SPE and UPE, which had a sensitivity of 96% (95% CI 89 to 99) and a specificity of 95% (95% CI 93 to 97), although only this was based on fewer patients (n=579) and there is overlap in the confidence intervals for sensitivity and specificity of the two testing strategies.
One study reported the diagnostic accuracy of different testing strategies in 833 patients investigated for monoclonal gammopathy. SPE with follow-up immunofixation electrophoresis (IFE) plus sFLC had a sensitivity of 82% and a specificity of 97%. Serum IFE plus urine IFE had a sensitivity of 92% and a specificity of 100%. Neither of these testing strategies missed a case of myeloma (Vermeersch et al., 2008).

A further study only included patients with an existing plasma cell disorder (including 467 myeloma, 191 smouldering myeloma, 524 MGUS, 581 primary amyloidosis) (Katzmann et al., 2009). The combinations of SPE/IFE/sFLC and SPE/sFLC both detected 100% of the 467 patients with multiple myeloma.

Behdad et al (2014) reported that multiparameter flow cytometry had sensitivity 94% and specificity 68% for the diagnosis of plasma cell neoplasm versus not in a study of 361 patients with suspected plasma cell neoplasm.

Diagnostic accuracy of tests for the discrimination of myeloma versus MGUS

Serum protein electrophoresis – monoclonal protein

M-protein in serum ≥ 30 g/l is one of the International Myeloma Working Group (2003) consensus diagnostic criteria – so by definition it has 100% specificity for the diagnosis of myeloma versus MGUS in studies using those criteria. Some patients with myeloma have lower M-protein levels so this criterion alone has imperfect sensitivity for myeloma. Frebert et al (2011) in a study of 161 patients with myeloma or MGUS estimated the sensitivity for myeloma of this 30 g/L cutoff as only 41%.

In a study of 67 patients with monoclonal gammopathy, Wolff et al (2007) reported that the presence of a monoclonal band on serum protein electrophoresis had a sensitivity of 85% for intact immunoglobulin myeloma but only 40% for light chain myeloma.

Bone marrow plasma cell percentage

Similarly a clonal bone marrow plasma cell percentage ≥ 10% is one of the International Myeloma Working Group (2003) diagnostic criteria – so by definition it has 100% specificity for the diagnosis of myeloma versus MGUS in studies using those criteria. Some patients with myeloma have lower clonal bone marrow plasma cell percentages so this criterion alone has imperfect sensitivity for myeloma. In two studies including 229 patients with myeloma or MGUS (Milla et al 2001, Frebert et al 2011) with myeloma or MGUS, a ≥10% threshold had a sensitivity of 79% and a ≥30% threshold a sensitivity of 58% for myeloma.

Goyal et al (2014) reported that bone marrow aspirate was less sensitive than bone marrow trephine biopsy for myeloma, 74% versus 84% respectively, in a series of 31 patients with myeloma. In 5/31 patients however neither bone marrow aspirate or trephine biopsy showed plasmacytosis.

Cytomorphology

Evidence from one study (Milla et al 2001) including 68 patients with MGUS or myeloma suggests that a cytomorphologist's diagnosis has a sensitivity of 100% for myeloma with a specificity of 88%. In this study the use of a formal cytomorphologic atypia scoring system reduced the sensitivity for myeloma to 83%.

Serum free light chain analysis

Evidence about the use of serum free light chains for discrimination of myeloma from MGUS came from two studies (Wolff et al 2007 and Bergon et al 2005) including 484 patients. In Wolf et al (2007) free light chain quantification had a sensitivity of 76% and specificity of 75% for the discrimination of myeloma from MGUS when using a normal range for κ/λ ratio of 0.19 – 1.48. FLC testing had a sensitivity of 100% in the subgroup of five patients with light chain multiple myeloma.
Bergon et al (2005) explored the use of different thresholds for lower and higher bounds of the normal κ/λ ratio. Expanding the normal range for κ/λ ratio has the effect of increasing specificity but lowering sensitivity for the diagnosis of myeloma versus MGUS.

Flow cytometry

Two studies (Carulli et al, 2012 and Frebert et al, 2011), including 297 patients, evaluated multiparameter flow cytometry (MFC) for the discrimination of myeloma from MGUS. MFC measurement of the ratio of immunophenotypically abnormal to normal plasma cells had sensitivity of 74% to 98% and specificity 85% to 92% for myeloma.

Bacher et al (2010) compared the proportion of plasma cells identified using bone marrow cytomorphology with those found using MFC in 682 patients. This proportion was higher with bone marrow cytomorphology than with MFC: the median proportion of plasma cells was 8.5% versus 2% for cytomorphology and MFC respectively. However in 1.3% of cases MFC was able to detect monoclonal plasma cells when cytomorphology did not.

Cytogenetic abnormalities on FISH

Evidence from about cytogenetic abnormalities came from one study (Bacher et al, 2010) including 682 patients with myeloma or MGUS. Although cytogenetic abnormalities were more likely in myeloma than MGUS (87% versus 56% respectively, P<0.001) there was no cytogenetic abnormality unique to either diagnosis. FISH testing was more likely to be successful in patients with myeloma than in those with MGUS (90% versus 79% respectively) – test failures were related to insufficient amounts of plasma cells.

Diagnostic accuracy of tests for detection of myeloma in patients with renal failure (see Table 2.2)

In one study of 82 patients with acute renal failure, seven were diagnosed with multiple myeloma using SPE, IFE and bone marrow biopsy. The FLC κ/λ ratio based on FLC measurement (using the published range of 0.26-1.65) had a sensitivity of 71% (95% CI 0.29 to 0.96) and a specificity of 96% (95% CI 89 to 99) for the diagnosis of multiple myeloma, with 3 false positives and 2 false negatives (Cirit et al., 2012). Another study of 471 patients with renal insufficiency reported that renal range FLC showed the highest sensitivity (92%) to differentiate multiple myeloma from non-multiple myeloma among four tests (conventional range FLC, SPE, UPE). Combined analysis with FLC and SPE improved the diagnostic accuracy to 98% sensitivity (Park et al., 2012). In a UK study, 142 patients with dialysis-dependant renal failure were assessed with SPE, IFE, and FLC (Hutchison et al., 2008). 41 patients had a clinical diagnosis of multiple myeloma, all of whom had abnormal serum FLC ratios. The modified renal reference FLC range (0.37-3.1) increased specificity from 93% to 99%, with no loss of sensitivity.

Figure 2.1 Diagnostic accuracy of tests for suspected plasma cell disorders

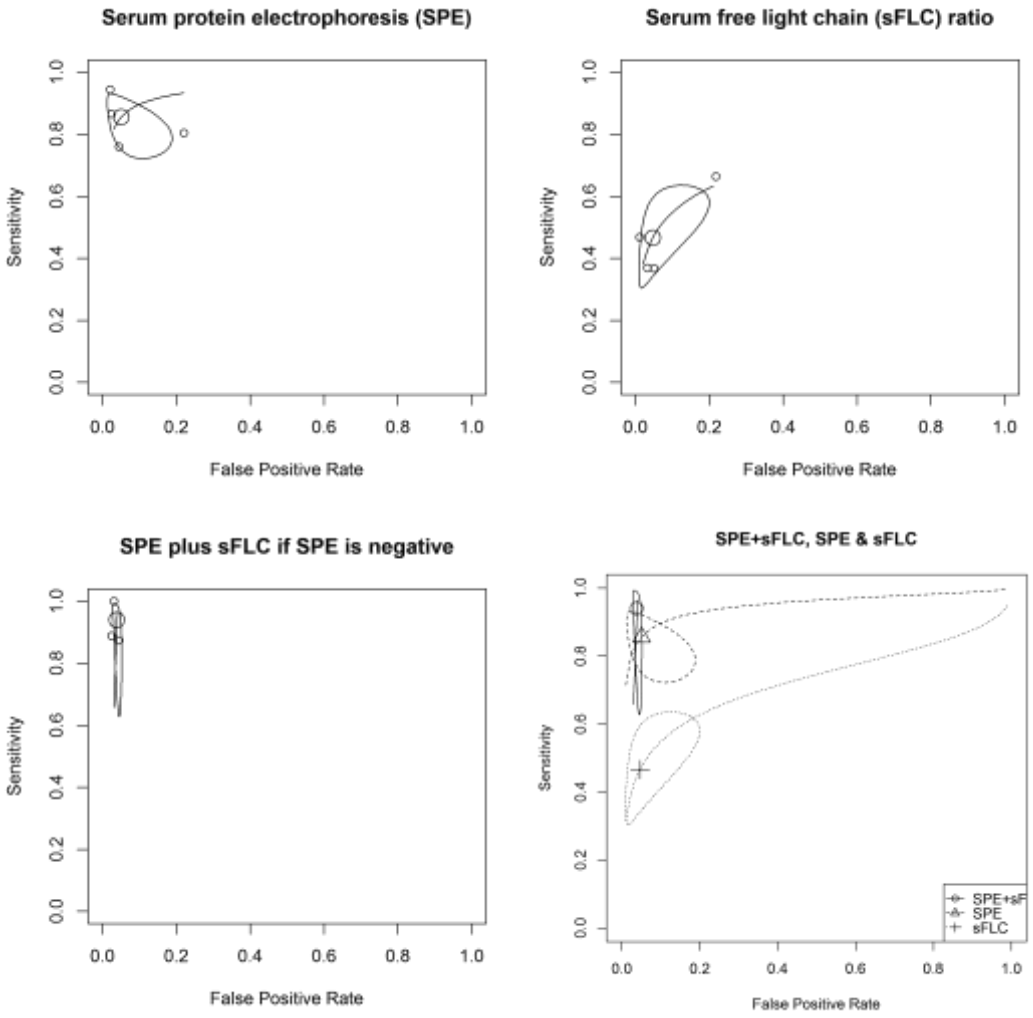


Table 2.1 Pooled sensitivities and specificities for SPE, sFLC and their combination. Using bivariate diagnostic random-effects meta-analysis

Test	Sensitivity [95%C.I.]	Specificity [95%C.I.]
Serum protein electrophoresis	0.85 [0.75 – 0.92]	0.95 [0.85 – 0.98]
Serum free light chain κ/λ ratio	0.47 [0.33 – 0.60]	0.95 [0.85 – 0.99]
SPE plus sFLC if SPE is negative	0.94 [0.72 – 0.99]	0.96 [0.95 – 0.97]

Table 2.2: Diagnostic accuracy of tests for detection of myeloma in patients with renal failure

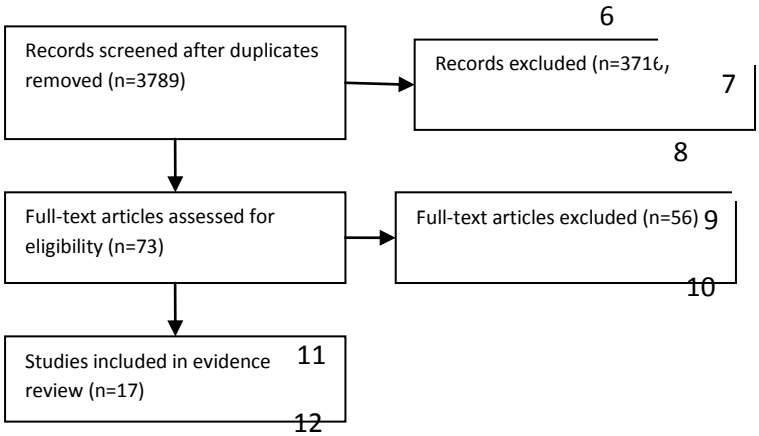
sFLC, serum free light chain; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis; SIFE, serum immunofixation electrophoresis

Study	Population	N myeloma	Test	Sensitivity (published range)	Specificity (published range)	Sensitivity (renal failure range)	Specificity (renal failure range)
Park 2012	471 who visited nephrologist	N=110 (23%)	sFLC	91	90	92	95
			SPE	82	98		
			UPE	70	99		

	due to renal insufficiency		sFLC+SPE			98	95
Cirit 2012	82 with acute renal failure	N=7 (9%)	sFLC	71 (29-96)	96 (89-99)		
			SPE+SIFE	86	100		
			SPE + sFLC	71	100		
Hutchison 2008	142 presenting with new dialysis-dependant renal failure	N=41 (29%)	sFLC	100 (91-100)	93 (86-97)	100 (91-100)	99 (95-100)

NB: Park 2012 reports diagnostic accuracy for distinguishing between MM and non-MM patients. Cirit 2012 and Hutchison 2008 report diagnostic accuracy of multiple myeloma. Published κ/λ ratio reference range for FLC = 0.26 to 1.65. Renal κ/λ ratio reference range for FLC =0.37-3.17.

Figure 2.2. Study flow diagram



Study Quality

The studies were at generally low risk of bias and there were few applicability concerns (Figure 2.3). There was an unclear risk of bias due to reference standard and flow/timing, due to poor reporting. Three studies had unclear applicability concerns due to patient selection (Park 2012, Cirit 2012, and Hutchison 2008) because they included only patients with renal failure. In other studies there were applicability concerns because patients were included on the basis of the index test results (e.g. Bergon 2010, Frebert 2011). In Katzmann (2005) although myeloma patients were the largest group their results were excluded from the analysis. For studies looking at discrimination of myeloma from MGUS, the reference standard consensus diagnostic criteria often included the index test itself.

Figure 2.3. Study quality assessment

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Reason: unclear if population relevant to PICO

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Reason: abstract only, insufficient data for inclusion

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Reason: unclear if population relevant to PICO

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Reason: population not relevant (includes patients treated for MM)

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Reason: not relevant to PICO (diagnosing lymphoma)

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Reason: not relevant to PICO (not diagnosis of MM)

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Reason: outcomes not relevant to PICO

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Reason: not relevant to PICO (not MM diagnosis)
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Reason: outcomes not relevant to PICO
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Reason: population not relevant to PICO (healthy donors)
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Reason: case study

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Reason: likely to include same patients as in Katzmann et al. 2009
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Reason: not relevant to PICO – not diagnostic accuracy for MM
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Reason: not relevant to PICO – not reporting diagnostic accuracy for MM
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Reason: does not use standard diagnostic criteria for Myeloma (international myeloma working group criteria).

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Reason: outcomes not relevant to PICO

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Reason: outcomes not relevant to PICO

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Reason: outcomes not relevant to PICO

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Reason: outcomes not relevant to PICO – not MM diagnosis

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Reason: population not relevant to PICO

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Reason: outcomes not relevant – prognostic study

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Reason: population not relevant to PICO

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Reason: population not relevant to PICO

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Reason: test not in PICO
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Reason: final diagnosis not reported

1 Evidence tables

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>McTaggart et al. 2013
Prospective observational study
UK

Aimed to determine most effective first-line test for plasma cell disorders.</td>
<td>2799 patient samples included if serum sample had been sent to clinical immunology lab for investigation of suspected plasma cell dyscrasia.

Median age 66 years (IQR 26).
60% female.</td>
<td>Serum protein electrophoresis (SPE)
and
Serum free light chain (sFLC) were performed on all samples.
Urine protein electrophoresis (UPE) performed when an acceptable paired urine sample was received within 30 days of serum sample. Acceptable paired urine tests received for 579 (20.7%) of study cohort.

sFLC scored as positive if the κ/λ ratio was outside the published diagnostic reference range 0.26 to 1.65. Alternative reference range for patients on dialysis 0.37 to 3.1 and those with eGFR <15ml/min/1.73m^2</td>
<td>Samples with abnormal SPE, UPE or sFLC analysed by immunofixation electrophoresis. Diagnosis by clinical haematologist, using local protocol based on national guidelines was the reference standard (UK myeloma forum and Nordic Myeloma Study Group 2009; Haemato-oncology Task Force of the British Committee for Standards in Haematology 2013).</td>
<td>124 (4.4%) had plasma cell disorders, 17 (0.6%) had malignant disease. Myeloma (n=13), LCDD (n=1), plasmacytoma (n=1), amyloidosis (n=2), MGUS (n=107).

<table>
<tr><th>Ref standard</th><th>+ve</th><th>-ve</th></tr>
<tr><td colspan="3">Index test</td></tr>
<tr><td colspan="3">sFLC</td></tr>
<tr><td>+ve</td><td>58</td><td>66</td></tr>
<tr><td>-ve</td><td>30</td><td>2645</td></tr>
<tr><td colspan="3">SPE</td></tr>
<tr><td>+ve</td><td>117</td><td>7</td></tr>
<tr><td>-ve</td><td>55</td><td>2620</td></tr>
<tr><td colspan="3">UPE</td></tr>
<tr><td>+ve</td><td>29</td><td>48</td></tr>
<tr><td>-ve</td><td>4</td><td>498</td></tr>
<tr><td colspan="3">Testing algorithm</td></tr>
<tr><td colspan="3">sFLC+SPE</td></tr>
<tr><td>+ve</td><td>124</td><td>0</td></tr>
<tr><td>-ve</td><td>84</td><td>2591</td></tr>
<tr><td colspan="3">SPE+UPE</td></tr>
<tr><td>+ve</td><td>74</td><td>3</td></tr>
<tr><td>-ve</td><td>24</td><td>478</td></tr>
<tr><td colspan="3">sFLC+UPE</td></tr>
<tr><td>+ve</td><td>46</td><td>31</td></tr>
<tr><td>-ve</td><td>11</td><td>491</td></tr>
<tr><td colspan="3">sFLC+SPE+UPE</td></tr>
<tr><td>+ve</td><td>77</td><td>0</td></tr>
<tr><td>-ve</td><td>30</td><td>472</td></tr>
</table>

<table>
<tr><th>Test</th><th>Sensitivity (95% CI) %</th><th>Specificity (95% CI) %</th></tr>
<tr><td>sFLC</td><td>47 (38-56)</td><td>99 (98-99)</td></tr>
<tr><td>SPE</td><td>94 (88-98)</td><td>98 (97-98)</td></tr>
<tr><td>UPE</td><td>38 (27-50)</td><td>99 (98-100)</td></tr>
<tr><td>sFLC+SPE</td><td>100 (96-100)</td><td>97 (96-98)</td></tr>
<tr><td>SPE+UPE</td><td>96 (88-99)</td><td>95 (93-97)</td></tr>
<tr><td>sFLC+UPE</td><td>60 (48-71)</td><td>98 (96-99)</td></tr>
<tr><td>sFLC+SPE+</td><td>100 (94-100)</td><td>94 (92-96)</td></tr>
</table>
</td>
<td>Not all patients received same index tests. Unclear if interpretation of reference standard and index tests were blinded to results of other tests.

Diagnostic accuracy for all plasma cell disorders (including MM, MGUS, AL)- included in RevMan</td>
</tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>UPE</td><td></td><td></td></tr>
</table>

SPE had best sensitivity (94%) of individual tests. The addition of sFLC gave an increase in sensitivity to 100%, while the addition of UPE gave a smaller increase in sensitivity to 96%. .</td><td></td></tr>
<tr><td>Vermeersch et al 2008
Observational study
Belgium</td><td>833 consecutive patients in whom a B-cell disorder was suspected. Excluded those with known B-cell disorder.</td><td>Serum protein electrophoresis (PE) and serum and urine immunofixation electrophoresis (IFE) performed in all patients as part of routine laboratory investigation for monoclonal gammopathies. IFE performed using semi-automated Hydrasys electrophoresis apparatus. Moncolonal bands identified by visual inspection of gels by two immunologists with more than 8 years experience.

Serum free light chains (FLC) also performed in all patients using Freelite assay and reference values established by Katzmann (2002). Sera with abnormal FLC κ/λ ratio (<0.26 or > 1.65) were considered positive.</td><td>Medical records of all patients 1) who were positive on serum or urine IFE, 2) had abnormal κ/λ ratio, 3) underwent bone marrow biopsy, 4) immunophenotyping on bone marrow or peripheral blood were checked to determine whether they had a malignant B-cell disorder or MGUS.</td><td>28 diagnosed with malignant plasma cell disorder (18 MM, 2 light chain MM, 3 AL amyloidosis), 156 MGUS and 25 with B-NHL.

Diagnostic accuracy for diagnosis of malignant monoclonal B-cell disorders or MGUS:
<table>
<tr><th>Test</th><th>Sensitivity (95% CI) %</th><th>Specificity (95% CI) %</th><th>Missed B-cell disorders and MGUS</th></tr>
<tr><td>FLC κ/λ ratio</td><td>37</td><td>97</td><td>3 MM, 1 PC, 112 MGUS, 16 B-NHL</td></tr>
<tr><td>SPE</td><td>80</td><td>78</td><td>1 MM, 1 ALA, 1 PC, 25 MGUS, 13 B-NHL</td></tr>
<tr><td>SPE±IFE</td><td>79</td><td>100</td><td>1 MM, 1 ALA, 1 PC, 26 MGUS, 16 B-NHL</td></tr>
<tr><td>SPE±IFE + UIFE</td><td>82</td><td>100</td><td>24 MGUS, 14 B-NHL</td></tr>
<tr><td>SPE±IFE + FLC κ/λ ratio</td><td>82</td><td>97</td><td>1 PC, 23 MGUS, 13 B-NHL</td></tr>
<tr><td>SIFE</td><td>92</td><td>100</td><td>15 B-NHL, 2 MGUS</td></tr>
<tr><td>SIFE + FLC κ/λ ratio</td><td>94</td><td>97</td><td>12 B-NHL, 1 MGUS</td></tr>
<tr><td>SIFE + UIFE</td><td>92</td><td>100</td><td>14 B-NHL, 2 MGUS</td></tr>
</table>
SPE±IFE = serum IFE on positive serum PE samples
<table>
<tr><th></th><th colspan="6">Number of positive patients</th></tr>
<tr><th></th><th>n</th><th>κ/λ ratio</th><th>SPE*</th><th>SPE±IFE*</th><th>SIFE</th><th>UIFE</th></tr>
<tr><td>Intact MM</td><td>18</td><td>15</td><td>17 (1)</td><td>17 (1)</td><td>18</td><td>17</td></tr>
<tr><td>Light chain MM</td><td>2</td><td>2</td><td>2</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>Plasmacytoma</td><td>1</td><td>0</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Osteosclerotic MM</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Plasma cell Leukaemia</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>WM</td><td>2</td><td>2</td><td>2</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>Primary amyloidosis</td><td>3</td><td>3</td><td>2</td><td>2</td><td>3</td><td>2</td></tr>
<tr><td>All</td><td>28</td><td>24</td><td>25</td><td>25</td><td>28</td><td>26</td></tr>
<tr><td>MGUS</td><td>156</td><td>44</td><td>131 (3)</td><td>130 (3)</td><td>154</td><td>71</td></tr>
</table>
</td><td>Diagnostic accuracy for all plasma cell disorders (including MM, MGUS, AL, B-NHL) – included in RevMan

International Myeloma Working Group criteria cited.</td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>*Values in parentheses indicate the number of patients in which hypogammaglobulinaemia on CZE was the only abnormality.</td><td></td></tr>
<tr><td>Park et al 2012
Retrospective observational study
Korea</td><td>471 patients who visited nephrologist due to renal insufficiency.
204 acute kidney injury, 252 chronic kidney disease. 22 patients had already undergone dialysis.

Excluded those with previous monoclonal gammopathy diagnosis.</td><td>Routine serum and urine protein electrophoresis (s/u PE) and serum free light chain (sFLC) quantification determined cause of renal insufficiency (using Freelite immunoassay). Renal reference range for rFLC =0.37-3.17.
Bone marrow aspiration and section biopsy performed in patients who showed abnormal serum immunoglobuline (Ig) levels, monoclonal peak in PEP tests, abnormal sFLC quantification, or κ/λ ratio, abnormal complete blood cell analysis, or abnormal bone lesions in radiologic examinations.</td><td>Not reported?
Clinical diagnosis and differentiation of disease made by haematologist in accordance with International Myeloma Working Group criteria.</td><td>110 (23.4%) diagnosed with multiple myeloma (81 intact MM, 29 light chain MM). 5 MGUS, 1 solitary plasmacytoma, 3 systemic amyloidosis. 6 other (lymphoblastic leukaemia or lymphoma).

<table><tr><th></th><th>Renal rFLC</th><th>Conventional rFLC</th><th>s-PE</th><th>u-PE</th><th>Combined rFLC+s-PE</th></tr><tr><td>Total</td><td>456</td><td>456</td><td>427</td><td>326</td><td>456</td></tr><tr><td>Number MM</td><td>110</td><td>110</td><td>110</td><td>104</td><td>110</td></tr><tr><td>sensitivity</td><td>92</td><td>91</td><td>82</td><td>70</td><td>98</td></tr><tr><td>specificity</td><td>95</td><td>90</td><td>98</td><td>99</td><td>95</td></tr><tr><td>PPV</td><td>86</td><td>74</td><td>92</td><td>96</td><td>86</td></tr><tr><td>NPV</td><td>97</td><td>97</td><td>94</td><td>88</td><td>99</td></tr></table></td><td>Diagnostic accuracy for differentiating MM from non-MM.

2x2 table data not reported. Unable to include in RevMan</td></tr>
<tr><td>Cirit et al. 2012
Observational study
Turkey</td><td>82 patients with acute renal failure.
Excluded <50years, kidney disease, pregnancy, malignancy, collagen tissue disease.
Mean age=69.
54% male</td><td>Serum protein electrophoresis (SPE), serum immunofixation electrophoresis (SIFE) and free light chain measurement (Freelite immunoassay kit with reference range 0.26 to 1.65) performed in all patients.
Bone marrow aspiration and biopsy if indicated.</td><td>Unclear.
Diagnosis of MM made by consultant haematologist in accordance with international diagnostic criteria.</td><td>7 patients diagnosed as MM via SPE, SIFE and bone marrow biopsy.

<table><tr><th></th><th>Abnormal κ/λ ratio</th><th>normal κ/λ ratio</th></tr><tr><td>MM positive</td><td>5 (TP)</td><td>2 (FN)</td></tr><tr><td>MM negative</td><td>3 (FP)</td><td>72 (TN)</td></tr></table>
<table><tr><th></th><th>FLC κ/λ ratio</th><th>SPE+SIFE</th><th>SPE+ FLC κ/λ ratio</th></tr><tr><td>PPV %</td><td>63</td><td>100</td><td>100</td></tr><tr><td>NPV %</td><td>97</td><td>99</td><td>97</td></tr><tr><td>Specificity %</td><td>96</td><td>100</td><td>100</td></tr><tr><td>Sensitivity %</td><td>71</td><td>86</td><td>71</td></tr></table></td><td>Low number of events (MM diagnosis)
Unclear if interpretation of tests blinded to results of other tests.
Diagnostic accuracy for MM.
International Myeloma Working Group criteria cited.</td></tr>
<tr><td>Katzmann et al. 2009
Retrospective</td><td>1877 patients with a monoclonal</td><td>Serum PEL (agarose gel electrophoresis), IFE and FLC performed on same day as</td><td>Not reported</td><td>Patients grouped into 9 disease groups (467 MM, 191 SMM, 524 MGUS, 26 plasmacytoma, 10 extramedullary plasmacytoma, 26 WM, 581 AL, 18 LCDD, and 31 POEMS syndrome)
<u>Sensitivity:</u></td><td>Study reports only sensitivity of tests as all</td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>observational study
USA</td>
<td>gammopathy who also had serum protein electrophoresis (PEL), immunofixation electrophoresis (IFE) and free light chain (FLC), and urine PEL and IFE within 30 days of diagnosis.</td>
<td>venipuncture. FLC (Freelite assay, κ/λ ratio diagnostic range 0.26 to 1.65).
Abnormal PEL was defined by presence of a quantifiable M spike, fuzzy band, hypogammaglobulinemia (<5.5 g/L), increased β fraction (≥16 g/L), or increased α 2 fraction (≥15 g/L)
Some serum PEL abnormalities were not abnormal by serum IFE, they were coded as abnormal PEL if urine or serum FLC assay was also abnormal and therefore the PEL had flagged the abnormality.
All serum and urine PEL and IFE gels were reviewed by 2 technicians and well as 4 authors.</td>
<td></td>
<td>
<table>
<tr><th>diagnosis</th><th>n</th><th>All tests</th><th>Serum PEL +IFE, urine IFE</th><th>Serum PEL, IFE, + FLC</th><th>Serum PEL +FLC</th><th>Serum IFE</th><th>Serum PEL</th><th>Serum FLC</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All</td><td>1877</td><td>99</td><td>97</td><td>97</td><td>94</td><td>87</td><td>79</td><td>74</td></tr>
<tr><td>MM</td><td>467</td><td>100</td><td>99</td><td>100</td><td>100</td><td>94</td><td>88</td><td>97</td></tr>
<tr><td>WM</td><td>26</td><td>100</td><td>100</td><td>100</td><td>100</td><td>100</td><td>100</td><td>73</td></tr>
<tr><td>SMM</td><td>191</td><td>100</td><td>100</td><td>100</td><td>100</td><td>98</td><td>94</td><td>81</td></tr>
<tr><td>MGUS</td><td>524</td><td>100</td><td>100</td><td>97</td><td>97</td><td>93</td><td>82</td><td>42</td></tr>
<tr><td>Plasma-cytoma</td><td>29</td><td>90</td><td>90</td><td>90</td><td>90</td><td>72</td><td>72</td><td>55</td></tr>
<tr><td>POEMS</td><td>31</td><td>97</td><td>97</td><td>97</td><td>97</td><td>97</td><td>74</td><td>10</td></tr>
<tr><td>Extram plasma-cytoma</td><td>10</td><td>20</td><td>20</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>AL</td><td>581</td><td>98</td><td>94</td><td>97</td><td>96</td><td>74</td><td>66</td><td>88</td></tr>
<tr><td>LCDD</td><td>18</td><td>83</td><td>78</td><td>78</td><td>78</td><td>56</td><td>56</td><td>78</td></tr>
</table>

The use of all the urine and serum tests identified 1851 patients (98.6%) as abnormal. There were 26 patients whose diagnosis was not detected with these tests: 11 with AL (1.9% of total AL); 8 with extramedullary plasmacytoma (80%); 3 with plasmacytoma (10.3%); 3 with LCDD (16.7%); and 1 with POEMS syndrome (3%).
The testing panel of urine IFE plus serum PEL and IFE (without serum FLC) missed 30 additional patients. The 30 patients included 6 MM, 23 AL, and 1 LCDD.
A testing panel of serum PEL, IFE and FLC (without urine studies) missed 23 patients in addition to those missed when using all the urine and serum tests. The 23 patients missed by omission of urine tests included 15 MGUS, 1 extramedullary myeloma, 1 LCDD, and 6 AL. The 6 AL patients all had monoclonal λ light chains detected in the urine.
When serum PEL plus FLC was the testing panel, 58 patients were missed compared to a panel of serum PEL, IFE, and FLC. These 58 patients included 44 patients with MGUS, 7 with POEMS, 5 with AL, 1 with plasmacytoma, and 1 with SMM . The use of serum PEL plus FLC compared with serum PEL, IFE, and FLC did not miss any patients with
</td>
<td>patients had a monoclonal gammopathy.

Diagnostic accuracy for all plasma cell disorders (including MM, MGUS, AL, POEMS)

International Myeloma Working Group criteria cited.</td>
</tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>MM, macroglobulinemia, or LCDD.
Serum PEL, IFE, and FLC assays did not perform well as single tests. PEL and IFE missed patients in every disease category except macroglobulinemia, whereas FLC did not identify 100% of the patients in any category. Among the 57 AL patients that were missed by the serum FLC assay but identified by urine and/or serum IFE, 52 (91%) expressed λ light chains.</td><td></td></tr>
<tr><td>Hutchison et al. 2008
Observational study
UK</td><td>142 patients who presented with new dialysis-dependant renal failure.

Median age=70.
39% male</td><td>Serum protein electrophoresis (SPE), serum immunofixation electrophoresis (SIFE) undertaken using the Sebia Hydragel 15/30 Protein kit and Hydragel 4 Immunofixation PE kit on the Hydrasys system. FLC κ/λ ratio (Freelite assay) using published reference range (0.26 to 1.65) and proposed renal failure reference range (0.37 to 3.1). All sera assessed with SPE and FLC, samples with abnormal results further investigated by SIFE. Urine of patients with suspected MM assessed for monoclonal FLCs by immunofixation.

Attribution of cause of renal failure to MM based on renal histology or, in cases where renal biopsy was contraindicated, when all other potential causes were excluded.</td><td>Diagnosis of myeloma made by haematologist in accordance with international criteria.</td><td>41/142 had clinical diagnosis of MM. All had abnormal FLC ratios by both the published reference range and the proposed reference range. The proposed reference range increased the specificity of assay for diagnosis of MM to 99% (from 93%), with no loss in sensitivity (100%).

<table><tr><td></td><td>Renal rFLC</td><td>Conventional rFLC</td></tr><tr><td>Total</td><td>142</td><td>142</td></tr><tr><td>Number MM</td><td>41</td><td>41</td></tr><tr><td>TP</td><td>41</td><td>41</td></tr><tr><td>FP</td><td>1</td><td>7</td></tr><tr><td>TN</td><td>100</td><td>94</td></tr><tr><td>FN</td><td>0</td><td>0</td></tr></table>
<table><tr><td></td><td>Renal rFLC</td><td>Conventional rFLC</td></tr><tr><td>Sensitivity</td><td>100%</td><td>100%</td></tr><tr><td>Specificity</td><td>99%</td><td>93%</td></tr></table></td><td></td></tr>
<tr><td>Milla et al 2001.
Spain</td><td>68 patients in whom bone marrow study was done for: monoclonal gammopathy, osteolytic lesions, pain & suspected MM or anaemia with renal</td><td>Cytomorphology of bone marrow aspirates. Samples were stained with May-Grunwald-Giesma. Cytomorphologist classified samples as MGUS or myeloma; gave the percentage of plasma cells in the sample and noted 3 predefined types of atypia (used to develop a score based diagnosis in a pilot study of 154</td><td>Chronic leukaemia-myeloma task force criteria (1977,1973)</td><td>Diagnosis: myeloma versus MGUS
<table><tr><td rowspan="2">Cytologist’s diagnosis</td><td colspan="2">Final clinical diagnosis</td></tr><tr><td>Myeloma</td><td>MGUS</td></tr><tr><td>Myeloma</td><td>24</td><td>5</td></tr><tr><td>MGUS</td><td>0</td><td>36</td></tr></table>Sensitivity (for myeloma) 100%, specificity 87.8%

<table><tr><td rowspan="2">Plasma cells >30%</td><td colspan="2">Final clinical diagnosis</td></tr><tr><td>Myeloma</td><td>MGUS</td></tr><tr><td>Myeloma</td><td>14</td><td>0</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td>insufficiency. and increased ESR. Included 41 cases of MGUS and 24 with myeloma.</td><td>patients).</td><td></td><td>
<table>
<tr><td>MGUS</td><td>10</td><td>41</td></tr>
</table>
Sensitivity (for myeloma) 58%, specificity 100%

<table>
<tr><td rowspan="2">cytomorophologic atypia score diagnosis</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>Myeloma</td><td>MGUS</td></tr>
<tr><td>Myleoma</td><td>20</td><td>4</td></tr>
<tr><td>MGUS</td><td>4</td><td>37</td></tr>
</table>
Sensitivity (for myeloma) 83%, specificity 87.8%
</td><td></td></tr>
<tr><td>Wolff et al 2007. Belgium</td><td>67 patients with monoclonal gammopathy and results for SPE, IFE, FLC and bone marrow aspirate. Intact immunoglobulin myeloma (IIMM, N=20), light chain myeloma (LCMM, N=5) and MGUS (N=67)</td><td>SPE: results classified as monoclonal band detected or not
Free light chains (FLC) κ/λ ratio: normal range was 0.19 – 1.48.</td><td>International myeloma working group criteria (for MGUS versus MM)</td><td>
No patients without monoclonal gammopathy were included – so no specificity could be calculated.

<table>
<tr><th></th><th>N with monoclonal band on SPE</th><th>total N</th><th>Sensitivity</th></tr>
<tr><td>MGUS</td><td>63</td><td>67</td><td>94%</td></tr>
<tr><td>IIMM</td><td>17</td><td>20</td><td>85%</td></tr>
<tr><td>LCMM</td><td>2</td><td>5</td><td>40%</td></tr>
</table>

<table>
<tr><td rowspan="2">Monoclonal band on SPE</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>19</td><td>63</td></tr>
<tr><td>Test negative</td><td>6</td><td>4</td></tr>
</table>
Sensitivity 76%, specificity 98%

<table>
<tr><th></th><th>N with abnormal FLC</th><th>total N</th><th>Sensitivity</th></tr>
<tr><td>MGUS</td><td>17</td><td>67</td><td>25%</td></tr>
<tr><td>IIMM</td><td>14</td><td>20</td><td>70%</td></tr>
<tr><td>LCMM</td><td>5</td><td>5</td><td>100%</td></tr>
</table>

<table>
<tr><td rowspan="2">abnormal sFLC</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>19</td><td>17</td></tr>
<tr><td>Test negative</td><td>6</td><td>50</td></tr>
</table>
Sensitivity 76%, specificity 75%
</td><td></td></tr>
<tr><td>Piehler et al 2008.</td><td>332 patients with suspected</td><td>SPE: results classified as monoclonal band detected or</td><td>International Myeloma Working Group criteria</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Norway</td>
<td>monoclonal gammopathy with sera sent for SPE in 2005-2006 and with serum FLC and immunoglobulin measurement.</td>
<td>not
Free light chains (FLC) κ/λ ratio: normal range was 0.26 – 1.65.</td>
<td>(2003)</td>
<td>
<table>
<tr><th rowspan="2">Monoclonal band on SPE</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>not monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>77</td><td>6</td></tr>
<tr><td>Test negative</td><td>12</td><td>237</td></tr>
</table>
Sensitivity 87%, specificity 98%

<table>
<tr><th rowspan="2">sFLC κ/λ ratio abnormal (<0.26 or > 1.65)</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>not monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>59</td><td>53</td></tr>
<tr><td>Test negative</td><td>30</td><td>190</td></tr>
</table>
Sensitivity 66%, specificity 78%

<table>
<tr><th rowspan="2">SPE +sFLC</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>not monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>79</td><td>6</td></tr>
<tr><td>Test negative</td><td>10</td><td>237</td></tr>
</table>
Sensitivity 89%, specificity 98%

1 non-secretory MM identified on FLC (but not on SPE).
7/7 light chain MM identified on FLC but only 2/7 on SPE.
</td>
<td></td>
</tr>
<tr>
<td>Katzmann et al 2005.
USA</td>
<td>1020 patients tested with FLC assay during 2003: 899 had monoclonal gammopathy, 121 did not</td>
<td>Free light chains (FLC) κ/λ ratio: normal range was 0.26 – 1.65</td>
<td>Reference standard test not reported</td>
<td>
Diagnostic classification: monoclonal gammopathy versus not (prevalence of gammopathy 88%)

<table>
<tr><th rowspan="2">FLC κ/λ ratio abnormal (<0.26 or > 1.65)</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>non-monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>N.R.</td><td>0</td></tr>
<tr><td>Test negative</td><td>N.R.</td><td>121</td></tr>
</table>
Sensitivity N.R., specificity 100%

Sensitivities were reported for individual gammopathies:

<table>
<tr><th>PCD</th><th>N abnormal FLC ratio</th><th>total N</th><th>Sensitivity (%)</th></tr>
<tr><td>AL (untreated)</td><td>100</td><td>110</td><td>91</td></tr>
<tr><td>MGUS</td><td>50</td><td>114</td><td>44</td></tr>
<tr><td>smouldering MM</td><td>63</td><td>72</td><td>88</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>non secretory MM</td><td>14</td><td>20</td><td>70</td></tr>
<tr><td>MM</td><td>N.R.</td><td>330</td><td>N.R.</td></tr>
</table>
</td><td></td></tr>
<tr><td>Hill et al
2006
UK</td><td>923 patients who had serum protein electrophoresis (SPEP), without known MGUS, myeloma, lymphoma or Waldenstrom’s macroglobulinaemia.</td><td>SPEP: results classified as probable monoclonal band, raised globulins, polyclonal increase in gamm0-globulin, hypogammaglobulinaemia, or no abnormality detected
Free light chains (FLC) κ/λ ratio: normal range was 0.26 – 1.65.</td><td>Final diagnosis based on other tests (not all patients had all tests) including: bone marrow biopsy, skeletal survey, serum/urine fixation electrophoresis,</td><td>Diagnostic classification: monoclonal gammopathy versus not (prevalence of gammopathy %)
<table>
<tr><th rowspan="2">SPE</th><th colspan="2">Final clinical diagnosis</th><th></th></tr>
<tr><th>monoclonal gammopathy</th><th>No monoclonal gammopathy</th><th></th></tr>
<tr><td>Test positive</td><td>60</td><td>38</td><td>98</td></tr>
<tr><td>Test negative</td><td>19</td><td>806</td><td>825</td></tr>
<tr><td></td><td></td><td></td><td>923</td></tr>
</table>
Sensitivity 76%, specificity 95%
<table>
<tr><th rowspan="2">sFLC ratio (<0.26 or >1.65</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>No monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>29</td><td>42</td></tr>
<tr><td>Test negative</td><td>50</td><td>802</td></tr>
</table>
Sensitivity 37%, specificity 95%
<table>
<tr><th rowspan="2">SPE + sFLC</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>monoclonal gammopathy</th><th>No monoclonal gammopathy</th></tr>
<tr><td>Test positive</td><td>69</td><td>38</td></tr>
<tr><td>Test negative</td><td>10</td><td>806</td></tr>
</table>
Sensitivity %, specificity %</td><td></td></tr>
<tr><td>Frebert et al
2011
Observational study
France</td><td>197 patients with monoclonal gammopathy (of an isotype other than IgM).: including myeloma (N=103), smouldering myeloma (N=22), MGUS (N=54). Controls (N=25) were also</td><td>Multiparameter immunophenotyping by flow cytometry (FCM). The GEIL consensus protocol was used.</td><td>WHO criteria</td><td>The following data are from N=163 patients: MGUS (N=52), smouldering multiple myeloma (N=22) and multiple myeloma (N=87)

Diagnostic classification: MGUS versus myeloma (prevalence of myeloma 67%)
<table>
<tr><th rowspan="2">Monoclonal component quantification (> 30 g/L)</th><th colspan="2">Final clinical diagnosis</th></tr>
<tr><th>myeloma</th><th>MGUS</th></tr>
<tr><td>Test positive</td><td>45</td><td>0</td></tr>
<tr><td>Test negative</td><td>64</td><td>52</td></tr>
</table>
Sensitivity 41%, specificity 100%
<table>
<tr><td>Plasma-cell infiltration</td><td>Final clinical diagnosis</td></tr>
</table></td><td></td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td>included. Patients were separated into 3 cohorts: one for training (N=79) and two validation sets (N=68 and N=75).</td><td></td><td></td><td>
<table>
<tr><td>(morphology; >10%)</td><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>86</td><td>0</td></tr>
<tr><td>Test negative</td><td>23</td><td>52</td></tr>
</table>
Sensitivity 79%, specificity 100%

<table>
<tr><td rowspan="2">FCM: proportion of abnormal plasma cells (aPC; >5%)</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>81</td><td>8</td></tr>
<tr><td>Test negative</td><td>28</td><td>44</td></tr>
</table>
Sensitivity 74%, specificity 85%

<table>
<tr><td rowspan="2">FCM: ratio plasma cells/precursors (PC/P; >2)</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>88</td><td>8</td></tr>
<tr><td>Test negative</td><td>21</td><td>44</td></tr>
</table>
Sensitivity 81%, specificity 84%

<table>
<tr><td rowspan="2">FCM: ratio CD19neg plasma cells/precursors (PC/P; >2)</td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Test positive</td><td>95</td><td>8</td></tr>
<tr><td>Test negative</td><td>16</td><td>44</td></tr>
</table>
Sensitivity 87%, specificity 84%
</td><td></td></tr>
<tr><td>Carulli et al 2012.
Observational study
Italy</td><td>100 consecutive patients with monoclonal gammopathy – excluding IgM gammopathies, Waldenstrom disease and lymphoplasmacytic lymphoma. MGUS (N=39) and myeloma (N=61).</td><td>Multiparameter immunophenotyping by flow cytometry. Data were analysed using FacsDiva software: when iaPCS were ≤ 3% myeloma was predicted and MGUS when iaPCS were ≥ 3.1%.</td><td>International Myeloma Working Group criteria (2003)</td><td>Diagnostic classification: MGUS versus myeloma (prevalence of myeloma 61%)

<table>
<tr><td></td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td></td><td>myeloma</td><td>MGUS</td></tr>
<tr><td>Flow cytometric predicted myeloma</td><td>60</td><td>3</td></tr>
<tr><td>Flow cytometric predicted MGUS</td><td>1</td><td>36</td></tr>
</table>
Sensitivity 98%; Specificity 92%</td><td>Double blind</td></tr>
<tr><td>Bergon et al 2005</td><td>417 patients identified from</td><td>Serum light chains (κ/λ ratio).</td><td>Durie criteria, histopathologic findings</td><td>Diagnostic classification: MGUS versus myeloma (prevalence of myeloma 30.8%)
<table>
<tr><td>κ/λ threshold value</td><td>Sensitivity</td><td>Specificity</td></tr>
</table></td><td></td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Observational study
Spain</td><td>monoclonal component database with with MGUS (N=220), myeloma or plasmacytoma (N=146) or other lymphoproliferative disorder (N=51).</td><td></td><td>on trephine biopsies, plasma cell morphology in bone marrow aspirate, immunophenotypic markers and organ/tissue damage consistent with myeloma.
At least 2 years of follow-up/monitoring for non-myeloma patients</td><td>
<table>
<tr><td>M-protein κ</td><td></td><td></td></tr>
<tr><td>0.15</td><td>0.25 (0.09 – 0.49)</td><td>0.96 (0.85 – 0.99)</td></tr>
<tr><td>0.40</td><td>0.75 (0.51 – 0.91)</td><td>0.82 (0.68 – 0.92)</td></tr>
<tr><td>0.60</td><td>0.90 (0.68 – 0.99)</td><td>0.73 (0.58 – 0.86)</td></tr>
<tr><td>1.00</td><td>0.95 (0.75 – 1.00)</td><td>0.36 (0.22 – 0.52)</td></tr>
<tr><td>M-protein λ</td><td></td><td></td></tr>
<tr><td>2.80</td><td>0.96 (0.83 – 1.00)</td><td>0.29 (0.18 – 0.45)</td></tr>
<tr><td>4.20</td><td>0.93 (0.78 – 0.99)</td><td>0.67 (0.51 – 0.79)</td></tr>
<tr><td>7.00</td><td>0.82 (0.65 – 0.94)</td><td>0.85 (0.71 – 0.79)</td></tr>
<tr><td>10.00</td><td>0.68 (0.51 – 0.85)</td><td>0.94 (0.84 – 0.99)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Bacher et al 2010
Case-Control study
Germany</td><td>682 patients with plasma cell myeloma or MGUS, identified retrospectively. To be included patients had to have bone marrow cytomorphology (CM), multiparameter flow cytometry (MFC) and interphase FISH.</td><td>Cytogenetic alterations detected with FISH,</td><td>Combination of all test results, physician's findings and morphological findings according to WHO classification (2008).</td><td>
Diagnostic classification: MGUS versus myeloma
<table>
<tr><th>Cytogenetic alteration</th><th>MGUS</th><th>Plasma cell myeloma</th><th>P</th></tr>
<tr><td>Chromosomal abnormalities</td><td>162/302 (56%)</td><td>237/272 (87.1%)</td><td><0.001</td></tr>
<tr><td>del(13q)</td><td>59/267 (22%)</td><td>99/251 (39%)</td><td><0.001</td></tr>
<tr><td>del(17p)</td><td>6/267 (2%)</td><td>15/251 (6%)</td><td>0.029</td></tr>
<tr><td>t(11:14)/IGH-CCND1</td><td>50/267 (19%)</td><td>38/251 (15%)</td><td>NS</td></tr>
<tr><td>t(4:14)/IGH-FGFR3</td><td>5/267 (2%)</td><td>28/251 (11%)</td><td><0.001</td></tr>
<tr><td>t(14:16)/IGH-MAF</td><td>3/267 (1%)</td><td>7/251 (3%)</td><td>NS</td></tr>
<tr><td>other 14q32/IGH rearrangements</td><td>12/267 (5%)</td><td>9/251 (4%)</td><td>NS</td></tr>
<tr><td>+3</td><td>21/89 (24%)</td><td>40/102 (39%)</td><td>0.021</td></tr>
<tr><td>+9</td><td>28/89 (32%)</td><td>59/102 (58%)</td><td><0.001</td></tr>
<tr><td>+11</td><td>25/89 (28%)</td><td>50/102 (49%)</td><td>0.003</td></tr>
<tr><td>+15</td><td>11/52 (21%)</td><td>31/64 (48%)</td><td>0.002</td></tr>
<tr><td>tetraploid cells</td><td>0/52 (0%)</td><td>6/64 (9%)</td><td>0.014</td></tr>
</table>
<table>
<tr><th></th><th>MGUS</th><th>Plasma cell myeloma</th><th>P</th></tr>
<tr><td>FISH test success*</td><td>302/381 (79%)</td><td>272/301 (90%)</td><td><0.001</td></tr>
</table>
*failures due to insufficient plasma cell amounts
<table>
<tr><th></th><th>Cytomorphology</th><th>Multiparameter flow</th></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Study, Design, Country</th><th>Population</th><th>Index test(s)</th><th>Reference standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td></td><td>cytometry</td></tr>
<tr><td>median proportion of plasma cells (range)</td><td>8.5% (0 to 96%)</td><td>2% (0 to 84%)</td></tr>
</table>
Cytomorphology detected higher numbers of plasma cells than MFC.
</td><td></td></tr>
<tr><td>Behad et al, 2014
Observational study,
USA</td><td>361 patients with suspected or diagnosed plasma cell neoplasia</td><td>Multiparameter flow cytometry (MFC; using bone marrow aspirate), plasma cell percentage (> 5%), imuunohistochemistry (classified as positive, negative or equivocal for plasma cell neoplasm)</td><td>Final diagnosis by hematopathologist based on morphology and immunohistochemical studies</td><td>In the following tables equivocal results are grouped with test positive.
<table>
<tr><td></td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td></td><td>plasma cell neoplasm</td><td>not plasma cell neoplasm</td></tr>
<tr><td>MFC positive</td><td>144</td><td>45</td></tr>
<tr><td>MFC negative</td><td>10</td><td>95</td></tr>
</table>
sensitivity 93.5%; specificity 67.9%

MFC was inadequate in 61 cases (4 with plasma cell neoplasm and 57 without)</td><td></td></tr>
<tr><td>Goyal et at, 2014.
Observational study.
India</td><td>Patients who underwent bone marrow aspirate and biopsy simultaneously and who were diagnosed with haematological malignancy(N=382). 31 patients had multiple myeloma</td><td>Bone marrow aspirate & immunohistochemistry, Bone marrow trephine biopsy & immunohistochemistry</td><td>Final clinical diagnosis</td><td>in 5/31 patients with multiple myeloma – neither aspirate or trephine biopsy was positive for plasmacytosis.
<table>
<tr><td></td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td></td><td>myeloma</td><td>not myeloma</td></tr>
<tr><td>BM aspirate positive</td><td>23</td><td>0</td></tr>
<tr><td>BM aspirate negative</td><td>8</td><td>0</td></tr>
</table>
sensitivity of BM aspirate: 74%
<table>
<tr><td></td><td colspan="2">Final clinical diagnosis</td></tr>
<tr><td></td><td>myeloma</td><td>not myeloma</td></tr>
<tr><td>BM trephine positive</td><td>26</td><td>0</td></tr>
<tr><td>BM trephine negative</td><td>5</td><td>0</td></tr>
</table>
sensitivity of BM trephine biopsy: 84%</td><td></td></tr>
</table>

Laboratory investigations to provide prognostic information

Review Question:
Can investigations done at the diagnosis of myeloma, including trephine biopsy, immunophenotyping and cytogenetic and molecular genetic tests accurately predict treatment outcomes (for example, can they identify patients with a poor prognosis for whom an alternative treatment approach may be preferable)?

Question in PICO format

Population	Factors	Outcomes
People referred to secondary care with probable myeloma	• Bone marrow trephine biopsy and immunohistochemistry • FISH • Serum free light chains • heavy/light chain ratio • Bone marrow immunophenotyping/FACS/flow cytometry	• Response to treatment • Adverse events • Overall survival • Progression-free survival • Time to next treatment (for asymptomatic patients)

Evidence statements

(a) Immunohistochemistry
Five studies were identified that investigated the prognostic value of immunohistochemistry. Each of the 5 studies investigated different markers. P53 expression and ki-67 antigen expression were found to be independent risk factors for OS (Chang et al., 2007 and Gastinee et al., 2007), whilst CD56, CD99 and cyclin D1 expression were not associated with patient survival (Chang et al., 2006; Shin et al., 2014; Tinguely et al., 2007).

(b) Flow cytometry
Fourteen studies were identified that investigated the prognostic value of flow cytometry. All 14 studies found flow cytometry was able to identify myeloma patients with a poor prognosis. However not all studies could confirm their results in a multivariate model.

The identified studies all used flow cytometry to investigate a number of different markers. Five studies assessed the prognostic value of clonal circulating plasma cells and all 5 studies concluded that clonal circulating plasma cells were an independent risk factor for patient survival (Gonsalves et al., 2014; Nowakowski et al., 2005; Paiva et al., 2009a; 2009b; 2013).

CD antigens were investigated by flow cytometry in a number of studies. CD28+ (Mateo et al., 2008), CD81+ (Paiva et al., 2012a) and $CD19^{+}/CD117^{-}$ (Caltagirone et al., 2014) were all found to be independent prognostic risk factors for survival in myeloma patients, whereas CD19 (Caltagirone et al., 2014; Mateo et al., 2008), CD45 (Caltagirone et al., 2014; Mateo et al., 2008), CD20 (Caltagirone et al., 2014; Mateo et al., 2008), CD56 (Caltagirone et al., 2014; Mateo et al., 2008) and CD33 (Mateo et al., 2008) were all reported to not be associated with clinical outcomes. CD117 was found to be prognostic in one study (Mateo et al., 2008) but not in another (Caltagirone et al., 2014).

DNA content/ hyperdiploidy was assessed in 3 studies. All 3 studies found that hyperdiploid patients had increased survival compared to non-hyperdiploid patients. But whether DNA content is an independent risk factor remains uncertain. One study reported that DNA content remained significant in a multivariate model (Paiva et al., 2012b), but another study reported that it lost significance (Mateos et al. 2011) whilst a third study did not include a multivariate model (Chng et al., 2006).

A high plasma cell proliferation index was reported to be associated with worse survival compared to a lower plasma cell proliferation index in 4 studies. The association remained significant after taking into account other risk factors in a multivariate model in one study (Paiva et al., 2012b). A multivariate model was not included in the other 3 studies (Minarik et al., 2005; 2010; 2011). The poor prognosis associated with a high proliferative index may be overcome by the use of novel agents (Minarik et al., 2010; Paiva et al., 2012b).

A low plasma cell apoptosis index was reported to be associated with worse survival compared to a higher plasma cell apoptosis index in 2 studies (Minarik et al., 2005; 2011). These studies did not include a multivariate model so it is uncertain whether the apoptosis index is an independent prognostic factor for patient survival in myeloma.

(c) Serum free light chains

Eight studies were identified that investigated the prognostic value of serum free light chains (FLC). All 8 studies found serum FLC to be prognostic. Two studies reported that abnormal FLC was independently prognostic for a higher risk of progression from smoldering myeloma to active myeloma (Dispenzieri et al., 2008a; Larsen et al., 2013) and three studies reported that abnormal FLC was independently prognostic for myeloma patient survival (Kumar et al., 2010; Snozek et al., 2008; Van Rhee et al., 2007; Xu et al., 2013). Two further studies also reported serum FLC to be predictive for patient survival in myeloma, however multivariate analysis was not done and so it is unclear whether serum free chains were an independent prognostic factor in these studies (Dispenzieri et al., 2008b; Maltezas et al., 2013).

(d) Heavy/light chain ratio

Three studies were identified that investigated the prognostic value of heavy/light chain ratio (Bradwell et al., 2013; Koulieris et al., 2012, Ludwig et al., 2013). All 3 studies found the heavy/light chain ratio to be independently prognostic for either OS or PFS.

(e) FISH

Thirty four studies were identified that investigated the prognostic value of FISH. Thirty one studies examined genetic abnormalities in newly diagnosed myeloma patients and determined the prognostic impact of these genetic abnormalities on patient survival (PFS and/or OS) and three studies examined genetic abnormalities in smoldering myeloma patients and determined the prognostic impact of these genetic abnormalities on time to progression to active myeloma.

The most common genetic abnormalities assessed were: t(11;14), t(4;14), t(14;16), del(17p), del(13q), del(1p), 1q gains, del(p53) and hyperdiploidy.

To summarise the results in newly diagnosed myeloma patients (Table 2.3):
t(11:14) was included in 13 studies (Table 2.4) (An et al., 2013, Avet-Loiseau et al., 2007, Avet-Loiseau et al., 2012, Avet-Loiseau et al., 2013a, Bang et al., 2006, Boyd et al., 2012, Caltagitone et al., 2014, Chang et al., 2005a, Chang et al., 2010, Gutierrez et al., 2007, Neben et al., 2010, Nemec et al., 2012 and Walker et al., 2010) but only 1 study found an association with patient survival. This association did not remain significant in the multivariate model.

t(4:14) was included in 16 studies (Table 2.5) (Avet-Loiseau et al., 2007, Avet-Loiseau et al., 2010, Avet-Loiseau et al., 2011, Avet-Loiseau et al., 2012, Avet-Loiseau et al., 2013a, Avet-Loiseau et al., 2013b, Boyd et al., 2012, Caltagitone et al., 2014, Chang et al., 2005a, Chang et al., 2010, Grzasko et al., 2013, Gutierrez et al., 2007, Moeau et al., 2007, Neben et al., 2010, Nemec et al., 2012 and Walker et al., 2010) and 12 of these reported an association between the genetic abnormality and patient survival. 9 of the 12 studies reported t(4;14) to be an independent prognostic factor after multivariate analysis whilst no multivariate analysis was undertaken in the other 3 studies.

t(14:16) was included in 8 studies (Table 2.6) (Avet-Loiseau et al., 2011, Avet-Loiseau et al., 2012, Avet-Loiseau et al., 2013a, Boyd et al., 2012, Caltagitone et al., 2014, Gutierrez et al., 2007, Neben et al., 2010 and Walker et al., 2010) only 1 of which reported this genetic abnormality to be prognostic for patient survival.

Del(17p) was included in 12 studies (Table 2.7) (Avet-Loiseau et al., 2007, Avet-Loiseau et al., 2010, Avet-Loiseau et al., 2011, Avet-Loiseau et al., 2012, Avet-Loiseau et al., 2013a, Avet-Loiseau et al., 2013b, Boyd et al., 2012, Caltagitone et al., 2014, Grzasko et al., 2013, Neben et al., 2010, Nemec et al., 2012 and Walker et al., 2010) and 10 of these reported an association between the genetic abnormality and patient survival. 7 of the 10 studies reported del(17p) to be an independent prognostic factor after multivariate analysis whilst no multivariate analysis was undertaken in the other 3 studies.

Del(13q) was included in 14 studies (Table 2.8) (Avet-Loiseau et al., 2007, Avet-Loiseau et al., 2011, Avet-Loiseau et al., 2012, Avet-Loiseau et al., 2013a, Avet-Loiseau et al., 2013b, Bang et al., 2006, Boyd et al., 2012, Caltagitone et al., 2014, Chang et al., 2005a, Chang et al., 2010, Grzasko et al., 2013, Lai et al., 2012, Neben et al., 2010 and Nemec et al., 2012) and 9 of these reported an association between the genetic abnormality and patient survival. 4 of the 9 studies reported del(13q) to be an independent prognostic factor after multivariate analysis and 4 reported del(13q) to not be an independent prognostic factor whilst no multivariate analysis was undertaken in 1 study.

Del(1p) was included in 6 studies (Table 2.9) (Boyd et al., 2012, Caltagitone et al., 2014, Chang et al., 2010, Chng et al., 2010, Hebraud et al., 2014 and Walker et al., 2010) and 5 of these reported an association between the genetic abnormality and patient survival. 3 of the 5 studies reported del(1p) to be an independent prognostic factor after multivariate analysis whilst no multivariate analysis was undertaken in the other 2 studies.

Amp(1q) was included in 13 studies (Table 2.10) (An et al., 2014, Avet-Loiseau et al., 2012, Bang et al., 2006, Boyd et al., 2012, Caltagitone et al., 2014, Chang et al., 2010, Fonseca et al., 2006, Grzasko et al., 2013, Hanamura et al., 2006, Lai et al., 2012, Neben et al., 2010, Nemec et al., 2012 and Walker et al., 2010) and 9 of these reported an association between the genetic abnormality and patient survival. 5 of the 9 studies reported amp(1q) to be an independent prognostic factor after multivariate analysis and 2 reported amp(1q) to not be an independent prognostic factor whilst no multivariate analysis was undertaken in 2 studies.

Del(p53) was included in 3 studies (Table 2.11) (Avet-Loiseau et al., 2007, Boyd et al., 2012 and Walker et al., 2010) but only 1 study found an association with patient survival. This association did not remain significant in the multivariate model.

Hyperdiploidy was included in 5 studies (Table 2.12) (Chang et al., 2005a, Chang et al., 2005b, Chang et al., 2010, Gutierrez et al., 2007 and Lai et al., 2012) and 3 of these found an association with patient survival all of which remained significant in the multivariate model.

To summarise the results in asymptomatic patients (Table 2.13)
t(11:14) was included in 3 studies (Talbe 2.14) (Lopez-Coral et al., 2012, Neben et al., 2013 and Rajkumar et al., 2013) but none of these found t(11;14) to be prognostic for progression to symptomatic myeloma.

t(4:14) was included in 3 studies (Table 2.15) (Lopez-Coral et al., 2012, Neben et al., 2013 and Rajkumar et al., 2013) and 2 of these reported an association between the genetic abnormality and TTP. 1 study reported t(4;14) to be an independent prognostic factor after multivariate analysis whilst in the other study the result lost significance after multivariate analysis.

t(14:16) was included in 1 study (Table 2.16) (Lopez-Coral et al., 2012) but it was not found to be prognostic for progression to symptomatic myeloma.

Del(17p) was included in 2 studies (Table 2.17) (Lopez-Coral et al., 2012 and Neben et al., 2013). One study reported an association between the genetic abnormality and TTP but the result lost significance after multivariate analysis.

Del(13q) was included in 3 studies (Table 2.18) (Lopez-Coral et al., 2012, Neben et al., 2013 and Rajkumar et al., 2013) but none of these found del(13q) to be prognostic for progression to symptomatic myeloma.

Amp(1q) was included in 2 studies (Table 2.19) (Lopez-Coral et al., 2012 and Neben et al., 2013) One study reported an association between the genetic abnormality and TTP but the result lost significance after multivariate analysis.

Hyperdiploidy was included in 2 studies (Table 2.20) (Lopez-Coral et al., 2012 and Neben et al., 2013) One study reported an association between the genetic abnormality and TTP but the result lost significance after multivariate analysis.

No studies investigated the prognostic importance of del(1p) or del(p53) in asymptomatic myeloma.

A number of studies divided patients into high, standard or low risk groups based on the genetic abnormalities they carried (or lacked). It is difficult to compare across studies as different studies used different genetic abnormalities. However all studies reported that myeloma patients classed as high risk (with adverse genetic abnormalities) had a worse prognosis for survival compared to patients that were in the low risk group (without the established adverse genetic abnormalities) (Boyd et al., 2012; Chang et al., 2005a; Jacobus et al., 2011; Kapoor et al., 2010; Kumar et al., 2012; Lu et al., 2014; Mateos et al., 2011; Paiva et al., 2012c). Similarly, smoldering myeloma patients defined as high risk had a worse prognosis for progression to active myeloma (Neben et al., 2013; Rajkumar et al., 2013).

Table 2.3: Summary of prognostic FISH studies for newly diagnosed myeloma

Genetic abnormality	Number of studies	Number of studies suggesting prognostic impact	Multivariate analysis
t(11;14)	13	1	Result not significant after multivariate analysis
t(4;14)	16	12	3 studies: multivariate analysis not done 9 studies: result remained significant after multivariate analysis
t(14;16)	8	1	Result remained significant after multivariate analysis
del(17p)	12	10	3 studies: multivariate analysis not done 7 studies: result remained significant after multivariate analysis
del(13q)	14	9	4 studies: result not significant after multivariate analysis 1 study: multivariate analysis not done 4 studies: result remained significant after multivariate analysis
del(1p)	6	5	2 studies: multivariate analysis not done 3 studies: result remained significant after multivariate analysis
1q gains	13	9	2 studies: result not significant after multivariate analysis 2 studies: multivariate analysis not done 5 studies: result remained significant after multivariate analysis
del(p53)	3	1	Result not significant after multivariate analysis
hyperdiploidy	5	3	All studies: result remained significant after multivariate analysis

Table 2.4: t(11;14)

Study	Sample size	Treatment	Prognostic?	Remained significant after multivariate analysis?	HR	Additional comments
An et al., 2013	253	Thalidomide or bortezomib	No			Patients with t(11;14): no difference in outcome depending on treatment with thalidomide or bortezomib.
Avet-Loiseau et al., 2007	1064	VAD followed by double intensive therapy	No			
Avet-Loiseau et al., 2012	520	VAD + ASCT	No			
Avet-Loiseau et al., 2013a	2642	High dose melphalan or conventional treatment	No			
Bang et al., 2006	130	?	Yes	No		
Boyd et al., 2012	1069	Myeloma IX trial	No			
Caltagitone et al., 2014	376	VMP or VMPT	No			
Chang et al., 2005a	126	High dose chemotherapy & ASCT	No			
Chang et al., 2010	203	High dose chemotherapy & ASCT	No			
Gutierrez et al., 2007	260	High dose therapy & ASCT	No			
Neben et al., 2010	315	High dose therapy & ASCT	No			
Nemec et al., 2012	207	High dose therapy & ASCT	No			
Walker et al., 2010	1177	Myeloma IX	No			

1 **Table 2.5: t(4;14)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Avet-Loiseau et al., 2007	1064	VAD followed by double intensive therapy	Yes	Yes	2.79 (EFS) 2.78 (OS)	
Avet-Loiseau et al., 2010	507	Vel/dex	Yes	n/a		Bortezomib improved prognosis of patients with t(4;14) compared with patients treated with VAD.
Avet-Loiseau et al., 2011	1003	IFM 99 trials	Yes	Yes	2.56 (OS)	
Avet-Loiseau et al., 2012	520	VAD + ASCT	Yes	Yes	2.45 (PFS) 3.04 (OS)	
Avet-Loiseau et al., 2013a	2642	High dose melphalan or conventional treatment	Yes	n/a		
Avet-Loiseau et al., 2013b	1890	Mixed	Yes	Yes	2.03 (PFS) 1.89 (OS)	
Boyd et al., 2012	1069	Myeloma IX trial	Yes	Yes	1.65 (PFS) 1.54 (OS)	
Caltagitone et al., 2014	376	VMP or VMPT	No			
Chang et al., 2005a	126	High dose chemotherapy & ASCT	Yes	Yes	n/a	
Chang et al., 2010	203	High dose chemotherapy & ASCT	No			
Grzasko et al., 2013	104	mixed	No			
Gutierrez et al., 2007	260	High dose therapy & ASCT	Yes	Yes		
Moeau et al., 2007	716	Double intensive therapy	Yes	n/a		
Neben et al., 2010	315	High dose therapy & ASCT	Yes	Yes	n/a	
Nemec et al., 2012	207	High dose therapy & ASCT	Yes	Yes	13.7 (OS)	
Walker et al., 2010	1177	Myeloma IX	No			

2

3 **Table 2.6: t(14;16)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Avet-Loiseau et al., 2011	1003	IFM 99 trials	No			
Avet-Loiseau et al., 2012	520	VAD + ASCT	No			
Avet-Loiseau et al., 2013a	2642	High dose melphalan or conventional treatment	No			
Boyd et al., 2012	1069	Myeloma IX trial	Yes	Yes	1.65 (PFS) 1.54	

					(OS)	
Caltagitone et al., 2014	376	VMP or VMPT	No			
Gutierrez et al., 2007	260	High dose therapy & ASCT	No			
Neben et al., 2010	315	High dose therapy & ASCT	No			
Walker et al., 2010	1177	Myeloma IX	No			

1

2 **Table 2.7: Del (17p)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Avet-Loiseau et al., 2007	1064	VAD followed by double intensive therapy	Yes	Yes	3.29 (EFS) 3.93 (OS)	
Avet-Loiseau et al., 2010	507	Vel/dex	Yes	n/a		
Avet-Loiseau et al., 2011	1003	IFM 99 trials	Yes	Yes	2.47 (OS)	
Avet-Loiseau et al., 2012	520	VAD + ASCT	Yes	Yes	2.86 (PFS) 3.04 (OS)	
Avet-Loiseau et al., 2013a	2642	High dose melphalan or conventional treatment	Yes	n/a		
Avet-Loiseau et al., 2013b	1890	Mixed	Yes	Yes	1.96 (PFS) 2.14 (OS)	
Boyd et al., 2012	1069	Myeloma IX trial	Yes	Yes	1.41(PFS) 1.53 (OS)	
Caltagitone et al., 2014	376	VMP or VMPT	No			
Grzasko et al., 2013	104	Mixed	Yes	Yes	n/a	
Neben et al., 2010	315	High dose therapy & ASCT	Yes	Yes	n/a	
Nemec et al., 2012	207	High dose therapy & ASCT	No			
Walker et al., 2010	1177	Myeloma IX	Yes	n/a		

3

4 **Table 2.8: Del(13)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Avet-Loiseau et al., 2007	1064	VAD followed by double intensive therapy	Yes	No		
Avet-Loiseau et al., 2011	1003	IFM 99 trials	Yes	Yes	1.36 (OS)	
Avet-Loiseau et al., 2012	520	VAD + ASCT	Yes	Yes	1.46 (PFS)	
Avet-Loiseau et al., 2013a	2642	High dose melphalan or conventional treatment	Yes	n/a		
Avet-Loiseau et al., 2013b	1890	Mixed	Yes	Yes	1.31 (PFS)	
Bang et al., 2006	130	?	No			
Boyd et al., 2012	1069	Myeloma IX trial	Yes	No		
Caltagitone et al., 2014	376	VMP or VMPT	No			
Chang et al., 2005a	126	High dose chemotherapy & ASCT	Yes	No		

Chang et al., 2010	203	High dose chemotherapy & ASCT	No			
Grzasko et al., 2013	104	mixed	Yes	Yes	n/a	
Lai et al., 2012	608	mixed	No			
Neben et al., 2010	315	High dose therapy & ASCT	Yes	No		
Nemec et al., 2012	207	High dose therapy & ASCT	No			

1
2
3 **Table 2.9: Del (1p)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Boyd et al., 2012	1069	Myeloma IX trial	No			
Caltagitone et al., 2014	376	VMP or VMPT	Yes	n/a		
Chang et al., 2010	203	High dose chemotherapy & ASCT	Yes	Yes	2.33 (PFS) 2.5 (OS)	
Chng et al., 2010	127	Melphalan high dose therapy	Yes	Yes	n/a	
Hebraud et al., 2014	1195	VAD or bortezomib-based induction followed by ASCT	Yes	Yes	1p22: 1.56 (PFS) 1.82 (OS) 1p32: 2.84 (PFS) 4.07 (OS)	
Walker et al., 2010	1177	Myeloma IX	Yes	n/a		

4
5 **Table 2.10: 1q gains**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
An et al., 2014	290	Thalidomide or bortezomib	Yes	Yes	3.8 (PFS) 3.2 (OS)	Survival of patients without 1q21 gains was extended with bortezomib compared to thalidomide treatment. But there was no difference in patients with 1q21 gains treated with either chemotherapy.
Avet-Loiseau et al., 2012	520	VAD + ASCT	Yes	Yes	1.58 (OS)	
Bang et al., 2006	130	?	No			
Boyd et al., 2012	1069	Myeloma IX trial	Yes	Yes	1.46 (PFS) 1.53 (OS)	
Caltagitone et al., 2014	376	VMP or VMPT	Yes	n/a		
Chang et al., 2010	203	High dose chemotherapy & ASCT	No			
Fonseca et al., 2006	159	High dose chemotherapy & ASCT	No			
Grzasko et al., 2013	104	mixed	Yes	Yes	n/a	
Hanamura et al.,	479	Melphalan based	Yes	Yes	1.86 (EFS)	Thalidomide improved

2006		tandem ASCT randomised to receive thalidomide or not			1.78 (OS)	5yr EFS in patients lacking amp1q21 but not in those without amp1q21, and had no effect on OS.
Lai et al., 2012	608	mixed	No			
Neben et al., 2010	315	High dose therapy & ASCT	Yes	No		
Nemec et al., 2012	207	High dose therapy & ASCT	Yes	No		
Walker et al., 2010	1177	Myeloma IX	Yes	n/a		

1

2 **Table 2.11: hyperploidy**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Avet-Loiseau et al., 2007	1064	VAD followed by double intensive therapy	Yes	No		
Boyd et al., 2012	1069	Myeloma IX trial	No			
Walker et al., 2010	1177	Myeloma IX	No			

3

4 **Table 2.12: Del(p53)**

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Chang et al., 2005a	126	High dose chemotherapy & ASCT	Yes	Yes	n/a	
Chang et al., 2005b	105	High dose chemotherapy & ASCT	Yes	Yes	n/a	
Chang et al., 2010	203	High dose chemotherapy & ASCT	Yes	Yes	2.64 (PFS) 4.8 (OS)	
Gutierrez et al., 2007	260	High dose therapy & ASCT	No			
Lai et al., 2012	608	mixed	No			

5

6 **Table 2.13: Summary of prognostic FISH studies for smoldering myeloma**

Genetic abnormality	Number of studies	Number of studies suggesting prognostic impact	Multivariate analysis
t(11;14)	3	0	
t(4;14)	3	2	1 study: result not significant after multivariate analysis 1 study: result remained significant after multivariate analysis
t(14;16)	1	0	
del(17p)	2	1	Result not significant after multivariate analysis
del(13q)	3	0	
del(1p)	0		
1q gains	2	1	Result not significant after multivariate analysis
del(p53)	0		
hyperdiploidy	2	1	Result remained significant after multivariate analysis

7

8

9

Table 2.14: t(11;14)

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		No			
Rajkumar et al., 2013	351		No			

Table 2.15: t(4;14)

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		Yes	No		
Rajkumar et al., 2013	351		Yes	Yes	n/a	

Table 2.16: t(14;16)

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			

Table 2.17: Del(17p)

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		Yes	No		

Table 2.18: Del(13q)

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		No			
Rajkumar et al., 2013	351		No			

Table 2.19: Amp(1q)

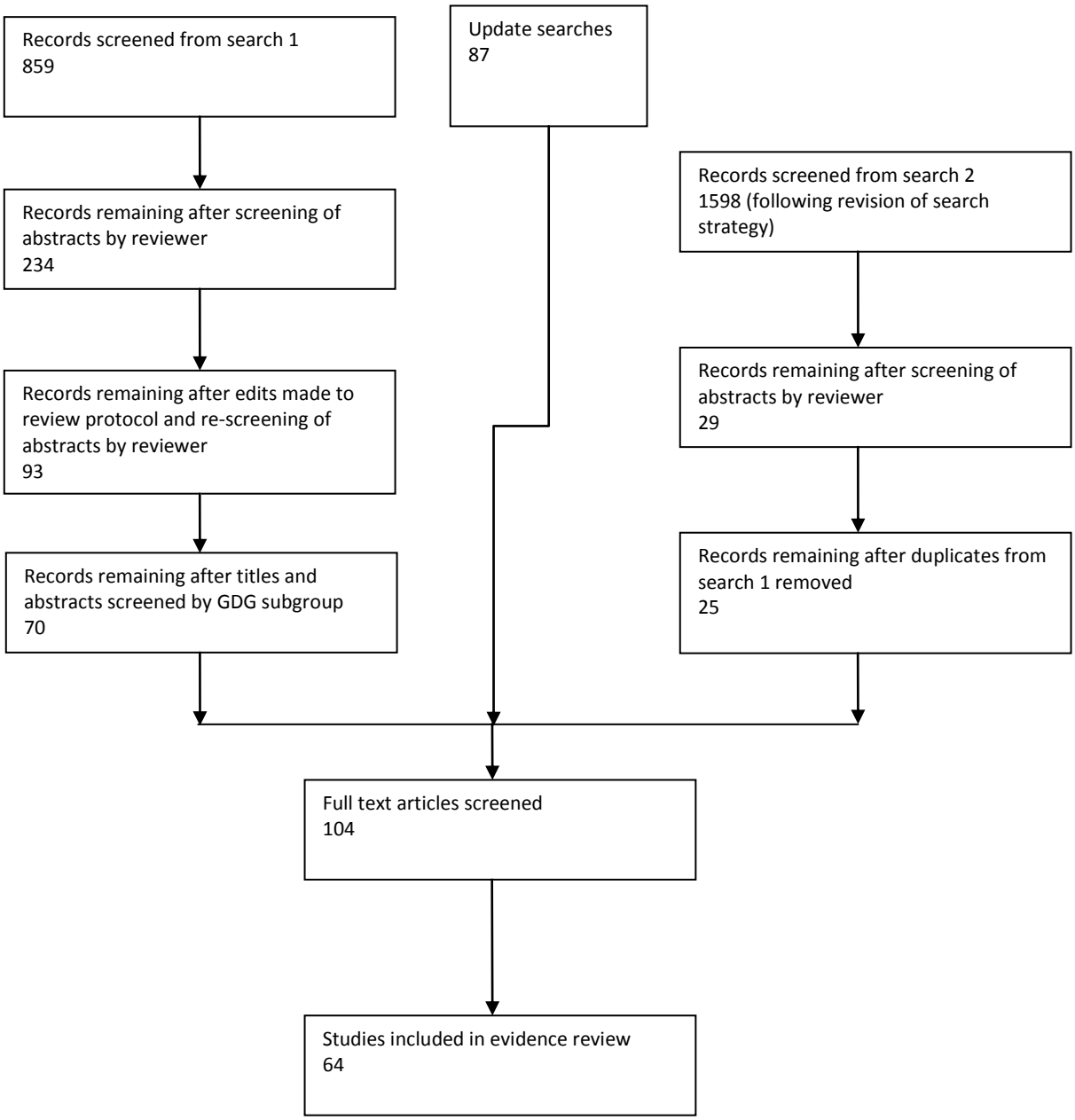
Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		Yes	No		

Table 2.20: hyperdiploidy

Study	Sample size	Treatment	Prognostic?	Remained after multivariate analysis?	HR	Additional comments
Lopez-Coral et al., 2012	123	Len-Dex or no treatment	No			
Neben et al., 2013	248		Yes	Yes	1.72 (TTP)	

Search Results

Figure 2.4: Screening results



Quality of studies

The included studies are high quality studies with a low risk of bias (table 5), although some studies do not include a multivariate model in the analysis to determine whether the assessed prognostic risk factor is independent of other risk factors. Treatment heterogeneity is an issue between as well as within studies.

Evidence tables

(a) Immunohistochemistry

<table>
<tr><th>Study</th><th>Population</th><th>Specialist diagnostic investigation</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Chang et al., 2006

Toronto</td><td>107 myeloma patients treated with melphalan-based high-dose chemotherapy and ASCT

66 Male
41 Female

Median age: 54 years
(range 32-71)

Median post transplant follow-up: 20 months</td><td>Immunohistochemistry

CD56 expression was measured in paraffin samples of 107 bone marrow biopsies collected at initial diagnosis</td><td>Patient survival not associated with CD56 expression in bone marrow biopsies.

<table><tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr><tr><td>CD56 positive</td><td>76</td><td>48.1 months</td><td>25.8 months</td></tr><tr><td>CD56 negative</td><td>31</td><td>44.8 months</td><td>33.1 months</td></tr><tr><td></td><td></td><td>p=0.67</td><td>p=0.28</td></tr></table></td><td>-</td></tr>
<tr><td>Chang et al., 2007

Toronto</td><td>105 myeloma patients treated with melphalan-based high-dose chemotherapy and ASCT

63 Male
42 Female

Median age: 54 years
(range 32-71)

Median post transplant follow-up: 20 months</td><td>Immunohistochemistry

p53 expression was measured in paraffin samples of 105 bone marrow biopsies collected at initial diagnosis</td><td>OS was associated with p53 expression in bone marrow biopsies.

<table><tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr><tr><td>p53 positive</td><td>12</td><td>24.5 months</td><td>14.2 months</td></tr><tr><td>p53 negative</td><td>93</td><td>47.7 months</td><td>24.7 months</td></tr><tr><td></td><td></td><td>P<0.001</td><td>p=0.24</td></tr></table>
Multivariate analysis found p53 expression was an independent risk factor for OS (p=0.002)
Other risk factors included:
CKS1B amplification
t(4:14)
t(11:14)
13q deletions</td><td>-</td></tr>
</table>

<table>
<tr>
<td>Gastinee et al., 2007

France</td>
<td>174 myeloma patients

130 symptomatic
(treated according to IFM protocols MY90 and IFM90 for conventional treatment)
44 asymptomatic

93 Male
81 Female

Median age: 64 years
(IQR 59 – 68)

Median follow-up: 121 months</td>
<td>Immunohistochemistry

Ki-67 antigen expression was determined after double immunocytochemistry on either BM films or BM mononuclear cell cytospins.</td>
<td>A significant impact on survival was found in myeloma with a threshold of ki-67 index of 4%.

<table><tr><th></th><th>n</th><th>Median OS</th></tr><tr><td>Ki-67 < 4</td><td>103</td><td>49 months</td></tr><tr><td>Ki ≥ 4</td><td>71</td><td>26 months</td></tr><tr><td></td><td></td><td>P<0.001</td></tr></table>
Multivariate analysis found ki-67 expression was an independent risk factor for OS (p=0.001)</td>
<td>-</td>
</tr>
<tr>
<td>Shin et al., 2014

Korea</td>
<td>170 myeloma patients

No treatment
(conservative management) n=22
Chemotherapy n=78
Chemotherapy + ASCT n=60
Radiotherapy n=10

89 Male
81 Female

Mean age: 60 years
(range 29-84)

Median follow-up: 999 days
(range: 2 - 4,686 days)</td>
<td>Immunohistochemistry

CD99 expression was measured in paraffin samples of 136 bone marrow biopsies collected at initial diagnosis</td>
<td>Low CD99 expression (score 0-2): 47% of patients
High CD99 expression)score 3-6): 53% of patients
(score based on intensity of staining and percentage of positive cells)

OS not associated with CD99 expression in bone marrow biopsies.
(data not provided)

ASCT significantly enhanced OS in patients with both high and low CD99 expression.</td>
<td>-</td>
</tr>
<tr>
<td>Tinguely et al., 2007

Switzerland</td>
<td>119 myeloma patients

59.5% Male

62% over 60 years of age at diagnosis

Follow-up: 1 week – 14.3 years</td>
<td>Immunohistochemistry

CyclinD1 expression was measured in 135 paraffin embedded biopsies (127 osseous, 8 extra – osseous)from 119 patients</td>
<td>Survival data was available for 111 patients

Patient survival not associated with cyclin D1 expression.
(data not provided)</td>
<td>No treatment information</td>
</tr>
</table>

1

2 ***(b) Flow cytometry***

<table>
<tr><th>Study</th><th>Population</th><th>Specialist diagnostic investigation</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Caltagirone et al., 2014

Italy</td><td>511 elderly myeloma patients
From 61 centres

GIMEMA-MM-03-05 trial
Patients randomised to receive VMP or VMPT

252 male
259 female

Median follow up: 54 months
(1-80 months)</td><td>Flow cytometry

four-colour multiparameter flow cytometry

CD19, CD45, CD20, CD117, CD56

N=399</td><td>CD19, CD45, CD20, CD117, CD56 – no association with survival

Combination $CD19^{+}/CD117^{-}$ independent risk factor for OS (HR 2.62, p=0.012)</td><td>-</td></tr>
<tr><td>Chng et al., 2006

USA</td><td>366 transplant eligible myeloma patients enrolled in ECOG E9486 trial
Randomised to receive variations of VBMCP

227 male
139 female

Median follow-up 12 years</td><td>Flow cytometry

dual channel flow cytometry to determine total DNA content</td><td>DNA content
DNA index <0.95: hypodiploid
DNA index 0.95 – 1.05: pseudodiploiddiploid
DNA index 1.06 – 1.74: hyperdiploid
DNA index >1.74: tetraploid/near-tetraploid

<table><tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr><tr><td>hyperdiploid</td><td>220</td><td>32 months</td><td>48 months</td></tr><tr><td>nonhyperdiploid</td><td>146</td><td>25 months</td><td>35 months</td></tr><tr><td></td><td></td><td>P=0.023</td><td>P=0.023</td></tr></table></td><td>-</td></tr>
</table>

<table>
<tr>
<td>Gonsalves et al., 2014

USA</td>
<td>157 myeloma patients
(2009-2011)

Initial induction treatment:
Novel agents n=150
Thalidomide n=12
Lenalidomide n=106
Bortezomib n=52
Post-induction ASCT n=56

93 Male
64 Female

Median age: 65 years
(range 39-95)

Median follow up: 21 months
(17-23 months)</td>
<td>Flow cytometry

Peripheral blood evaluated for clonal circulating plasma cells (cPCs) by six-colour multiparameter flow cytometry before beginning therapy</td>
<td>54% had cPCs detected.
Median number of cPCs in entire cohort: 40 (range: 0 – 46,413)/150,000 gated events.

<table>
<tr><th></th><th>n</th><th>Median OS</th><th>2yr OS</th><th>3yr OS</th></tr>
<tr><td>cPCs present</td><td>85</td><td>Not reached</td><td>76%</td><td>67%</td></tr>
<tr><td>cPCs absent</td><td>72</td><td>Not reached</td><td>91%</td><td>87%</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Though the median OS was not reached for either group it was significantly shorter for the patients with cPCs (p-0.019)

≥400 cPCs was considered as the optimal cut off for defining high disease
<table>
<tr><th></th><th>n</th><th>Median time-to-next-treatment</th><th>Median OS</th></tr>
<tr><td>≥400 cPCs</td><td>37</td><td>14 months</td><td>32 months</td></tr>
<tr><td><400 cPCs</td><td>120</td><td>26 months</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>
In the multivariate model the presence of ≥400 cPCs adversely affected OS (p=0.024) and TTNT (p=0.028)</td>
<td>Retrospective study.

Cut-off of 400 cPCs is based on single institution data.

Heterogenity in induction treatments used.</td>
</tr>
<tr>
<td>Mateo et al., 2008

Spain</td>
<td>685 myeloma patients

All were treated with the GEM2000 protocol: six alternating cycles of VBCMP/VBAD followed by high-dose therapy: melphalan and ASCT.

377 Male
308 Female

Median age: 59 years
(range 32-70)

Median follow up: 48 months</td>
<td>Flow cytometry

multiparameter flow cytometry at diagnosis

CD19, CD20, CD45, CD56, CD117, CD28, CD33</td>
<td>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD19 -</td><td>655</td><td>38 months</td><td>68 months</td></tr>
<tr><td>CD19 +</td><td>30</td><td>26 months</td><td>40 months</td></tr>
<tr><td></td><td></td><td>P=0.04</td><td>P=0.02</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD20 -</td><td>524</td><td>37 months</td><td>73 months</td></tr>
<tr><td>CD20 +</td><td>106</td><td>35 months</td><td>63 months</td></tr>
<tr><td></td><td></td><td>P=0.89</td><td>P=0.87</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD28 -</td><td>420</td><td>38 months</td><td>Not reached</td></tr>
<tr><td>CD28 +</td><td>240</td><td>31 months</td><td>53 months</td></tr>
<tr><td></td><td></td><td>P=0.04</td><td>P=0.001</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD33 -</td><td>521</td><td>37 months</td><td>66 months</td></tr>
<tr><td>CD33 +</td><td>118</td><td>32 months</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.08</td><td>P=0.7</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD45 -</td><td>490</td><td>38 months</td><td>68 months</td></tr>
</table>
</td>
<td>-</td>
</tr>
</table>

CD45 +	180	35 months	53 months		
		P=0.8	P=0.4		

	n	Median PFS	Median OS
CD56 -	271	34 months	66 months
CD56 +	414	39 months	67 months
		P=0.1	P=0.1

	n	Median PFS	Median OS
CD117 -	431	32 months	Not reached
CD117 +	208	44 months	63 months
		P=0.04	P=0.01

Expression of both CD19 and CD28 as well as absence of CD117 were associated with a significantly shorter PFS and OS.

Poor risk: CD28 positive, CD117 negative
intermediate risk: CD28 positive, CD117 positive or CD28 negative, CD117 negative
good risk: CD28 negative, CD117 positive

	n	Median PFS	Median OS
Poor risk	149	30 months	45 months
Intermediate risk	362	37 months	68 months
Good risk	128	45 months	Not reached
		P=0.01	P=0.0001

Multivariate analysis of prognostic factors for survival was performed in the whole series of patients(n=685) and subsequently in cases with available cytogenetic information (n=231).
In the whole series:
More than 10% BM PC by flow cytometry and CD28 positive CD117 negative phenotype had an independent adverse impact on OS.
More than 10% BM PC by flow cytometry had an independent adverse impact on PFS.
Once cytogenetic information was included, the antigen expression lost their independent prognostic value.

<table>
<tr>
<td>Mateos et al., 2011

Spain</td>
<td>260 elderly myeloma patients

Received an induction with weekly bortezomib. Randomised.
VMP: 130
VTP: 130
Then maintenance therapy.
Randomised to VT or VP.

Median age: 72 years
(range 62-85)

Median follow-up 32 months</td>
<td>Flow cytometry

multiparameter flow cytometry at diagnosis to evaluate DNA content</td>
<td>DNA ploidy analysis was possible in 224 of 260 patients.

DNA index <0.95: hypodiploid
DNA index 1.06 – 1.74: hyperdiploid
DNA index >1.74: tetraploid/near-tetraploid

Response was similar in hyperdiploid and nonhyperdiploid groups both after induction and maintenance.

PFS was almost identical in hyperdiploid and nonhyperdiploid patients. However OS was found to be significantly shorter for nonhyperdiploid patients, particularly those receiving VTP induction.

<table>
<tr><th></th><th>n</th><th>PFS from 1st randomization</th><th>PFS from 2nd randomization</th><th>3yr OS</th></tr>
<tr><td>hyperdiploid</td><td>132</td><td>29 months</td><td>26 months</td><td>77%</td></tr>
<tr><td>nonhyperdiploid</td><td>92</td><td>29 months</td><td>26 months</td><td>63%</td></tr>
<tr><td></td><td></td><td>P=0.9</td><td>P=0.6</td><td>P=0.04</td></tr>
</table>

OS in non-hyperdiploid
<table>
<tr><th></th><th>n</th><th>3yr OS</th></tr>
<tr><td>VMP</td><td>?</td><td>72%</td></tr>
<tr><td>VTP</td><td>?</td><td>52%</td></tr>
<tr><td></td><td></td><td>P=0.1</td></tr>
</table>

Non-hyperdiploid patients receiving VMP as induction had a 3yr OS of 72% - similar to hyperdiploid patients.

Multivariate analysis:
DNA ploidy was not independently prognostic.</td>
<td>-</td>
</tr>
<tr>
<td>Minarik et al., 2005

Czech Republic</td>
<td>117 myeloma patients
Treated using conventional induction chemotherapy

Median age 66 years (44 – 85)</td>
<td>Flow cytometry

plasma cell proliferation index (propidium iodide index (PC-PI)).

apoptosis (annexin V index PC-AI))</td>
<td>PC-PI
Median 2.6%
Range 0.4 – 4.8%

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 2.6</td><td>?</td><td>32 months</td></tr>
<tr><td>≥ 2.6</td><td>?</td><td>18 months</td></tr>
<tr><td></td><td></td><td>P=0.05</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 2.8</td><td>?</td><td>42 months</td></tr>
<tr><td>≥ 2.8</td><td>?</td><td>13 months</td></tr>
<tr><td></td><td></td><td>P=0.0005</td></tr>
</table>

PC-AI
Median 5.1%</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range 1.4 – 24.5%

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 5.1</td><td>?</td><td>20 months</td></tr>
<tr><td>≥ 5.1</td><td>?</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.04</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 4</td><td>?</td><td>16 months</td></tr>
<tr><td>≥ 4</td><td>?</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.01</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Minarik et al., 2010

Czech Republic</td>
<td>217 myeloma patients
Treated using induction conventional chemotherapy
Then n=50 received biological agents, thalidomide and bortezomib in relapse.

109 male
108 female

Median age 67 years (33 – 89)</td>
<td>Flow cytometry

plasma cell proliferation index (propidium iodide index (PC-PI)).</td>
<td>Patients treated with conventional chemotherapy and new biological agents (n=217)
<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 2.8</td><td>144</td><td>30 months</td></tr>
<tr><td>≥ 2.8</td><td>73</td><td>12 months</td></tr>
<tr><td></td><td></td><td>P=0.06</td></tr>
</table>
After 40 months from diagnosis the curves merged suggesting the influence of novel drugs.

Patients treated only with conventional chemotherapy (n=167)
<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 2.8</td><td>110</td><td>25 months</td></tr>
<tr><td>≥ 2.8</td><td>57</td><td>10 months</td></tr>
<tr><td></td><td></td><td>P=0.015</td></tr>
</table>
Patients treated with novel biological therapy (n=50)
<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>< 2.8</td><td>34</td><td>39 months</td></tr>
<tr><td>≥ 2.8</td><td>16</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.68</td></tr>
</table>
</td>
<td>-</td>
</tr>
<tr>
<td>Minarik et al., 2011

Czech Republic</td>
<td>181 myeloma patients
Treated using conventional induction chemotherapy

90 male
91 female

Median age 67 years (22 – 89)

Median follow-up 25 months (range 1-117 months)</td>
<td>Flow cytometry

plasma cell proliferation index (propidium iodide index (PC-PI)).

apoptosis (annexin V index PC-AI))</td>
<td>PC-PI
Median 2.5%
Range 1.2 – 4.2%

PC-AI
Median 4.3%
Range 1.4 – 24.5%

Poor prognosis: PC-PI > 3% and PC-AI < 4.75%. n=20. median OS 8 months
Good prognosis: PC-PI ≤ 3% and PC-AI ≥ 4.75%. n=71. median OS 40 months
P=0.0002.
Patients not belonging to either of these subgroups had median OS of 25 months.</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td>Nowakowski et al., 2005

USA</td>
<td>302 myeloma patients
(1998-2003 – pre-novel agent era)

Initial induction treatment:
VAD 25%
dexamethasone 23%
MP 23%
Thalidomide + dexamethasone 16%
Others 13%
Post-induction ASCT 40%

180 Male
123 Female

Median age: 65 years
(range 29-94)</td>
<td>Flow cytometry

Peripheral blood collected within first week of diagnosis and before treatment was evaluated for clonal circulating plasma cells (cPCs) by three-colour multiparameter flow cytometry.</td>
<td>222 patients
73% had cPCs detected.
Median number of cPCs in entire cohort: 4 (range: 1 – 28,692)/50,000 gated events.

<table><tr><th></th><th>n</th><th>Median OS</th></tr><tr><td>cPCs ≤10</td><td>186</td><td>59 months</td></tr><tr><td>cPCs >10</td><td>115</td><td>37 months</td></tr><tr><td></td><td></td><td>P=0.001</td></tr></table>
In the multivariate model the prognostic value of cPCs was independent of B2M, albumin and age.</td>
<td>Pre-novel agent era

Non-quantitative flow-based method</td>
</tr>
<tr>
<td>Paiva et al., 2009a

Spain</td>
<td>765 myeloma patients

GEM2000 protocol:
VBMCP/VBAD followed by ASCT

421 Male
354 Female

Median age: 60 years
(range 32-74)

Median follow up: 51 months</td>
<td>Flow cytometry

Four-colour multiparameter flow cytometry before beginning therapy on erythrocyte-lysed bone marrow aspirate samples to assess bone marrow plasma cell count.</td>
<td>Median % of BMPC: 11% (range: 0.5 – 95%)

<table><tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th><th>5yr PFS</th><th>5yr OS</th></tr><tr><td><15% BMPCs</td><td>438</td><td>43 months</td><td>97 months</td><td>37%</td><td>68%</td></tr><tr><td>≥15% BMPCs</td><td>327</td><td>36 months</td><td>54 months</td><td>21%</td><td>53%</td></tr><tr><td></td><td></td><td>P=0.003</td><td>P<0.001</td><td>P=0.003</td><td>P<0.001</td></tr></table>
In the multivariate model the bone marrow plasma cell counts obtained by flow cytometry was an independent prognostic factor for OS (HR 2.3, p=0.006).</td>
<td>-</td>
</tr>
<tr>
<td>Paiva et al., 2009b

Spain</td>
<td>594 myeloma patients

GEM2000 protocol:
VBMCP/VBAD followed by ASCT

331 Male
263 Female

Median age: 58 years
(range 32-70)

Median follow up: 54 months</td>
<td>Flow cytometry

Four-colour multiparameter flow cytometry before beginning therapy on erythrocyte-lysed bone marrow aspirate samples to detect residual normal plasma cells</td>
<td>Response after induction:
<table><tr><th></th><th>CR</th><th>nCR</th><th>≤ PR</th></tr><tr><td>≤5% N-PCs/BMPCs</td><td>56 (11%)</td><td>61 (12%)</td><td>397 (77%)</td></tr><tr><td>>5% N-PCs/BMPCs</td><td>17 (21%)</td><td>19 (24%)</td><td>44 (55%)</td></tr><tr><td></td><td>P=0.01</td><td>P=0.005</td><td>P<0.001</td></tr></table>
Response after ASCT:
<table><tr><th></th><th>CR</th><th>nCR</th><th>≤ PR</th></tr><tr><td>≤5% N-PCs/BMPCs</td><td>168 (33%)</td><td>99 (19%)</td><td>247 (48%)</td></tr><tr><td>>5% N-PCs/BMPCs</td><td>51 (64%)</td><td>8 (10%)</td><td>21 (26%)</td></tr><tr><td></td><td>P<0.001</td><td>P<0.001</td><td>P<0.001</td></tr></table></td>
<td>-</td>
</tr>
</table>

			<table><tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr><tr><td>≤5% N-PCs/BMPCs</td><td>514</td><td>42 months</td><td>89 months</td></tr><tr><td>>5% N-PCs/BMPCs</td><td>80</td><td>54 months</td><td>Not reached</td></tr><tr><td></td><td></td><td>P=0.001</td><td>P=0.04</td></tr></table> Multivariate analysis performed in cases with cytogenetic information (n=176) showed only cytogenetics as an independent prognostic factor for PFS and OS. Due to small sample multivariate analysis was repeated in whole cohort. Percentage of N-PCs/BMPCs was independent prognostic factor for PFS (RR 1.6, p=0.008).	

<table>
<tr>
<td>Paiva et al., 2012a

Spain</td>
<td>1.n=230 elderly myeloma patients.
GEM(05)>65years trial.
Received an induction with weekly bortezomib. Randomised.
VMP: 130
VTP: 130
Then maintenance therapy.
Randomised to VT or VP.

2. n=325 myeloma patients.
GEM(05)<65years trial.
Randomised.
1.VBMCP/VBAD plus bortezomib.
2.Thalidomide/dexamethasone.
3.Bortezomib/thalidomide/dexamethasone.
Then ASCT.

3. n=56 smoldering myeloma patients.

Median follow-up 32 months and 22 months for the myeloma and smoldering myeloma patients, respectively.</td>
<td>Flow cytometry

multiparameter flow cytometry at diagnosis

CD81</td>
<td>1 >65yrs
<table>
<tr><th></th><th>n</th><th>≥PR to induction</th><th>CR to induction</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD81 -</td><td>127</td><td>88%</td><td>29%</td><td>37 months</td><td>Not reached</td></tr>
<tr><td>CD81 +</td><td>103</td><td>72%</td><td>18%</td><td>21 months</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.002</td><td>P=0.06</td><td>P<0.001</td><td>P=0.007</td></tr>
</table>
Treatment arm did not influence patient outcomes.

<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD81- & standard risk cytogenetics</td><td>92</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>CD81- & high risk cytogenetics</td><td>22</td><td>21 months</td><td>Not reached</td></tr>
<tr><td>CD81+ & standard risk cytogenetics</td><td>79</td><td>21 months</td><td>Not reached</td></tr>
<tr><td>CD81+ & high risk cytogenetics</td><td>18</td><td>21 months</td><td>19 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>
High risk: t(4:14), t(14:16), and/or del(17p)
Standard risk: all other cases

2 <65yrs
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>CD81 -</td><td>154</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>CD81 +</td><td>171</td><td>28 months</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P=0.002</td></tr>
</table>
CD81+ was an independent prognostic factor for PFS (HR 1.9, p=0.003) and OS (HR 2, p=0.02).
This adverse impact was validated in the additional series of 325 transplant-candidate patients in the GEM05<65years trial.

3 Smoldering myeloma
<table>
<tr><th></th><th>n</th><th>Median TTP</th></tr>
<tr><td>CD81 -</td><td>24</td><td>Not reached</td></tr>
<tr><td>CD81 +</td><td>32</td><td>31 months</td></tr>
<tr><td></td><td></td><td>P=0.02</td></tr>
</table>
</td>
<td>-</td>
</tr>
<tr>
<td>Paiva et al., 2012b</td>
<td>595 transplant eligible myeloma patients included in 2 trials: GEM2000</td>
<td>Flow cytometry

multiparameter flow</td>
<td>DNA content

DNA index <0.95: hypodiploid</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td>Spain</td>
<td>VBMCP/VBAD followed by ASCT
N=319
GEM2005<65y
Randomised induction with
1.VBMCP/VBAD plus bortezomib.
2.Thalidomide/dexamethasone.
3.Bortezomib/thalidomide/dexamethasone.
Then ASCT.
N=276

Patients included in the GEM2000 protocol with >65 yrs, levels of serum calcium >14mg/dL and/or serum creatinine >2mg/dL were excluded from analysis to avoid confounding survival bias.

Median follow-up 38 months
(range 1-23 months)</td>
<td>cytometry at diagnosis to evaluate DNA content and proliferation index</td>
<td>DNA index 0.95 – 1.05: diploid
DNA index 1.06 – 1.74: hyperdiploid
DNA index >1.74: tetraploid/near-tetraploid

<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>hyperdiploid</td><td>300</td><td>44 months</td><td>84 months</td></tr>
<tr><td>nonhyperdiploid</td><td>295</td><td>34 months</td><td>67 months</td></tr>
<tr><td></td><td></td><td>P=0.004</td><td>P=0.005</td></tr>
</table>

% PCs in S-phase
Median % of PCs in S-phase was 1.14%.
Range 0-13%.

<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td><1</td><td>259</td><td>43 months</td><td>93 months</td></tr>
<tr><td>≥1 - <3</td><td>244</td><td>40 months</td><td>76 months</td></tr>
<tr><td>≥3</td><td>92</td><td>22 months</td><td>45 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

Analysing by study (and so by treatment) it was found that treatment with novel agents can overcome the adverse prognosis of a high proliferating index (≥1% S-phase PCs) – little difference in PFS and OS between patients <1 and ≥1% S-phase PCs in GEM2005<65y.

Multivariate analysis:
Detection of nonhyperdiploid myeloma and a high proliferative index (≥1% S-phase PCs) assessed by multiparameter flow cytometry remain as independent prognostic factors in myeloma, but the latter may be overcome by incorporating novel agents in the HDT/ASCT setting.</td>
<td></td>
</tr>
<tr>
<td>Paiva et al., 2013

Spain</td>
<td>698 myeloma patients
included in 2 trials:
GEM2000
VBMCP/VBAD followed by ASCT
N=486
GEM2005<65y
Randomised induction with
1.VBMCP/VBAD plus bortezomib.
2.Thalidomide/dexamethasone.
3.Bortezomib/thalidomide/dexamethasone.
Then ASCT.
N=212</td>
<td>Flow cytometry

Erythrocyte-lysed whole BM was used in multiparameter flow cytometry at diagnosis.

Computerised algorithm based on simultaneous assessment of the tumour burden and degree of clonality of the bone marrow plasma-cell compartment.</td>
<td>59 myeloma patients (8%) showed an MGUS-like profile.
MGUS-like patients had lower tumour burden: 0.6% plasma cells (compared to 12% in other patients).

Despite achieving similar CR rates after ASCT VS other myeloma patients, MGUS-like patients had longer TTP and OS:

<table>
<tr><th></th><th>n</th><th>CR after ASCT</th><th>Median TTP</th><th>Median OS</th></tr>
<tr><td>MGUS-like</td><td>59</td><td>50%</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>Non MGUS-like</td><td>639</td><td>43%</td><td>44 months</td><td>67 months</td></tr>
<tr><td></td><td></td><td>P=0.21</td><td>P<0.001</td><td>P<0.001</td></tr>
</table>
</td>
<td>-</td>
</tr>
</table>

	Median follow-up 71 months (range 4-153 months) To investigate for an MGUS-like profile comparison was made with 497 MGUS patients.		MGUS-like patients: No difference for median TTP and OS between CR and <CR patients. Non-MGUS-like patients: CR predicts for longer TTP and OS than in <CR patients.	

1

2 ***(c) Serum free light chains***

<table>
<tr><th>Study</th><th>Population</th><th>Specialist diagnostic investigation</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Dispenzieri et al., 2008a

USA</td><td>273 smoldering myeloma patients
(seen at Mayo clinic 1970-1995)

169 Male
104 Female

Median age: 64 years
(range 26-90)

Median follow-up: 6 years
(range 0-29)</td><td>Serum free light chains

freelite

baseline serum obtained within 30 days of diagnosis</td><td>An increasingly abnormal FLC ratio (κ/λ) was associated with a higher risk for progression to active myeloma.

<table>
<tr><th>FLC ratio</th><th>n</th><th>Rate of progression (% per year)</th></tr>
<tr><td>0.25 – 4</td><td>63</td><td>5%</td></tr>
<tr><td>0.125 – 0.25
or
4 - 8</td><td>46</td><td>5.5%</td></tr>
<tr><td>0.0312 – 0.125
or
8 - 32</td><td>93</td><td>7%</td></tr>
<tr><td><0.0312
or
>32</td><td>71</td><td>8.1%</td></tr>
</table>

Multivariate analysis incorporating the FLC ratio into risk categories based on bone marrow plasmacytosis and/or serum M spike.
Independently prognostic:
Bone marrow plasma cells more than 10% (HR 3.1, p<0.01)
Abnormal FLC ratio less than 0.125 or more than 8 (HR 1.9, p<0.01)
Serum M protein size, more than 30 g/L (HR 1.9, p<0.01)</td><td>-</td></tr>
</table>

<table>
<tr>
<td>Dispenzieri et al., 2008b

USA</td>
<td>399 myeloma patients (from from 36 Eastern Cooperative Oncology Group (ECOG) institutions)

treatment
1. VBMCP
2. VBMCP plus recombinant alpha 2 interferon
3. VBMCP and high dose cyclophosphamide

258 Male
141 Female

Median age: 63 years
(range 24-83)</td>
<td>Serum free light chains

freelite

baseline serum</td>
<td>Baseline elevations in involved FLC predicted for OS and PFS.
However, results are similar regardless of whether absolute values or ratio of involved to uninvolved FLC is used.

The involved FLC (iFLC) is defined as the actual value of serum immunoglobulin kappa FLCs in patients with monoclonal kappa plasma cells or of serum immunoglobulin lambda FLCs in patients with clonal lambda plasma cells.

<table>
<tr><th>FLC difference</th><th>n</th><th>OS</th><th>PFS</th></tr>
<tr><td>0.03-11.77 mg/dL</td><td>132</td><td>49.4 months</td><td>34.9 months</td></tr>
<tr><td>11.77 – 85.56 mg/dL</td><td>135</td><td>42 months</td><td>38.7 months</td></tr>
<tr><td>85.56 – 3368.5 mg/dL</td><td>132</td><td>42 months</td><td>29.5 months</td></tr>
</table>

Multivariate analysis not done.</td>
<td>-</td>
</tr>
<tr>
<td>Kumar et al., 2010

USA</td>
<td>314 myeloma patients (recruited from 36 eastern cooperative oncology group intuitions 1988-1992)

treatment
4. VBMCP
5. VBMCP plus recombinant alpha 2 interferon
6. VBMCP and high dose cyclophosphamide

169 Male
104 Female

Median age: 64 years
(range 26-90)

Median follow-up: 6 years
(range 0-29)</td>
<td>Serum free light chains

freelite

baseline serum

If κ/λ ratio > 1.65, κ chain = involved chain
If κ/λ ratio < 1.65, λ chain = involved chain
Involved/uninvolved ratio with the monoclonal light chain in the numerator.
Absolute difference between involved and uninvolved light chain was also determined.</td>
<td>Multivariate analysis:
The prognostic value of FLC on PFS and OS were independent of high risk IgH translocations t(4:14) and t(14:16).
<table>
<tr><th></th><th colspan="2">PFS</th><th colspan="2">OS</th></tr>
<tr><th>FLC</th><th>HR (95% CI)</th><th>p</th><th>HR (95% CI)</th><th>p</th></tr>
<tr><td>FLC ratio
inv/uninv > 277
vs
inv/uninv ≤ 277</td><td>1.48
(1.14, 1.91)</td><td>0.0028</td><td>2.09
(1.53, 2.84)</td><td>0.0023</td></tr>
<tr><td>FLC difference
inv/uninv > 185
vs
inv/uninv ≤ 185</td><td>1.36
(1.03, 1.79)</td><td>0.032</td><td>1.49
(1.15, 1.95)</td><td>0.003</td></tr>
</table>
</td>
<td>Same cohort as Dispenzieri et al., 2008b</td>
</tr>
</table>

<table>
<tr>
<td>Larsen et al., 2013

USA</td>
<td>586 smoldering myeloma patients
(seen at Mayo clinic 1970-2010)

319 Male
267 Female

Median age: 64 years
(range 27-91)

Median follow-up: 52 months</td>
<td>Serum free light chains

freelite

baseline serum obtained within 30 days of diagnosis

If κ/λ ratio > 1.65, κ chain = involved chain
If κ/λ ratio < 1.65, λ chain = involved chain
Involved/uninvolved ratio with the monoclonal light chain in the numerator.
Absolute difference between involved and uninvolved light chain was also determined.</td>
<td>Serum involved/uninvolved FLC ratio ≥ 100 was found to be a predictor of imminent progression in SMM

<table>
<tr><th>FLC ratio</th><th>n</th><th>Median time to progression)</th><th>progression to MM within 24 months</th></tr>
<tr><td>≥100</td><td>90</td><td>15 months</td><td>72%</td></tr>
<tr><td><100</td><td>496</td><td>55 months</td><td>28%</td></tr>
<tr><td></td><td></td><td>P<0.0001</td><td>RR 2.6 (1.8-3.6)</td></tr>
</table>

Multivariate analysis for TTP incorporating the FLC ratio into risk categories based on bone marrow plasmacytosis and/or serum M spike.
Independently prognostic:
Bone marrow plasma cell % (HR 3.24, p=0.0004)
FLC ratio ≥ 100 (HR 3.23, p<0.0001)
Serum M-spike (HR 3.16, p=0.0013)</td>
<td>Update on Dispenzieri et al., 2008 cohort and using more stringent criteria for an elevated FLC ratio.

Limitations:
Long patient eligibility spanning 1970 – 2010 may have introduced an increased number of confounders because of changes in imaging, physician practise styles and the less rigorous clinical documentation in previous decades.</td>
</tr>
<tr>
<td>Maltezas et al., 2013

Greece</td>
<td>305 myeloma patients (diagnosed and followed in 10 Hellenic centres from 1997 – 2010).

Induction treatment was conventional (VAD type or alkylating agents) in 55.7% and included new treatments in 44.3%.
After induction 24% of them underwent ASCT whilst 82.5% received new agents at any line.

171 Male
134 Female

Median age: 68 years
(range 36-92)

Median follow-up: 38.7 months (0.3 – 160.2 months)</td>
<td>Serum free light chains

freelite

baseline serum</td>
<td>Median 27.04 and 47.97 for kappa-MM and lambda-MM patients, respectively.

Disease specific survival in patients with high FLCR (above median) according to treatment received:
<table>
<tr><th></th><th>Median 5yr disease specific survival</th></tr>
<tr><td>conventional treatment</td><td>7%</td></tr>
<tr><td>novel agents at any line</td><td>45%</td></tr>
<tr><td>Novel agents frontline</td><td>52%</td></tr>
</table></td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td>Snozek et al., 2008

USA</td>
<td>790 myeloma patients (seen at Mayo clinic 1985-1998)

Treatment: various

Median age: 66 years (range 20-92)

Median follow-up: 8.4 years</td>
<td>Serum free light chains

freelite

baseline serum obtained within 30 days of diagnosis</td>
<td>An abnormal FLC ratio (κ/λ) was associated with a worse OS.

<table>
<tr><th>FLC ratio</th><th>n</th><th>Median OS (mo)</th><th>5yr survival</th></tr>
<tr><td>0.03 - 32</td><td>311</td><td>39</td><td>34.5%</td></tr>
<tr><td><0.03 or >32</td><td>479</td><td>30</td><td>21.3%</td></tr>
</table>

When combined with ISS in a multivariate model an abnormal FLC ratio added significantly (p=0.029) to the prognostic capacity of ISS.</td>
<td>-</td>
</tr>
<tr>
<td>Van Rhee et al., 2007

USA</td>
<td>303 myeloma patients

Combination therapy with VTD-PACE as induction before and consolidation therapy after melphalan based high dose therapies.

Median follow-up: 21 months (range: 5.1 – 35.6)</td>
<td>Serum free light chains

baseline serum before initiation of therapy</td>
<td>
<table>
<tr><th>SFLC at baseline</th><th>% of n-CR</th><th>2yr OS</th><th>2yr EFS</th></tr>
<tr><td>>75mg/dL</td><td>37%</td><td>76%</td><td>73%</td></tr>
<tr><td><75mg/dL</td><td>20%</td><td>91%</td><td>90%</td></tr>
<tr><td></td><td>P=0.002</td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

Univariately significant baseline factors associated with inferior EFS and OS included advanced age of 65 years or older, presence of CA, advanced ISS stage as well as serum elevations of B2M, CRP, LDH, creatinine and SFLC.
Independently prognostic for EFS:
Baseline SFLC higher than 75 mg/dL, top tertile (HR 2.43, p=0.016)
LDH of 190 U/L (HR 2.59, p=0.009)
CAs (HR 2.43, p=0.013)
Independently prognostic for OS:
Baseline SFLC higher than 75 mg/dL, top tertile (HR 2.40, p=0.008)
LDH of 190 U/L (HR 2.10, p=0.023)
CAs (HR 2.21, p=0.012)

The frequency of near-complete response to induction therapy was higher when baseline SFLC levels exceeded 75 mg/dl.
Independently significant in multivariate analysis.</td>
<td>High baseline SFLC levels conferred inferior EFS and OS despite being associated with higher nCR rate. (more rapid cell kill initially but rapid disease regrowth between treatment cycles – early relapse and death).</td>
</tr>
</table>

<table>
<tr>
<td>Xu et al., 2013

China</td>
<td>122 myeloma patients

Treatment: conventional chemotherapy (n=72) or bortezomib (n=49)

80 male
42 female

Median age: 58 years
(range 30-83)

Median follow-up: 21 months</td>
<td>Serum free light chains

freelite

serum obtained prior to initiation of therapy</td>
<td>Low SFLC: SFLC-κ < 180 mg/L or SFLC-λ <592.5mg/L
High SFLC : SFLC-κ ≥ 180 mg/L or SFLC-λ ≥ 592.5mg/L
<table>
<tr><th>SFLC</th><th>n</th><th>Median OS</th><th>1yr OS</th><th>3yr OS</th></tr>
<tr><td>low</td><td>55</td><td>Not reached</td><td>94.3%</td><td>66.2%</td></tr>
<tr><td>high</td><td>66</td><td>23 months</td><td>70.1%</td><td>30.5%</td></tr>
<tr><td></td><td></td><td>P=0.001</td><td></td><td></td></tr>
</table>
Low SFLC ratio: 0.04 - 25
High SFLC ratio: < 0.04 or >25
<table>
<tr><th>SFLC ratio</th><th>n</th><th>Median OS</th><th>1yr OS</th><th>3yr OS</th></tr>
<tr><td>low</td><td>62</td><td>Not reached</td><td>91.8%</td><td>61.8%</td></tr>
<tr><td>high</td><td>59</td><td>21 months</td><td>71.7%</td><td>29.2%</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td></td><td></td></tr>
</table>
<table>
<tr><th>SFLC ratio</th><th>Median OS with conventional chemotherapy</th><th>Median OS With bortezomib</th></tr>
<tr><td>low</td><td>44 months</td><td>56 months</td></tr>
<tr><td>high</td><td>32 months</td><td>39 months</td></tr>
<tr><td></td><td>P=0.001</td><td>P=0.005</td></tr>
</table>
In the multivariate model both SFLC and the ratio had significant OS prognostic capacity (p<0.001 and p=0.002).</td>
<td>-</td>
</tr>
</table>

1

2 ***(d) Heavy/light chain ratio***

Study	Population	Specialist diagnostic investigation	Results	Additional comments
Bradwell et al., 2013 UK	339 myeloma patients (FLC-only disease excluded) 245 IgG 94 IgA Patients treated with bortezomib and dexamethasone or VAD as induction therapy plus or minus DCEP, followed by high-dose melphalan with a	Heavy/light chain ratio Measured in serum samples taken at initial clinical presentation by hevylite.	Multivariate analysis for PFS included: Del:13 T(4:14) Del:17p B2M>5.5MG/L B2m>3.5mg/l Albumin<35g/l FLC tertiles Monoclonal Ig tertiles HLC ratios of <200 to >0.01 vs more extreme values Independently prognostic:	-

	stem cell autograft as first line therapy.		B2M>3.3 (p=0.045) HLC ratio (p=0.001) A staging system using B2M and extreme HLC ratios had greater prognostic value than the widely used ISS staging system. Stage 1: normal values Stage 2: either B2M>3.5mg/l or extreme HLC ratios (<0.01 or >200) Stage 3: B2M>3.5mg/l and extreme HLC ratios (<0.01 or >200) Using this model stage 3 was more significantly associated with shorter PFS than ISS stage 3 (HR 1.7; p=0.00002 vs HR 1.3, p=0.017).	
Koulieris et al., 2012 Greece	103 myeloma patients 78 IgG 25 IgA 57 Male 46 Female Median age: 67 years Symptomatic patients(n=77) received treatment with conventional modalities. Asymptomatic patients (n=26) were followed. Median follow-up was 32.6 months.	Heavy/light chain ratio Measured in serum samples taken at initial clinical presentation by hevylite.	High HLCR was defined as any value above median Median HLCR in IgG was 21.47 Median HLCR in IgM was 72.42 High HLCR correlated with time to treatment (p<0.001) and shorter survival (p=0.022). Multivariate analysis for OS included: Durie-salmon stage ISS stage B2M>3.5mg/l Hb ≤10g/L Platelet counts ≤140 x10[9]/L Albumin<3.5g/L Cr >2mg/dL BM plasma infiltration SFLCR above median High HLCR values Independently prognostic: Platelet count B2M HLC R	-

<table>
<tr>
<td>Ludwig et al., 2013

Austria</td>
<td>156 myeloma patients
Started on first line therapy (various)

100 IgG
56 IgA

82 Male
74 Female

Median age: 66 years (range: 32-94)

Median follow-up: 46.1 months (range 0.5 – 157.8)</td>
<td>Heavy/light chain ratio

Measured in serum samples taken at initial clinical presentation by hevylite.</td>
<td>
<table>
<tr><th></th><th>n</th><th>Median OS</th><th>5 yr survival</th></tr>
<tr><td>Abnormal HLCR (0.022-45)</td><td>84</td><td>Not reached</td><td>58.9%</td></tr>
<tr><td>Highly abnormal HLCR (<0.022 or >45)</td><td>72</td><td>40.5 months</td><td>33.4%</td></tr>
<tr><td></td><td></td><td>p=0.016</td><td>p=0.01</td></tr>
</table>
Multivariate analysis for OS included:
B2M>5.5mg/l
B2M>3.5mg/l
HLC ratio <0.02, >40
FLC ratio <0.03, >32
Age >75 yrs
Albumin>35g/l
LDH >248 UI/l

Independently prognostic:
Highly abnormal HLC ratio (<0.02, >40) (HR:1.94, CI: 1.1-3.3, p=0.016)
Highly abnormal B2M (>5.5mg/l) (HR:2.01, CI: 1.1-3.6, p=0.016)
</td>
<td>-</td>
</tr>
</table>

1

2 ***(e) FISH***

<table>
<tr><th>Study</th><th>Population</th><th>Specialist diagnostic investigation</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>An et al., 2013

China</td>
<td>253 myeloma patients
According to their request patients were assigned to either thalidomide (n=106) or bortezomib based treatment (n=147).

Median age: 57.5 years (range 26-83)

Median follow-up: 3 years</td>
<td>Interphase FISH

t(11:14)</td>
<td>t(11:14) positive = 60
t(11:14) negative = 193

Patients receiving thalidomide-based treatment:
<table>
<tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr>
<tr><td>t(11:14) positive</td><td>?</td><td>30.0 months</td><td>23.0 months</td></tr>
<tr><td>t(11:14) negative</td><td>?</td><td>21.0 months</td><td>18.0 months</td></tr>
<tr><td></td><td></td><td>P=0.9</td><td>p=0.8</td></tr>
</table>
Patients receiving bortezomib-based treatment:
<table>
<tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr>
<tr><td>t(11:14)</td><td>?</td><td>54.0 months</td><td>28.7 months</td></tr>
</table>
</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>positive</td><td></td><td></td><td></td></tr>
<tr><td>t(11:14) negative</td><td>?</td><td>36.0 months</td><td>32.5 months</td></tr>
<tr><td></td><td></td><td>P=0.6</td><td>p=0.7</td></tr>
</table>

Patients with t(11:14): no statistically significant difference in outcome depending on treatment with thalidomide or bortezomib.
</td>
<td></td>
</tr>
<tr>
<td>An et al., 2014

China</td>
<td>290 myeloma patients

According to their request patients were assigned to either thalidomide (n=120) or bortezomib based treatment (n=135).
35 lost to follow-up.

Median age: 57 years (range 26-83)

Median follow-up: 36 months</td>
<td>Interphase FISH

1q21</td>
<td>
142 patients had 1q21 gains
148 patients did not have 1q21 gains

Patients receiving thalidomide-based treatment:
<table>
<tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr>
<tr><td>1q21 gains</td><td>?</td><td>22 months</td><td>20 months</td></tr>
<tr><td>Without 1q21 gains</td><td>?</td><td>30 months</td><td>22.4 months</td></tr>
<tr><td></td><td></td><td>P=0.355</td><td>P=0.625</td></tr>
</table>
Gains of 1q21 had no impact on survival in patients receiving thalidomide-based treatment

Patients receiving bortezomib-based treatment:
<table>
<tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr>
<tr><td>1q21 gains</td><td>?</td><td>24 months</td><td>13.5 months</td></tr>
<tr><td>Without 1q21 gains</td><td>?</td><td>54 months</td><td>43 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>
Gains of 1q21 was an independent prognostic factor for PFS (HR 3.8, p<0.001) and OS (HR 3.2, p=0.002) in the multivariate model.

Survival of patients without 1q21 gains was extended with bortezomib compared to thalidomide treatment. But there was no difference in patients with 1q21 gains treated with either chemotherapy.

Patients with 3 copies of 1q21 had comparable survival with patients with more than 3 copies.
</td>
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</table>

<table>
<tr>
<td>Avet-Loiseau et al., 2007

France</td>
<td>1064 myeloma patients enrolled in the IFM99 trials (VAD followed by double intensive therapy)

Patients all younger than 66 years

Median follow up: 41 months</td>
<td>iFISH on bone marrow samples

del13
t(11:14)
t(4:14)
hyperdiploidy
MYC translocations
del(17p)</td>
<td>Chromosomal changes were observed in 90% of the patients.
del13 48%
t(11:14) 21%
t(4:14) 14%
hyperdiploidy 39%
MYC translocations 13%
del(17p) 11%

Univariate analysis revealed that del(13), t(4:14), nonhyperdiploidy and del(17p) negatively impacted both EFS and OS.
MYC translocations and t(11:14) did not influence prognosis.

<table>
<tr><th>Genomic aberration</th><th>Impact on EFS, mth* (P)</th><th>Impact on OS†(P)</th></tr>
<tr><td>del(13)</td><td>29 vs 41 (<0.001)</td><td>68% vs 83% (<0.001)</td></tr>
<tr><td>t(11;14)(q13;q32)</td><td>35 vs 34 (0.2)</td><td>80% vs 74% (0.28)</td></tr>
<tr><td>t(4;14)(p16;q32)</td><td>20.6 vs 36.5 (<0.001)</td><td>41.3 mths vs 79% (<0.001)</td></tr>
<tr><td>Hyperdiploidy</td><td>37 vs 33 (0.02)</td><td>82% vs 70% (0.006)</td></tr>
<tr><td>MYC translocation</td><td>35 vs 37 (0.94)</td><td>72% vs 78% (0.50)</td></tr>
<tr><td>del(17p)</td><td>15 vs 35 (<0.001)</td><td>22 mths vs 75% (<0.001)</td></tr>
</table>
* Median EFS for patients presenting the chromosomal abnormality versus that of those who did not present the genomic aberration.
†Median OS for patients presenting the chromosomal abnormality versus that of those who did not present the genomic aberration. When the median was not attained, the percentage alive at the time of median follow-up was reported.

In multivariate analysis only t(4:14) and del(17p) retained prognostic value for EFS and OS.
<table>
<tr><th></th><th>HR for EFS (95%CI)</th><th>p</th><th>HR for OS (95%CI)</th><th>p</th></tr>
<tr><td>del(17p) more than 60%</td><td>3.29 (2.23-4.87)</td><td><0.001</td><td>3.93 (2.54-6.08)</td><td><0.001</td></tr>
<tr><td>t(4:14)</td><td>2.79 (2.05-3.79)</td><td><0.001</td><td>2.78 (1.90-4.06)</td><td><0.001</td></tr>
</table>
</td>
<td>-</td>
</tr>
<tr>
<td>Avet-Loiseau et al., 2010

France</td>
<td>Cohort 1:
507 newly diagnosed myeloma patients
Received Vel/Dex induction.
Patients all younger than 65.
Median follow-up 24 months.

Cohort 2:
512 newly diagnosed</td>
<td>FISH

t(4;14)
del(17p)</td>
<td>Cohort 1 (Vel/dex)

<table>
<tr><th></th><th>n</th><th>relapse</th><th>4 yr OS</th></tr>
<tr><td>T(4;14)</td><td>106</td><td>41%</td><td>63%</td></tr>
<tr><td>No t(4;14)</td><td>401</td><td>36%</td><td>73%</td></tr>
<tr><td></td><td></td><td>P=0.0178</td><td>P=0.002</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>Median EFS</th><th>4 yr OS</th></tr>
<tr><td>Del(17p)</td><td>54</td><td>14 months</td><td>79%</td></tr>
<tr><td>No del(17p)</td><td>453</td><td>36 months</td><td>50%</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>
</td>
<td>-</td>
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</table>

<table>
<tr>
<td></td>
<td>myeloma patients.
Received VAD induction.</td>
<td></td>
<td>Both t(4;14) and del(17p) were prognostic even in context of bortezomib treatment.

Bortezomib significantly improves prognosis of patients with t(4;14) compared with patients treated with VAD.

t(4;14) patients
<table>
<tr><th></th><th>n</th><th>Median EFS</th><th>4yr OS</th></tr>
<tr><td>Vel/Dex</td><td>106</td><td>28 months</td><td>63%</td></tr>
<tr><td>VAD</td><td>98</td><td>16 months</td><td>32%</td></tr>
<tr><td></td><td></td><td>p<0.001</td><td>p<0.001</td></tr>
</table>
No improvement with Vel/Dex was observed for patients with del(17p).</td>
<td></td>
</tr>
<tr>
<td>Avet-Loiseau et al., 2011

France</td>
<td>1003 myeloma patients

Patients under 65 years (n=735)were treated in the IFM 99-02 or 99-04 trials.

Patients 65 years or older (n=233) were treated in the IFM 99-06 trial.</td>
<td>FISH on bone marrow samples

t(4:14)
del(17p)
del13
t(14:16)</td>
<td>32 patients had t(14:16).
t(14:16) not prognostic – no difference in survival between patients with and without the translocation.

Multivariate analysis
Independently prognostic for OS:
t(4:14) (HR 2.56, p<0.001)
del(17p) (HR 2.47, p<0.001)
del(13) (HR 1.36, p=0.03)</td>
<td>Published as brief report so limited study details.</td>
</tr>
<tr>
<td>Avet-Loiseau et al., 2012

France</td>
<td>520 myeloma patients

IFM (Intergroupe Francophone du Myelome) 99-02 or 99-04 trials (VAD & ASCT)

Patients all younger than 66 years

Median follow-up: 90.5 months</td>
<td>FISH on bone marrow samples

t(4:14)
del(17p)
t(11:14)
t(14:16)
del(13)
1q gains</td>
<td>t(4:14) 11%
del(17p) 5.4%
t(11:14) 19%
t(14:16) 2.7%
del(13) 44%
1q gains 33%

Multivariate analysis
Independently prognostic for PFS:
t(4:14) (HR 2.45, p<0.001)
del(17p) (HR 2.86, p<0.001)
del(13) (HR 1.46, p=0.004)

Multivariate analysis
Independently prognostic for OS:</td>
<td>.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(4:14) (HR 3.04, p<0.001)
del(17p) (HR 3.04, p<0.001)
1q gain (HR 1.58, p=0.006)

Patients with no high risk factors:
age <55, B2 microglobulin < 5.5 mg/L and absence of t(4:14), del(17p) and 1q gain, (20% of patients) = 8 year survival of 75%.</td>
<td></td>
</tr>
<tr>
<td>Avet-Loiseau et al., 2013a

International retrospective analysis</td>
<td>IMWG database of 12,137 patients treated worldwide for myeloma at diagnosis. 5387 had analyses by FISH. Comprehensive analyses used 2642 patients with sufficient iFISH data available.

59% received an intensive approach based on single or double high-dose melphalan courses, and 41% received more conventional treatment.

Median age: 60 years (range 23-93)</td>
<td>Interphase FISH was performed on sorted or immunologically recognised plasma cells.

Most of the iFISH studies were focussed on del(13), t(4:14), del(17p), t(11:14) and t(14:16).</td>
<td>del(13) 45%
t(4:14) 12.8%
del(17p) 13.6%
t(11:14) 20.5%
t(14:16) 2.9%

t(11:14) was prognostically neutral.

<table>
<tr><th></th><th>n</th><th>4 yr PFS</th><th>4yr OS</th></tr>
<tr><td>Del(13)</td><td>1189</td><td>26%</td><td>52%</td></tr>
<tr><td>Del(13) negative</td><td>1453</td><td>39%</td><td>66%</td></tr>
<tr><td></td><td></td><td>p<0.0001</td><td>p<0.0001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>4 yr PFS</th><th>4yr OS</th></tr>
<tr><td>t(4:14)</td><td>338</td><td>11%</td><td>35%</td></tr>
<tr><td>t(4:14) negative</td><td>2304</td><td>32%</td><td>60%</td></tr>
<tr><td></td><td></td><td>p<0.0001</td><td>p<0.0001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>4 yr PFS</th><th>4yr OS</th></tr>
<tr><td>Del(17p)</td><td>360</td><td>18%</td><td>46%</td></tr>
<tr><td>Del(17p) negative</td><td>2282</td><td>36%</td><td>65%</td></tr>
<tr><td></td><td></td><td>p<0.0001</td><td>p<0.0001</td></tr>
</table>

Because del(13) has been previously related to t(4;14) and del(17p), and because its prognostic value has been shown to be mainly related to these latter abnormalities, outcomes of patients with del(13), but lacking both t(4;14) and del(17p) was assessed. These del(13) patients displayed a poorer prognosis than patients lacking del(13), but with a lower impact (4-year PFS estimates of 28% versus 36%, and 4-year OS estimates of 59% and 65%, respectively). Thus, the final analyses incorporated ISS stages and t(4;14) and del(17p) only as the dominant genetic features.

ISS-iFISH model
Group 1 (51% of patients):
ISS stage I or II with neither t(4:14) nor del(17p)</td>
<td>None of the patients received bortezomib or lenalidomide as frontline therapy.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 (29% of patients):
ISS stage III with neither t(4:14) nor del(17p) OR ISS stage I with either t(4:14) or del(17p)
Group 3 (20% of patients):
ISS stage II or III with either t(4:14) or del(17p)

<table>
<tr><th></th><th>n</th><th>4 yr PFS</th><th>4yr OS</th></tr>
<tr><td>Group 1</td><td>1344</td><td>39%</td><td>71%</td></tr>
<tr><td>Group 2</td><td>756</td><td>20%</td><td>45%</td></tr>
<tr><td>Group 3</td><td>537</td><td>11%</td><td>33%</td></tr>
<tr><td></td><td></td><td>P value:
1 v 2<0.0001
2 v 3=0.08
1 v 3<0.0001</td><td>P value:
1 v 2<0.0001
2 v 3=0.0001
1 v 3<0.0001</td></tr>
</table>

The ISS-iFISH model was further assessed by stratification by age (<65 years: ≥ 65 years) and with or without the use of HDTx.

Age
Best outcome is for patients under 65 years in group 1 (4yr OS 75%)
Worst outcome is for patients > 65 years in group 3 (4yr OS 24%)

HDTx
Best outcome is for patients who received HDTx in group 1 (4yr OS 77%)
Worst outcome is for patients without HDTx in group 3 (4yr OS 18%)</td>
<td></td>
</tr>
<tr>
<td>Avet-Loiseau et al., 2013b

France</td>
<td>1890 newly diagnosed older myeloma patients (all patients >65 years)

Median age: 72 years (range 66-94)

1095 patients had updated data on treatment modalities and survival.
Treatment:
434 MPT
246 MP
168 high dose melphalan
118 lenalidomide plus dex
84 MPV
45 intermediate dose melphalan</td>
<td>FISH

del(13)
t(4;14)
del(17p)</td>
<td>Multivariate analysis
Independently prognostic for PFS:
del(13) (HR 1.31, p=0.02)
t(4;14) (HR 2.03, p<0.001)
del(17p) (HR 1.96, p<0.001)

Independently prognostic for OS:
t(4;14) (HR 1.89, p<0.001)
del(17p) (HR 2.14, p<0.001)

Conclusion: t(4;14) and del(17p) are prognostic in elderly patients.</td>
<td></td>
</tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bang et al., 2006

Korea</td><td>130 myeloma patients

85 male
45 female

Median age: 60 years
(range 32 – 80)</td><td>Interphase FISH

13q
1q
IGH
P53
MLL
P16
CEP7
CEP11
CEP12</td><td>t(11:14) was the only genetic abnormality prognostic for OS in univariate analysis (p=0.0147).
But lost significance in multivariate analysis.</td><td>-</td></tr>
<tr><td>Boyd et al., 2012

UK</td><td>1140 myeloma patients
in MRC myeloma IX trial</td><td>FISH
on bone marrow samples</td><td>FISH failure rate was 6% of analyzable bone marrow specimens providing results for 1069 patients

<table>
<tr><th>FISH lesion</th><th>Lesion present Median PS (months)</th><th>Lesion absent Median PFS (months)</th><th>p</th><th>Lesion present Median OS (months)</th><th>Lesion absent Median OS (months)</th><th>p</th></tr>
<tr><td>hyperdiploidy</td><td>18.9</td><td>17.8</td><td>0.110</td><td>49.7</td><td>43.7</td><td>0.150</td></tr>
<tr><td>t(4;14)</td><td>13.1</td><td>19.3</td><td><0.001</td><td>27.7</td><td>50.9</td><td><0.001</td></tr>
<tr><td>t(6;14)</td><td>27.2</td><td>18.2</td><td>0.361</td><td>Not reached</td><td>47.7</td><td>0.426</td></tr>
<tr><td>t(11;14)</td><td>21.3</td><td>17.5</td><td>0.292</td><td>51.6</td><td>46.9</td><td>0.209</td></tr>
<tr><td>t(14;16)</td><td>13.6</td><td>18.6</td><td>0.028</td><td>32.9</td><td>48.3</td><td>0.025</td></tr>
<tr><td>t(14;20)</td><td>10.2</td><td>18.5</td><td>0.152</td><td>16.9</td><td>48.3</td><td><0.001</td></tr>
<tr><td>Del(1p)</td><td>19.0</td><td>18.7</td><td>0.701</td><td>36.4</td><td>47.7</td><td>0.216</td></tr>
<tr><td>+1q</td><td>13.8</td><td>22.1</td><td><0.001</td><td>31.0</td><td>54.8</td><td><0.001</td></tr>
<tr><td>Del(13q)</td><td>16.3</td><td>20.1</td><td>0.002</td><td>40.9</td><td>52.1</td><td>0.005</td></tr>
<tr><td>Del(16q)</td><td>19.9</td><td>18.2</td><td>0.200</td><td>43.7</td><td>48.3</td><td>0.462</td></tr>
<tr><td>Del(17p)</td><td>14.7</td><td>18.3</td><td>0.002</td><td>26.7</td><td>48.5</td><td><0.001</td></tr>
<tr><td>Del(22q)</td><td>18.7</td><td>18.0</td><td>0.265</td><td>53.2</td><td>45.8</td><td>0.653</td></tr>
</table>

Multivariate analysis:
Shorter PFS and OS:
+1q21
(HR 1.46, p<0.001 for PFS; HR 1.53, p=0.001 for OS)
Del(17p13)
(HR 1.41, p=0.022 for PFS; HR 1.53, p=0.02 for OS)
Adverse IGH translocations (t(4:14), t(14:15) and t(14:20))
(HR 1.65, p<0.001 for PFS; HR 1.54, p=0.003 for OS)

Low risk group: absence of adverse genetic lesions</td><td>-</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate risk group: one adverse lesion
High risk group: >1 adverse lesion

<table><tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr><tr><td>Low risk</td><td>451</td><td>60.6 months</td><td>23.5 months</td></tr><tr><td>Intermediate risk</td><td>289</td><td>41.9 months</td><td>17.8 months</td></tr><tr><td>High risk</td><td>129</td><td>21.7</td><td>11.7 months</td></tr><tr><td></td><td></td><td>P<0.0001</td><td>P<0.0001</td></tr></table>
Genetic risk was independent of ISS.

Combining FISH+ISS:

favourable risk group
ISS I or II and no adverse genetic lesions or ISS I and one adverse lesion
median OS 67.8 months

intermediate risk group
ISS I and >1 adverse lesion, ISS II and one adverse lesion and ISS III with 0–1 adverse lesions,
median OS of 41.3 months

ultra-high-risk disease
ISS II or III in the presence of >1 adverse lesion
median OS of 19.4 months</td>
<td></td>
</tr>
<tr>
<td>Caltagirone et al., 2014

Italy</td>
<td>376 elderly myeloma patients
From 61 centres

GIMEMA-MM-03-05 trial
Patients randomised to receive VMP or VMPT

Median follow up: 54 months
(1-80 months)</td>
<td>i-FISH

Del(13)
Del(17p)
Del(1p)
Gain(1q)
t(11;14)
t(4;14)
t(14;16)</td>
<td>The amount of BMPC allowed evaluation of chr1 abnormalities in 278/376 patients

Abnormal chr1 (del1p and/or gain1q) was an adverse prognostic factor for OS
(HR 4.01, p=0.047)

Del(13), del(17p), IGH translocations and high-risk chromosomal abnormalities did not show a significant impact on survival.</td>
<td>-</td>
</tr>
<tr>
<td>Chang et al., 2005a

Toronto</td>
<td>126 myeloma patients treated with high-dose chemotherapy and ASCT

76 Male</td>
<td>FISH combined with cytoplasmic light chain detection (cIg-FISH) on BM aspirates</td>
<td><table><tr><th></th><th>n</th><th>Median OS</th><th>RR</th><th>p</th><th>Median PFS</th><th>RR</th><th>p</th></tr><tr><td>p53 del</td><td>10</td><td>14.7 months</td><td>4.5</td><td>0.0025</td><td>7.9 months</td><td>2.5</td><td>0.0248</td></tr></table></td>
<td></td>
</tr>
</table>

	47 Female Median age: 53 years (range 31-71)	t(4:14) t(11:14) del(13q) del(p53)		

t(4:14)	15	18.3 months	4.8	0.0005	9.9 months	3.4	0.0019
t(11:14)	16	37.2 months	1.5	0.5	25.2 months	1.1	0.8
13q del	39	34.4 months	2.3	0.0498	20.2 months	2.1	0.0178
none	43	Not reached	0.99		32.1 months	0.99	

Prognostic: t(4:14), del(13q) and del(p53)
Not prognostic: t(11:14)

Low risk (n=55): no genetic abnormalities or only t(11:14)
Intermediate risk (n=34): any one of the genetic abnormalities other than t(11:14)
High risk (n=15): any two or more of the genetic abnormalities other than t(11:14)

	n	**Median OS**	**Median PFS**
Low risk	55	Not reached	32.1 months
Intermediate risk	34	46 months	20 months
High risk	15	18 months	10 months
		P<0.0001	p=0.0009

High risk patients do not benefit from ASCT.

Multivariate analysis including all 4 genetic risk factors confirmed that t(4:14) and p53 deletions were independent adverse factors for OS and PFS.

Chang et al., 2005b Toronto	105 myeloma patients treated with high-dose therapy and ASCT 62 Male 42 Female Median age: 53 years (range 31-71) Median post transplant follow-up: 20 months	FISH combined with cytoplasmic light chain detection (clg-FISH) on BM aspirates del(p53)		

	n	**ORR**	**Median OS**	**Median PFS**
P53 deletions	10	67%	14.7 months	7.9 months
No p53 deletions	95	71%	48.1 months	25.7 months
			P=0.0008	P=0.0324

Multivariate analysis confirmed that p53 deletions were independently prognostic for PFS (p=0.0009) and OS (p=0.0002).

<table>
<tr>
<td>Chang et al., 2010

Toronto</td>
<td>203 myeloma patients treated with high-dose therapy and ASCT

118 Male
85 Female

Median age: 55 years (range 31-73)

Median post transplant follow-up: 36 months</td>
<td>FISH combined with cytoplasmic light chain detection (cIg-FISH) on BM aspirates

del(1p21)
t(4:14)
t(11:14)
del(13q)
del(p53)
1q21amp</td>
<td>del(1p21) 18%
t(4:14) 11%
t(11:14) 14.5%
del(13q) 47%
del(p53) 7.5%
1q21amp 38%

<table>
<tr><th></th><th>n</th><th>Median OS</th><th>Median PFS</th></tr>
<tr><td>1p21 deletions</td><td>36</td><td>39.4 months</td><td>14.2 months</td></tr>
<tr><td>No 1p21 deletions</td><td>167</td><td>82.3 months</td><td>25.4 months</td></tr>
<tr><td></td><td></td><td>P=0.001</td><td>P<0.001</td></tr>
</table>

Multivariate analysis
Independently prognostic for OS and PFS:
Del(1q21) (HR 2.5, p=0.013 for OS; HR 2.33, p=0.003 for PFS)
del(p53) (HR 4.8, p<0.001 for OS; HR 2.64, p=0.03 for PFS)</td>
<td>-</td>
</tr>
<tr>
<td>Chng et al., 2010

USA</td>
<td>127 myeloma patients Treatment with melphalan-based high-dose therapy.</td>
<td>cIg-FISH on BM samples

1p31-32 loss

20q12.3-12.1 loss</td>
<td>
<table>
<tr><th></th><th>n</th><th>CR</th><th>Median CR duration</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>1p31-32 loss</td><td>24</td><td>7 (29%)</td><td>14.4 months</td><td>12.8 months</td><td>24.5 months</td></tr>
<tr><td>No 1p31-32 loss</td><td>98</td><td>31 (32%)</td><td>32.2 months</td><td>16.3 months</td><td>40 months</td></tr>
<tr><td></td><td></td><td></td><td>P=0.37</td><td>P=0.28</td><td>P=0.01</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>CR</th><th>Median CR duration</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>20p12 loss</td><td>15</td><td>5 (33%)</td><td>19.9 months</td><td>10.4 months</td><td>26.3 months</td></tr>
<tr><td>No 20p12 loss</td><td>111</td><td>37 (33%)</td><td>30 months</td><td>16.9 months</td><td>40 months</td></tr>
<tr><td></td><td></td><td></td><td>P=0.35</td><td>P=0.1</td><td>P=0.06</td></tr>
</table>

Multivariate analysis:
1p31-32 was independently prognostic for OS</td>
<td>-</td>
</tr>
<tr>
<td>Fonseca et al., 2006

USA</td>
<td>159 myeloma patients

treated with high-dose therapy and ASCT</td>
<td>cIg-FISH on BM

1q21</td>
<td>1q21 gain was not prognostic for survival

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
</table>
</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>106 Male
53 Female</td>
<td></td>
<td>
<table>
<tr><td>1p21 gain</td><td>46</td><td>29.9 months</td></tr>
<tr><td>No 1p21 gain</td><td>113</td><td>38 months</td></tr>
<tr><td></td><td></td><td>P=0.12</td></tr>
</table>
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<td></td>
</tr>
<tr>
<td>Grzasko et al., 2013

Poland</td>
<td>104 myeloma patients
First-line therapy:
CTD 63.5%
MPT 20.2%
VAD 9.6%
VMBCP 6.7%
ASCT: 33.7%

48 Male
56 Female

Median age: 59 years (range 36-85)

Median follow-up: 16.5 months</td>
<td>cIg-FISH on BM aspirates

amp(1q21)
Del(13q14)
Del(17p13)
t(4:14) (p16;q32)</td>
<td>
<table>
<tr><th>Genetic abnormality</th><th>n</th></tr>
<tr><td>Hyperdiploid myeloma (H-MM)</td><td>51</td></tr>
<tr><td>Non-hyperdiploid myeloma (NH-MM)</td><td>53</td></tr>
<tr><td>amp(1q21)</td><td>49</td></tr>
<tr><td>del(13q14)</td><td>47</td></tr>
<tr><td>t(4:14)(p16:q32)</td><td>19</td></tr>
<tr><td>del(17p13)</td><td>16</td></tr>
<tr><td>amp(1q21) + del(13q14)</td><td>26</td></tr>
<tr><td>amp(1q21) + t(4:14)(p16:q32)</td><td>15</td></tr>
<tr><td>amp(1q21) + del(17p13)</td><td>7</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th><th>ORR</th><th>CR</th></tr>
<tr><td>Amp(1q21)</td><td>49</td><td>10.3 months</td><td>26.6 months</td><td>55.1%</td><td>4.1%</td></tr>
<tr><td>No amp(1q21)</td><td>55</td><td>33.9 months</td><td>62.4 months</td><td>74.5%</td><td>18.2%</td></tr>
<tr><td></td><td></td><td>P=0.002</td><td>P=0.018</td><td>P=0.025</td><td>P=0.024</td></tr>
</table>
<table>
<tr><th>FISH lesion</th><th>Without amp(1q21) Median PFS (months)</th><th>With amp(1q21) Median PFS (months)</th><th>p</th><th>Without amp(1q21) Median OS (months)</th><th>With amp(1q21) Median OS (months)</th><th>p</th></tr>
<tr><td>NH-MM</td><td>35.2</td><td>10.4</td><td>0.015</td><td>48.7</td><td>16.4</td><td>0.006</td></tr>
<tr><td>H-MM</td><td>Not reached</td><td>23.5</td><td>>0.05</td><td>Not reached</td><td>43.7</td><td>>0.05</td></tr>
</table>
Impact of additional genetic abnormalities in patients carrying amp(1q21)
<table>
<tr><th>FISH lesion</th><th>Lesion absent Median PFS (months)</th><th>Lesion present Median PFS (months)</th><th>p</th><th>Lesion absent Median OS (months)</th><th>Lesion present Median OS (months)</th><th>p</th></tr>
<tr><td>Del(13q14)</td><td>29</td><td>7.8</td><td>0.024</td><td>58.4</td><td>18.9</td><td>0.004</td></tr>
<tr><td>Del(17p13)</td><td>24.9</td><td>4.0</td><td>0.034</td><td>46.6</td><td>12.0</td><td>0.036</td></tr>
<tr><td>t(4:14) (p16;q32)</td><td>27.5</td><td>10.2</td><td>>0.05</td><td>43.8</td><td>27.5</td><td>>0.05</td></tr>
</table>
<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>Median OS</th></tr>
<tr><td>Complex genetic abnormalities (≥3)</td><td>12</td><td>6.9 months</td><td>15.3 months</td></tr>
<tr><td>No Complex genetic abnormalities</td><td>92</td><td>27.8 months</td><td>46.7 months</td></tr>
</table>
</td>
<td>Limitations:
Heterogeneous treatments.
Short follow up period.
Small sample size.</td>
</tr>
</table>

<table>
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<table>
<tr><td></td><td></td><td>P=0.003</td><td>P=0.049</td></tr>
</table>

Multivariate analysis
Independently prognostic for PFS and OS:
Amp(1q21)
Del(13q14)
Del(17p13)
</td>
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<tr>
<td>Gutierrez et al., 2007

Spain</td>
<td>260 elderly myeloma patients
GEM-2000 Spanish protocol (6 alternating cycles of VBCMP/VBAD followed by high dose therapy and ASCT)

143 Male
117 Female

Median age: 60 years (range 39-70)

Median follow-up 34 months</td>
<td>Interphase FISH

IGH translocations
RB deletions
P53 deletions</td>
<td>
Chromosomal abnormalities explored by FISH were identified in 151 patients.
IGH translocations n=95
RB deletions n=109
P53 deletions n=22

Only t(4:14) showed a significant influence on survival as a single aberration, with patients displaying a shorter OS as compared to normal patients (21 vs 54 months, p=0.008).

RB deletions as a sole abnormality did not influence survival.
<table>
<tr><th></th><th>n</th><th>Median OS (months)</th><th>p</th></tr>
<tr><td>Normal RB
RB deletion</td><td>151
109</td><td>51
32</td><td><0.0001</td></tr>
<tr><td>Normal patients
RB deletion as single abnormality</td><td>109
46</td><td>54
46</td><td>0.3</td></tr>
<tr><td>RB deletion without IGH translocations
RB deletion with t(4:14)</td><td>50
23</td><td>40
25</td><td>0.0002</td></tr>
<tr><td>RB deletion without IGH translocations
RB deletion with IGH translocations involving other unknown partners</td><td>50
13</td><td>40
26</td><td>0.02</td></tr>
<tr><td>RB deletion without IGH translocations
RB deletion with t(11:14)</td><td>50
17</td><td>40
49</td><td>0.2</td></tr>
<tr><td>RB and p53 normal
RB deletion plus P53 deletion</td><td>144
15</td><td>51
28</td><td><0.0001</td></tr>
</table>
Multivariate analysis:
Independently prognostics:
</td>
<td>-</td>
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</table>

<table>
<tr>
<td></td>
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<td></td>
<td>t(4:14) (p<0.001)
RB deletions associated with other abnormalities (p<0.001)</td>
<td></td>
</tr>
<tr>
<td>Hanamura et al., 2006

USA</td>
<td>479 newly diagnosed myeloma patients

Enrolled in UARK 98-026 protocol (total therapy 2) (melphalan-based tandem ASCT randomised to receive thalidomide or not)

274 Male
205 Female

Median follow-up: 53 months
(range 25-89)</td>
<td>Interphase FISH combined with cytoplasmic light chain detection (cIg-FISH) on BM aspirates

1q21amp</td>
<td>7 patients with 1 copy
267 patients with 2 copies
117 patients with 3 copies
88 patients with at least 4 copies

<table>
<tr><th></th><th>n</th><th>5yr EFS</th><th>5yr OS</th></tr>
<tr><td>Amp1q21 (≥ 3 copies)</td><td>205</td><td>38%</td><td>52%</td></tr>
<tr><td>without amp1q21 (≤ 2 copies)</td><td>274</td><td>62%</td><td>78%</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>5yr EFS</th><th>5yr OS</th></tr>
<tr><td>≤ 2 copies</td><td>274</td><td>62%</td><td>78%</td></tr>
<tr><td>3 copies</td><td>117</td><td>40%</td><td>53%</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>5yr EFS</th><th>5yr OS</th></tr>
<tr><td>3 copies</td><td>117</td><td>40%</td><td>53%</td></tr>
<tr><td>≥4 copies</td><td>88</td><td>38%</td><td>50%</td></tr>
<tr><td></td><td></td><td>P=0.344</td><td>P=0.453</td></tr>
</table>

Thalidomide improved 5yr EFS in patients lacking amp1q21 but not in those with amp1q21 (p=0.004) and had no effect on OS.

Patients lacking amp1q21
<table>
<tr><th></th><th>n</th><th>5yr EFS</th><th>5yr OS</th></tr>
<tr><td>without thal</td><td>150</td><td>54%</td><td>73%</td></tr>
<tr><td>Thal</td><td>124</td><td>73%</td><td>84%</td></tr>
<tr><td></td><td></td><td>P=0.004</td><td>P=0.226</td></tr>
</table>

Patients with amp1q21
<table>
<tr><th></th><th>n</th><th>5yr EFS</th><th>5yr OS</th></tr>
<tr><td>without thal</td><td>102</td><td>37%</td><td>49%</td></tr>
<tr><td>Thal</td><td>103</td><td>42%</td><td>55%</td></tr>
<tr><td></td><td></td><td>P=0.392</td><td>P=0.638</td></tr>
</table>
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<table>
<tr>
<td></td>
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<td></td>
<td>Multivariate analysis revealed am1q21 to be an independent poor prognostic factor for EFS (HR 1.86, p<0.001) and OS (HR 1.78, p=0.005).</td>
<td></td>
</tr>
<tr>
<td>He et al, 2015

China</td>
<td>310 myeloma patients (2011-2013)

All treated with bortezomib and/or thalidomide based chemotherapy

155 Male
96 Female

Median age 60 years</td>
<td>FISH
IGH deletion</td>
<td>
<table>
<tr><th></th><th>n</th><th>2yr PFS</th><th>2 yr OS</th><th>Overall response rate</th></tr>
<tr><td>IGH deletion</td><td>73</td><td>46.9%</td><td>76.9%</td><td>87.5%</td></tr>
<tr><td>No IGH deletion</td><td>237</td><td>55.7%</td><td>69.8%</td><td>73.6%</td></tr>
<tr><td></td><td></td><td>P=0.177</td><td>P=0.158</td><td>P<0.001</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Hebraud et al., 2014

France</td>
<td>1195 newly diagnosed myeloma patients
Younger than 66 years

Treatment: VAD or bortezomib-based induction, followed by ASCT.

Median age: 57.7 years

673 Male
522 Female

Median follow-up: 81.3 months
(range 35.3 – 105.9)</td>
<td>FISH

1p22 deletions
1p32 deletions</td>
<td>1p deletions were present in 261 patients
1p22 n=176
1p32 n=85

<table>
<tr><th></th><th>n</th><th>PFS</th><th>OS</th></tr>
<tr><td>1p22 del</td><td>176</td><td>19.8 months</td><td>44.2 months</td></tr>
<tr><td>Without 1p22 del</td><td>1019</td><td>33.6 months</td><td>96.8 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P=0.002</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>PFS</th><th>OS</th></tr>
<tr><td>1p32 del</td><td>85</td><td>14.4 months</td><td>26.7 months</td></tr>
<tr><td>Without 1p32 del</td><td>1110</td><td>33.6 months</td><td>96.8 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

Multivariate analysis: 1p22 and 1p32 deletions were independent poor prognostic factor for PFS (HR 1.56, p=0.001 and HR 2.84, p<0.001) and OS (HR 1.82, p=0.008 and HR=4.07, P<0.001).</td>
<td>-</td>
</tr>
<tr>
<td>Jacobus et al., 2011

USA</td>
<td>126 newly diagnosed myeloma patients in trial E4A03
Treatment: lenalidomide plus dexamethasone in low or high doses</td>
<td>FISH on BM aspirate samples</td>
<td>High risk: t(4;14), t(14;16) or 17p13 deletion.

t(4:14) n=14
t(14;16) n=2
17p13 deletions n=6</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Median age: 62 years

71 Male
55 Female

Median follow-up: 36 months</td>
<td></td>
<td>
<table>
<tr><th></th><th>n</th><th>2yr PFS</th><th>2yr OS</th></tr>
<tr><td>High risk</td><td>21</td><td>24%</td><td>76%</td></tr>
<tr><td>Standard risk</td><td>105</td><td>59%</td><td>91%</td></tr>
</table>
Risk status remained prognostic in multivariate model.
</td>
<td></td>
</tr>
<tr>
<td>Kapoor et al., 2010

USA</td>
<td>290 newly diagnosed myeloma patients predominately treated with novel agents (81% received thalidomide, lenalidomide or bortezomib)

Median age: 64 years (range: 22-89)

177 Male
113 Female

Median follow-up: 29 months</td>
<td>Interphase FISH on BM aspirate samples</td>
<td>high risk = any one of more of:
deletion p53
IGH translocations t(4;14) or t(14;16)

<table>
<tr><th></th><th>n</th><th>median OS</th></tr>
<tr><td>High risk</td><td>51</td><td>30 months</td></tr>
<tr><td>Standard risk</td><td>239</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.006</td></tr>
</table>
FISH remained prognostic in multivariate model (HR 2.0, p=0.02)
</td>
<td>-</td>
</tr>
<tr>
<td>Kumar et al., 2012

USA</td>
<td>484 newly diagnosed myeloma patients

Varied treatments (78% received thalidomide, lenalidomide or bortezomib)

Median age: 66 years (range: 22-91)

290 Male
194 Female

Median follow-up: 3 years</td>
<td>cIg-FISH on BM aspirates</td>
<td>No abnormality was found by FISH in 15 patients.
The remaining 469 patients had 1 or more abnormalities.

high risk = presence of t(4;14), t(14;16) t(14;20), or loss of p53
standard risk: any other abnormality

<table>
<tr><th></th><th>n</th><th>median OS</th></tr>
<tr><td>High risk</td><td>114</td><td>3.9 years</td></tr>
<tr><td>Standard risk</td><td>370</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P<0.001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>median OS</th></tr>
<tr><td>High risk + any trisomy</td><td>48</td><td>Not reached</td></tr>
<tr><td>High risk - any trisomy</td><td>66</td><td>3 years</td></tr>
<tr><td></td><td></td><td>P=0.01</td></tr>
</table>
</td>
<td>-</td>
</tr>
</table>

<table>
<tr>
<td>Lai et al., 2012

China</td>
<td>672 newly diagnosed myeloma patients
from 52 hospitals in China

Varied treatments:
25 ASCT
124 bortezomib-based regimens
523 others

Median age: 59 years

429 Male
243 Female

Median follow-up: 12 months
(range 3 – 60 months)</td>
<td>interphase FISH

del(13q)
IGH rearrangement
Del(p53)
1q21 amp</td>
<td>Of the 672 cases 608 had complete follow up information.

There were no significant differences in survival between patients with and without FISH abnormalities.

<table>
<tr><th></th><th>n</th><th>median OS</th><th>median PFS</th></tr>
<tr><td>1q21 amp</td><td>303</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>No 1q21 amp</td><td>305</td><td>40 months</td><td>35 months</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>median OS</th><th>median PFS</th></tr>
<tr><td>P53 del</td><td>215</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>No p53 del</td><td>393</td><td>40 months</td><td>35 months</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>median OS</th><th>median PFS</th></tr>
<tr><td>IGH rearrangement</td><td>357</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>No IGH rearrangement</td><td>251</td><td>40 months</td><td>35 months</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>median OS</th><th>median PFS</th></tr>
<tr><td>13q del</td><td>374</td><td>Not reached</td><td>Not reached</td></tr>
<tr><td>No 13q del</td><td>234</td><td>40 months</td><td>35 months</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td><u>Study limitations</u>

• Short follow-up

• Translocation of IGH detected by IGH break-apart rearrangement probe and not specific probes for specific translocations.

• Treatment heterogeneity</td>
</tr>
<tr>
<td>Li et al, 2015

China</td>
<td>275 patients with newly diagnosed myeloma

Treatment thalidomide-based (N=138) or bortezomib based (N=137)
Median age: 58 years

Median follow-up: 36 months</td>
<td>FISH

del(12p13)</td>
<td>
<table>
<tr><th></th><th>n</th><th>median OS</th><th>median PFS</th></tr>
<tr><td>12p13 del</td><td>29</td><td>17.0 months</td><td>11.0 months</td></tr>
<tr><td>No 12p13 del</td><td>246</td><td>40.0 months</td><td>24.0 months</td></tr>
<tr><td></td><td></td><td>P<0.001</td><td>P<0.001</td></tr>
</table>

In multivariate analysis del(12p13) was an independent prognostic factor for PFS (HR 2.29; 95% CI 1.25 to 4.18) and OS (HR 2.11; 95% CI 1.07 to 4.17).</td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>Lopez-Corral et al., 2012

Spain</td>
<td>123 high risk smoldering myeloma patients.
Randomised to receive Len-Dex vs. no treatment.

Median follow-up: 24 months</td>
<td>interphase FISH

t(4;14)
t(11;14)
t(14;16)
17p deletion
13q deletion
1q gains</td>
<td>t(4;14) n=15
t(11;14) n=21
t(14;16) n=7
17p deletion n=9
13q deletion n=51
1q gains n=47

Chromosomal abnormalities detected by FISH at diagnosis were not associated to risk of progression to symptomatic myeloma.</td>
<td>-</td>
</tr>
<tr>
<td>Lu et al., 2014

China</td>
<td>940 newly diagnosed myeloma patients from 3 centres

Median age: 59 years (range 23 -88)

570 Male
370 Female

Median follow-up 32 months</td>
<td>interphase FISH

RB1 deletion
1q21 amp
IGH rearrangement
del(p53)
del(13q)</td>
<td>422 cases had FISH results.
Number of FISH abnormalities (1 vs 2 or more) did not show any prognostic value on survival</td>
<td>-</td>
</tr>
<tr>
<td>Mateos et al., 2011

Spain</td>
<td>260 elderly myeloma patients

Received an induction with weekly bortezomib.
Randomised.
VMP: 130
VTP: 130
Then maintenance therapy.
Randomised to VT or VP.

Median age: 72 years (range 62-85)

Median follow-up: 21 months (1 – 63)</td>
<td>FISH in CD138-purified plasma cells:
t(4:14)
t(11:14)
t(14:16)
del(13q)
del(17p)</td>
<td>FISH analysis was possible in 232 of 260 patients.

High-risk:
t(4:14) ± del(13q), n=17
del (17p) ± del(13q), n=21
t(4:14) + del(17p), n=3
t(14:16), n=3

standard risk:
no abnormalities, n=110
del(13q), n=52
t(11:14), n=26

Response was similar in high risk and standard risk groups both after induction (21% vs 27%) and maintenance (39% vs 45%).

<table>
<tr><th></th><th>n</th><th>PFS from 1st randomization</th><th>PFS from 2nd randomization</th><th>Median OS</th></tr>
</table>
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<table>
<tr>
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<td></td>
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<table>
<tr><td>High risk</td><td>44</td><td>24 months</td><td>17 months</td><td>38 months</td></tr>
<tr><td>Standard risk</td><td>188</td><td>33 months</td><td>27 months</td><td>Not reached</td></tr>
<tr><td></td><td></td><td>P=0.04</td><td>P=0.01</td><td>P=0.001</td></tr>
</table>

No effect with type of treatment.

Multivariate analysis:
Presence of high risk cytogenetic abnormalities was independently prognostic for both PFS and OS.
</td>
<td></td>
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<tr>
<td>Moreau et al., 2007

France</td>
<td>1064 myeloma patients
Treated with double intensive therapy according to IFM99 protocols.
54% IFM99-02
14% IFM99-03
32% IFM99-04

543 male
521 female

Median age: 58 years (range 33-65)

Median follow-up: 46 months</td>
<td>FISH

t(4:14)</td>
<td>t(4;14) was analysed in 716 samples (because small number of purified cells in some samples).

<table>
<tr><th></th><th>n</th><th>Best response = CR or VGPR After induction</th><th>Best response = CR or VGPR After double HDT</th><th>Median OS</th><th>Median EFS</th></tr>
<tr><td>t(4;14)</td><td>100</td><td>19%</td><td>50%</td><td>41.4 months</td><td>21 months</td></tr>
<tr><td>No t(4;14)</td><td>616</td><td>16%</td><td>52.4%</td><td>65 months</td><td>37 months</td></tr>
<tr><td></td><td></td><td>p=0.62</td><td>p=0.75</td><td>p<0.001</td><td>p<0.001</td></tr>
</table>
</td>
<td>-</td>
</tr>
<tr>
<td>Neben et al., 2010

Germany</td>
<td>315 newly diagnosed myeloma patients

All patients underwent high dose chemotherapy and ASCT

178 male
137 female

Median age: 59 years (range 25-73)</td>
<td>Interphase FISH in CD138-purified plasma cells:

1q21
5p15/5q35
6q21
8p21
9q34
11q23
13q14.3
15q22
17p13
19q13
22q11
t(11;14)(q13;q32)
t(4;14)(p16.3;q32)
t(14;16)(q32.3;q23)</td>
<td>Univariate analysis of prognostic impact of chromosomal abnormalities on PFS and OS

While del(8p21), del(13q14), del(17p13), t(4;14), +1q21, +11q23, +19q13 and ploidy status showed a significant impact on progression-free survival, del(8p21), del(13q14), del(17p13), t(4;14), +1q21 and ploidy status were of statistical significance for overall survival.

When P values were adjusted for ISS classification, all chromosomal aberrations listed above, except del(8p21), remained of statistical significance for both progression-free and overall survival.

After adjustment of P values for multiple testing, del(13q14) as well as +1q21 had a significant impact on progression-free survival, while del(17p13) was of statistical significance for overall survival.

In multivariate model, t(4;14) and del(17p13) were the only aberrations with a statistically significant impact on PFS and OS.

Low risk: patients without del(17p13)/t(4;14) and ISS I
Intermediate risk: patients with del(17p12)/t(4;14) and ISS I OR</td>
<td>Because of small numbers of purified plasma cells in many specimens and failure of FISH in some cases the study was not able to test the full set of probes in all patients.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>patients without del(17p13)/t(4;14) and ISS II/III
High risk: patients with del(17p13)/t(4;14) and ISS II/III

<table>
<tr><th></th><th>n</th><th>Median PFS</th><th>5yr OS</th></tr>
<tr><td>low risk</td><td>113</td><td>2.7 years</td><td>72%</td></tr>
<tr><td>Standard risk</td><td>119</td><td>2 years</td><td>62%</td></tr>
<tr><td>High risk</td><td>38</td><td>1.2 years</td><td>41%</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Neben et al., 2013

Germany</td>
<td>248 smoldering myeloma patients

134 male
114 female

Median follow-up: 3.5 years</td>
<td>Interphase FISH in CD138-purified plasma cells:

1q21
5p15/5q35
9q34
13q14.3
15q22
17p13
t(11;14)(q13;q32)
t(4;14)(p16.3;q32)</td>
<td>
<table>
<tr><th></th><th>n</th><th>HR</th><th>95% CI</th><th>p</th><th>Median TTP (years)</th><th>TTP rate % at 3 years</th></tr>
<tr><td>Del(17p13)
No Del(17p13)</td><td>15
231</td><td>2.90</td><td>1.6 – 5.4</td><td>0.001</td><td>5.62
2.04</td><td>30
56</td></tr>
<tr><td>t(4;14)
No t(4;14)</td><td>22
224</td><td>2.28</td><td>1.3 – 3.9</td><td>0.003</td><td>5.71
2.91</td><td>28
55</td></tr>
<tr><td>+1q21
No +1q21</td><td>73
172</td><td>1.66</td><td>1.1 – 2.5</td><td>0.02</td><td>n/a
3.86</td><td>27
43</td></tr>
<tr><td>Low cytogenetic risk*
High cytogenetic risk</td><td>157
88</td><td>2.00</td><td>1.3 – 3.0</td><td>0.001</td><td>n/a
3.79</td><td>24
25</td></tr>
<tr><td>Non-hyperdiploidy
hyperdiploidy</td><td>139
106</td><td>1.67</td><td>1.1 – 2.5</td><td>0.016</td><td>n/a
3.92</td><td>29
35</td></tr>
<tr><td>t(11;14)
No t(11;14)</td><td>56
190</td><td>0.69</td><td>0.4 – 1.2</td><td>0.19</td><td>5.22
28</td><td>33
27</td></tr>
<tr><td>Del(13q14)
No del(13q14)</td><td>49
196</td><td>0.75</td><td>0.4 – 1.4</td><td>0.33</td><td>5.22
n/a</td><td>33
28</td></tr>
</table>
*patients were classified as high risk if one of del(17p13), t(4;14) or +1q21 were present and low risk if none of these were present.

The high-risk aberrations confer adverse prognosis in SMM

High risk aberrations remained independently prognostic in multivariate model.
</td>
<td>-</td>
</tr>
<tr>
<td>Nemec et al., 2012

Czech Republic</td>
<td>207 myeloma patients

CMG2002 trial:
High dose therapy followed by ASCT</td>
<td>cIg-FISH

t(4:14)
t(11:14)
del(13q)
del(17p13)</td>
<td>
<table>
<tr><th></th><th>ORR</th><th>p</th><th>n</th><th>TTP</th><th>p</th><th>n</th><th>OS</th><th>p</th></tr>
<tr><td>Del(13q)
No Del(13q)</td><td>72/75 (96.0%)
65.71 (91.5%)</td><td>0.32</td><td>74
70</td><td>24.1
28.6</td><td>0.34</td><td>106
97</td><td>53.4
52.9</td><td>0.48</td></tr>
<tr><td>17p13 del</td><td>6/6 (100%)</td><td>1</td><td>6</td><td>21.0</td><td>0.42</td><td>7</td><td>22.7</td><td>0.19</td></tr>
</table>
</td>
<td>17p13 del patients had poor outcome. But too few patients for data to be informative.</td>
</tr>
</table>

			No 17p13 del	71/76 (93.4%)		76	27.9		99	60.7	
			t(11;14)	19/21 (90.5%)	0.66	21	24.6	0.80	30	53.4	0.66
			No t(11;14)	90/97 (92.8%)		95	27.7		129	52.9	
			t(4;14)	20/22 (90.9%)	0.62	23	18.0	**0.004**	28	33.3	**0.003**
			No t(4;14)	68/72 (94.4%)		70	36.2		94	60.7	
			1q21 gain	24/26 (92.3%)	1	27	21.3	**0.034**	41	30.4	**<0.001**
			No 1q21 gain	40/43 (93.0%)		40	32.2		50	NR	
	124 male 83 female Median age: 57 years (range 33-69) Median follow-up: 35.4 months (0.4 – 70.3)	1q21 gain	Multivariate analysis: t(4;14) was an independent poor prognostic factor for OS (HR 13.7, p=0.001)								
Paiva et al., 2012c Spain	241 myeloma patients GEM200 (n=140) and GEM2006<65yr (n=101) CMG2002 trial: High dose therapy followed by ASCT Median follow-up: 49 months	Interphase FISH Performed at baseline in 110 patients t(4;14) t(14;16) del(17p)	FISH analysis was performed in 110 patients. High risk: t(4;14), t(14;16) or del(17p) **n** / **3yr TTP** / **OS** High risk: 18 / 40% / 73% Standard risk: 92 / 80% / 96% P<0.001 / P=0.07 Multivariate analysis: Presence of high risk cytogenetic abnormalities was independently prognostic for both TTP (HR 6.4, p<0.001) and OS (HR 4.3, p=0.03).							-
Rajkumar et al., 2013 USA Spain	351 smoldering myeloma patients 179 male 172 female Median age: 63 years (range 26-90) Median follow-up: 82 months	cIg-FISH	**n** / **Median TTP** / **Median OS** t(4;14): 36 / 28 months / 105 months t(11;14): 57 / 55 months / 147 months P=0.025 / P=0.036 High risk: t(4;14) 36 Intermediate risk: trisomies alone 154 Standard risk: t(11;14),57 MAF translocations, 11other/unknown IGH translocations, 23 monosomy13/del(13q) without other abnormalities, 3both trisomies and IGH translocations 14 Low risk: no detectable abnormalities							Trend to shorter TTP with 17p13 del patients(median TTP 24 months) but too few patients for data to be informative.

<table>
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<table>
<tr><th></th><th>n</th><th>Median TTP</th><th>Median OS</th><th>Median OS from time of symptomatic myeloma</th></tr>
<tr><td>High risk</td><td>36</td><td>28 months</td><td>105 months</td><td>51 months</td></tr>
<tr><td>intermediate risk</td><td>154</td><td>34 months</td><td>135 months</td><td>77 months</td></tr>
<tr><td>Standard risk</td><td>108</td><td>55 months</td><td>141months</td><td>86 months</td></tr>
<tr><td>Low risk</td><td>53</td><td>Not reached</td><td>135 months</td><td>112 months</td></tr>
<tr><td></td><td></td><td>P=0.001</td><td>P=0.25</td><td>P=0.04</td></tr>
</table>

Multivariate analysis:
The increased risk of progression associated with t(4;14) remained significant in a model that included bone marrow plasma cell %, but was not independent of serum FLC ratio.
Similarly the four-group risk model retained significance in a model that included bone marrow plasma cell %, but was not independent of serum FLC ratio.
</td>
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<tr>
<td>Walker et al., 2010

UK</td>
<td>1177 newly diagnosed myeloma patients in UK MRC Myeloma IX study

Intensive pathway:
Younger fitter patients.
ASCT after induction with CTD or VAD.

Non-intensive pathway:
Older less fit patients.
CTDa or MP.

All patients were randomised to thalidomide maintenance or no thalidomide maintenance.

Median follow-up:
3.7 years</td>
<td>Interphase FISH

t(4:14)
t(6:14)
t(11:14)
t(14:16)
t(14:20)
del(1p32.3)
gain 1q
del(17p)
hyperdiploidy (defined by gain of any 2 of chromosomes 5, 9 and 15)
del(8p)</td>
<td>Genetic abnormalities with a prognostic impact on OS = del(1p), gain 1q and del(17p).

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>Del(1p32.3)</td><td>?</td><td>34.5 months</td></tr>
<tr><td>No del(1p32.3)</td><td>?</td><td>>70 months</td></tr>
<tr><td></td><td>n=510</td><td>P<0.001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>Gain 1q</td><td>?</td><td>52.1 months</td></tr>
<tr><td>No gain 1q</td><td>?</td><td>>70 months</td></tr>
<tr><td></td><td>n=531</td><td>P<0.001</td></tr>
</table>

<table>
<tr><th></th><th>n</th><th>Median OS</th></tr>
<tr><td>Del(17p)</td><td>?</td><td>40.9 months</td></tr>
<tr><td>No del(17p)</td><td>?</td><td>67.8 months</td></tr>
<tr><td></td><td>n=501</td><td>P<0.001</td></tr>
</table>
</td>
<td>Importance of other genetic abnormalities should not be discounted as some of the datasets were small and were not studied extensively by FISH.</td>
</tr>
</table>

1

2

References of included studies

1. An, G., Xu, Y., Shi, L., Zou, D., Deng, S., Sui, W., Xie, Z., Hao, M., Chang, H. & Qiu, L. (2013) t(11;14) multiple myeloma: a subtype associated with distinct immunological features, immunophenotypic characteristics but divergent outcome. Leukemia Research, 37: 1251-1257.

2. An, G., Xu, Y., Shi, L. H., Zhong, S. Z., Deng, S. H., Xie, Z. Q., Sui, W. W., Zhan, F. H. & Qiu, L. G. (2014) Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation and percentage of plasma cells involved have no additional prognostic value. *Haematologica,* 99: 353-359.

3. Avet-Loiseau, H., Attal, M., Moreau, P., Charbonnel, C., Garban, F., Hulin, C., Leyvraz, S., Michallet, M., Yakoub-Agha, I., Garderet, L., Marit, G., Michaux, L., Voillat, L., Renaud, M., Grosbois, B., Guillerm, G., Benboubker, L., Monconduit, M., Thieblemont, C., Casassus, P., Caillot, D., Stoppa, A. M., Sotto, J. J., Wetterwald, M., Dumontet, C., Fuzibet, J. G., Azais, I., Dorvaux, V., Zandecki, M., Bataille, R., Minvielle, S., Harousseau, J. L., Facon, T. & Mathiot, C. (2007) Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood, 109: 3489-3495.

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Excluded papers (after checking full text) n=32

paper	Reasons for exclusion
1. An, G. (2015). The impact of clone size on the prognostic value of chromosome aberrations by fluorescence in situ hybridization in multiple myeloma. Clinical Cancer Research, 21, 2148-2156.	Includes patients with relapsed myeloma
2. An, G. (2015). Cytogenetic and clinical marks for defining high-risk myeloma in the context of bortezomib treatment. Experimental Hematology, 43, 168-176.	See An (2014)
3. Avet-Loiseau, H. (2007) Role of genetics in prognostication in myeloma. [Review] [61 refs]. *Bailliere's Best Practice in Clinical Haematology,* 20: 625-635.	Expert review.
4. Avet-Loiseau H, Li C, Magrangeas F, Gouraud W, Charbonnel C, Harousseau JL, Attal M, Marit G, Mathiot C, Facon T, Moreau P, Anderson KC, Campion L, Munshi NC, Minvielle S. (2009) Prognostic significance of copy-number alterations in multiple myeloma. Journal of Clinical Oncology, 27: 4585-4590.	Uses molecular technologies (PICO was revised to exclude such tests).
5. Boyle, E. M. (2014) IgA kappa/IgA lambda heavy/light chain assessment in the management of patients with IgA myeloma. *Cancer,* 120: 3952-3957.	Not relevant to PICO – comparison of HLC with SPEP
6. Brioli, A., Boyd, K. D., Kaiser, M. F., Pawlyn, C., Wu, P., Gregory, W. M., Owen, R., Ross, F. M., Jackson, G. H., Cavo, M., Davies, F. E. & Morgan, G. J. (2013) Response and biological subtype of myeloma are independent prognostic factors and combine to define outcome after high-dose therapy. British journal of haematology, 161: 291-294.	Extension of Boyd et al., 2012. Not relevant to PICO – study examines effect of response post induction and post ASCT on survival outcomes.
7. Brioli, A., Kaiser, M. F., Pawlyn, C., Wu, P., Gregory, W. M., Owen, R., Ross, F. M., Jackson, G. H., Cavo, M., Davies, F. E. & Morgan, G. J. (2013) Biologically defined risk groups can be used to define the impact of thalidomide maintenance therapy in newly diagnosed multiple myeloma. Leukemia & lymphoma, 54: 1975-1981.	Extension of Boyd et al., 2012. Not relevant to PICO – study examines effect of thalidomide maintenance therapy in FISH defined risk groups. Maintenance therapy not in scope.
8. Chng, W. J., Dispenzieri, A., Chim, C. S., Fonseca, R., Goldschmidt, H., Lentzsch, S., Munshi, N., Palumbo, A., Miguel, J. S., Sonneveld, P., Cavo, M., Usmani, S., Durie, B. G., Avet-Loiseau, H. & International Myeloma Working Group. (2014) IMWG consensus on risk stratification in multiple myeloma. [Review]. *Leukemia,* 28: 269-277.	Expert review and consensus recommendations. Cross checked for references. Relevant included references assessed separately.
9. Chretien, M. L. (2014). Age is a prognostic factor even among patients with multiple myeloma younger than 66 years treated with high-dose melphalan: the IFM experience on 2316 patients. Haematologica, 99, 1236-1238.	Factor not in PICO
10. Dingli, D., Nowakowski, G. S., Dispenzieri, A., Lacy, M. Q., Hayman, S. R., Rajkumar, S. V., Greipp, P. R., Litzow, M. R., Gastineau, D. A., Witzig, T. E. & Gertz, M. A. (2006) Flow cytometric detection of circulating myeloma cells before transplantation in patients with multiple myeloma: a simple risk stratification system. Blood, 107: 3384-3388.	Test not done at diagnosis
11. Dispenzieri, A., Rajkumar, S. V., Gertz, M. A., Fonseca, R., Lacy, M. Q., Bergsagel, P. L., Kyle, R. A., Greipp, P. R., Witzig, T. E., Reeder, C. B., Lust, J. A., Russell, S. J., Hayman, S. R., Roy, V., Kumar, S., Zeldenrust, S. R., Dalton, R. J. & Stewart, A. K. (2007) Treatment of newly diagnosed multiple myeloma based on Mayo stratification of myeloma and risk-adapted therapy	Expert review.

(mSMART): Consensus statement. *Mayo Clinic Proceedings,* 82: 323-341	
12. Drayson, M., Begum, G., Basu, S., Makkuni, S., Dunn, J., Barth, N. & Child, J. A. (2006) Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. Blood, 108: 2013-2019.	Study reporting outcomes by paraprotein class. Does not include heavy/light chain ratio.
13. Fonseca, R., Bergsagel, P. L., Drach, J., Shaughnessy, J., Gutierrez, N., Stewart, A. K., Morgan, G., Van, N. B., Chesi, M., Minvielle, S., Neri, A., Barlogie, B., Kuehl, W. M., Liebisch, P., Davies, F., Chen-Kiang, S., Durie, B. G., Carrasco, R., Sezer, O., Reiman, T., Pilarski, L., Avet-Loiseau, H. & International Myeloma Working Group. (2009) International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. [Review] [86 refs]. *Leukemia,* 23: 2210-2221.	Expert review
14. Gertz, M. A., Lacy, M. Q., Dispenzieri, A., Greipp, P. R., Litzow, M. R., Henderson, K. J., Van Wier, S. A., Ahmann, G. J. & Fonseca, R. (2005) Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. Blood, 106: 2837-2840.	Test not done at diagnosis
15. Giatromanolaki, A., Bai, M., Margaritis, D., Bourantas, K. L., Koukourakis, M. I., Sivridis, E. & Gatter, K. C. (2010) Hypoxia and Activated VEGF/Receptor Pathway in Multiple Myeloma. *Anticancer Research,* 30: 2831-2836.	37 patients – below sample size cut off.
16. Hebraud, B. (2015). Role of additional chromosomal changes in the prognostic value of t(4;14) and del(17p) in multiple myeloma: the IFM experience. Blood, 125, 2095-2100.	Study sample limited to patients with either t(4;14) or del(17p).
17. Jiang, A., Reece, D. & Chang, H. (2012) Genomic stratification of multiple myeloma treated with novel agents. [Review]. *Leukemia & lymphoma,* 53: 202-207.	Expert review
18. Johnsen, H. E., Bogsted, M., Klausen, T. W., Gimsing, P., Schmitz, A., Kjaersgaard, E., Damgaard, T., Voss, P., Knudsen, L. M., Mylin, A. K., Nielsen, J. L., Bjorkstrand, B., Gruber, A., Lenhoff, S., Remes, K., Dahl, I. M., Fogd, K., Dybkaer, K., Nordic Myeloma Study, N. & Myeloma Stem Cell Network (MSCNET) (2010) Multiparametric flow cytometry profiling of neoplastic plasma cells in multiple myeloma. Cytometry Part B, Clinical Cytometry, 78: 338-347.	80 patients – below sample size cut off.
19. Karlin, L., Soulier, J., Chandesris, O., Choquet, S., Belhadj, K., Macro, M., Bouscary, D., Porcher, R., Ghez, D., Malphettes, M., Asli, B., Brouet, J. C., Bories, J. C., Hermine, O., Fermand, J. P. & Arnulf, B. (2011) Clinical and biological features of t(4;14) multiple myeloma: a prospective study. Leukemia & lymphoma, 52: 238-246.	Below sample size cut off for reported outcomes
20. Kapoor, P., Kumar, S., Fonseca, R., Lacy, M. Q., Witzig, T. E., Hayman, S. R., Dispenzieri, A., Buadi, F., Bergsagel, P. L., Gertz, M. A., Dalton, R. J., Mikhael, J. R., Dingli, D., Reeder, C. B., Lust, J. A., Russell, S. J., Roy, V., Zeldenrust, S. R., Stewart, A. K., Kyle, R. A., Greipp, P. R. & Rajkumar, S. V. (2009) Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. Blood, 114: 518-521.	Mixture of different diagnostic tests used to define high risk patients and not all in PICO.
21. Kastritis E & Zagouri (2014). Preserved levels of uninvolved immunoglobulins are independently associated with favorable outcome in patients with symptomatic multiple myeloma. Leukemia, 28, 2075-2079.	Test / factor not in PICO.
22. Kraj, M., Sokolowska, U., Kopec-Szlezak, J., Poglod, R., Kruk, B., Wozniak, J. & Szpila, T. (2008) Clinicopathological correlates of plasma cell CD56 (NCAM) expression in multiple myeloma.	Not specific to test conducted at diagnosis: 204 myeloma patients

Leukemia & lymphoma, 49: 298-305.	157 newly diagnosed and untreated 17 in plateau phase 30 in progression of disease
23. Liu, N. (2015) Retrospective analysis of genetic abnormalities and survival in 131 patients with multiple myeloma. *Oncology Letters,* 9: 930-936.	Not specific to test conducted at diagnosis. 107 newly diagnosed patients 24 relapsed patients
24. Mithraprabhu S., K. (2014) Dysregulated Class I histone deacetylases are indicators of poor prognosis in multiple myeloma. *Epigenetics,* 9: 1511-1520.	97 patients – below sample size cut off.
25. Mori, S., Crawford, B. S., Roddy, J. V., Phillips, G., Elder, P., Hofmeister, C. C., Efebera, Y. & Benson, D. M., Jr. (2012) Serum free light chains in myeloma patients with an intact M protein by immunofixation: potential roles for response assessment and prognosis during induction therapy with novel agents. Hematological Oncology, 30: 156-162.	73 patients – below sample size cut off.
26. Munshi, N. C., Anderson, K. C., Bergsagel, P. L., Shaughnessy, J., Palumbo, A., Durie, B., Fonseca, R., Stewart, A. K., Harousseau, J. L., Dimopoulos, M., Jagannath, S., Hajek, R., Sezer, O., Kyle, R., Sonneveld, P., Cavo, M., Rajkumar, S. V., san, M. J., Crowley, J., Avet-Loiseau, H. & International Myeloma Workshop Consensus Panel (2011) Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood,* 117: 4696-4700.	Expert review
27. Ouyang, J., Gou, X., Ma, Y., Huang, Q. & Jiang, T. (2014) Prognostic value of 1p deletion for multiple myeloma: a meta-analysis. *International Journal of Laboratory Hematology,* 36: 555-565.	Meta-analysis. Many included studies are excluded from this evidence review as do not meet our selection criteria – less than 100 patients, before 2005, conventional cytogenetics. Those studies that do meet our selection criteria have been assessed separately.
28. Perosa, F. (2009) Staging multiple myeloma patients with active disease using serum levels of beta2m-free HLA class I heavy chain together with IgM or platelet count. *Blood Cells, Molecules, and Diseases,* 42: 71-76.	Not specific to test conducted at diagnosis. Also test not in PICO – serum B2M-free heavy chains.
29. Raja, K. R. M., Rihova, L., Zahradova, L., Klincova, M., Penka, M. & Hajek, R. (2012) Increased T Regulatory Cells Are Associated with Adverse Clinical Features and Predict Progression in Multiple Myeloma. *PLoS ONE,* 7.	79 patients – below sample size cut off.
30. Rawstron AC, Gregory WM, de Tute RM, Davies FE, Bell SE, Drayson MT et al. (2015). Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. Blood, 125, 1932-1935.	Not test conducted at diagnosis.
31. Roos-Weil, D., Moreau, P., Avet-Loiseau, H., Golmard, J. L., Kuentz, M., Vigouroux, S., Socie, G., Furst, S., Soulier, J., Le, G. S., Francois, S., Thiebaut, A., Buzyn, A., Maillard, N., Yakoub-Agha, I., Raus, N., Fermand, J. P., Michallet, M., Blaise, D., Dhedin, N. & Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) (2011) Impact of genetic abnormalities after allogeneic stem cell transplantation in multiple myeloma: a report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Haematologica, 96: 1504-1511.	Not specific to test conducted at diagnosis.
32. Ross, F. M. (2005) Age has a profound effect on the incidence and significance of chromosome abnormalities in myeloma. *Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U,* 19: 1634-1642.	Not specific to test conducted at diagnosis. A total of 163 patients were studied at diagnosis while samples from the remaining 65 were taken 3–130 months after diagnosis.

33. Sasaki, K., Lu, G., Saliba, R. M., Bashir, Q., Hosing, C., Popat, U., Shah, N., Parmar, S., Dinh, Y., Ahmed, S., Shpall, E. J., Kebriaei, P., Shah, J. J., Orlowski, R. Z., Champlin, R. & Qazilbash, M. H. (2013) Impact of t(11;14)(q13;q32) on the outcome of autologous hematopoietic cell transplantation in multiple myeloma. Biology of Blood & Marrow Transplantation, 19: 1227-1232.	Not specific to test conducted at diagnosis. Also translocation results by FISH or conventional cytogenetics reported together.
34. Schilling G, Hansen T, Shimoni A, Zabelina T, Pérez-Simón JA, Gutierrez NC, Bethge W, Liebisch P, Schwerdtfeger R, Bornhäuser M, Otterstetter S, Penas EM, Dierlamm J, Ayuk F, Atanackovic D, Bacher U, Bokemeyer C, Zander A, San Miguel J, Nagler A, Kröger N. (2008) Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma. *Leukemia,* 22: 1250-1255.	Not specific to test conducted at diagnosis.
35. Song MK, Chung JS, Lee JJ, Lee JH, Song IC, Lee SM et al. (2015). Risk stratification model in elderly patients with multiple myeloma: clinical role of magnetic resonance imaging combined with international staging system and cytogenetic abnormalities. Acta Haematologica, 134, 7-16.	Compares high-risk cytogenetics to other – however high risk not fully defined.
36. Sthaneshwar, P., Nadarajan, V., Maniam, J. A., Nordin, N. & Gin, G. G. (2009) Serum free light chains: diagnostic and prognostic value in multiple myeloma. Clinical Chemistry & Laboratory Medicine, 47: 1101-1107.	59 patients – below sample size cut off.
37. Tan, D., Teoh, G., Lau, L. C., Lim, A., Lim, T. H., Yap, K. C., Premalatha, P., Lao, Z. T., Wee, N., Choo, C., Wee, H. C., Su, S., Lee, Y. S., Lee, L. H., Hwang, W. & Goh, Y. T. (2010) An abnormal nonhyperdiploid karyotype is a significant adverse prognostic factor for multiple myeloma in the bortezomib era. American Journal of Hematology, 85: 752-756.	74 patients – below sample size cut off.
38. Yu, W. (2014) Prognostic value and efficacy evaluation of novel drugs for cytogenetic aberrations in multiple myeloma: A meta-analysis. *International Journal of Clinical and Experimental Medicine,* 7: 4051-4062.	Meta-analysis. Many included studies are excluded from this evidence review as do not meet our selection criteria – less than 100 patients, before 2005, conventional cytogenetics. Those studies that do meet our selection criteria have been assessed separately.
39. Zemanova, Z. (2008) Molecular cytogenetic analysis of immunofluorescence-labeled plasma cells of patients with multiple myeloma enrolled in CMG 2002 clinical trial. *Klinicka Onkologie,* 21: 204-206.	Paper not in English.
40. Zhuang, J., Da, Y., Li, H., Han, B., Wan, X., Zhu, T., Chen, M., Duan, M., Xu, Y., Zhao, Y., Shen, T., Wua, Y. & Zhou, D. (2014) Cytogenetic and clinical risk factors for assessment of ultra high-risk multiple myeloma. Leukemia Research, 38: 188-193.	95 patients – below sample size cut off.

1

1 ***Table 2.21: Checklists to identify risk of bias***

2

A	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results
B	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias
C	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias
D	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias
E	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest
F	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results

3
4

	A	B	C	D	E	F
An et al., 2013	Yes	Yes	Yes	Yes	No	No
An et al., 2014	Yes	Unclear	Yes	Yes	Yes	No
Avet et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes
Avet et al., 2009	Yes	Unclear	Yes	Yes	Yes	Yes
Avet et al., 2010	Yes	Unclear	Yes	Yes	No	No
Avet et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes
Avet et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes
Avet et al., 2013a	Yes	Yes	Yes	Yes	Yes	Yes
Avet et al., 2013b	Yes	Yes	Yes	Yes	Yes	Yes
Bang et al., 2006	Yes	Unclear	Yes	Yes	Yes	Yes
Boyd et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes
Bradwell et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Caltagirone et al., 2014	Yes	Unclear	Yes	Yes	Yes	Yes
Chang et al., 2005a	Yes	Yes	Yes	Yes	Yes	Yes
Chang et al.,2005b	Yes	Yes	Yes	Yes	Yes	Yes
Chang et al.,2006	Yes	Yes	Yes	Yes	Yes	No
Chang et al., 2007	Yes	Yes	Yes	Yes	Yes	No
Chang et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes
Chng et al., 2006	Yes	Yes	Yes	Yes	No	Yes
Chng et al., 2010	Unclear	Unclear	Yes	Yes	Yes	Yes
Dispenzieri et al., 2008a	Yes	Yes	Yes	Yes	Yes	Yes
Dispenzieri et al., 2008b	Yes	Yes	Yes	Yes	No	Yes
Fonseca et al., 2006	Yes	Yes	Yes	Yes	Yes	Yes
Gastinne et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes
Gonsalves et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes
Grzasko et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Gutierrez et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes
Hanamura et al., 2006	Yes	Yes	Yes	Yes	Yes	Yes
He at al 2015	Yes	Yes	Yes	Yes	No	Yes
Hebraud et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes
Jacobus et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes
Kapoor et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes

Koulieris et al., 2012	Yes	Yes	Yes	Yes	Yes	No
Kumar et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes
Kumar et al., 2012	Yes	Yes	Yes	Yes	No	Yes
Lai et al., 2012	Yes	Unclear	Yes	Yes	No	No
Larsen et al., 2013	Yes	Yes	Yes	Yes	Yes	No
Li et al, 2015	Yes	Yes	Yes	Yes	Yes	Yes
Lopez et al., 2012	Yes	Yes	Yes	Yes	Yes	No
Lu et al., 2014	Yes	Unclear	Yes	Yes	Yes	Yes
Ludwig et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Maltezas et al., 2013	Yes	Yes	Yes	Yes	No	No
Mateo et al., 2008	Yes	Yes	Yes	Yes	Yes	Yes
Mateos et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes
Minarik et al., 2005	Yes	Yes	Yes	Yes	No	No
Minarik et al., 2010	Yes	Yes	Yes	Yes	No	No
Minarik et al.,2011	Yes	Yes	Yes	Yes	No	Yes
Moreau et al., 2007	Yes	Unclear	Yes	Yes	No	Yes
Neben et al., 2010	Yes	Unclear	Yes	Yes	Yes	Yes
Neben et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Nemec et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes
Nowakowski et al., 2005	Yes	Yes	Yes	Yes	Yes	Yes
Paiva et al., 2009a	Yes	Yes	Yes	Yes	Yes	Yes
Paiva et al., 2009b	Yes	Yes	Yes	Yes	Yes	Yes
Paiva et al., 2012a	Yes	Yes	Yes	Yes	Yes	Yes
Paiva et al., 2012b	Yes	Yes	Yes	Yes	Yes	Yes
Paiva et al., 2012c	Unclear	Unclear	Yes	Yes	Yes	Yes
Paiva et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Rajkumar et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Shin et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes
Snozek et al., 2008	Yes	Yes	Yes	Yes	Yes	Yes
Tinguely et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes
Van Rhee et al., 2007	Yes	Yes	Unclear	Yes	Yes	Yes
Walker et al., 2010	Yes	Unclear	Yes	Yes	No	Yes
Xu et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes

Chapter 3: Imaging investigations

Imaging for people with suspected myeloma

Review Question

What is the optimal imaging strategy for patients with suspected myeloma?

Question in PICO format

Population	Index tests	Reference standard	Outcomes
Patients with suspected myeloma	• MRI (spinal and whole body) • Multiparametric MRI • Diffusion weighted MRI • Dynamic contrast MRI • CT (including low dose) • FDG-PET-CT • Skeletal survey • DEXA • ***Tc-99 MDP*** bone ***scintigraphy*** *+/-* SPECT +/- CT • Tc-99 MIBI	• Histo-pathologically confirmed myeloma related lesions or clinical radiological follow-up	• diagnostic accuracy (specificity and sensitivity) • lesion detection rate • radiation exposure • patient acceptability (e.g. claustrophobia, anxiety over procedure, clinical exclusions) • cost effectiveness

Evidence statements

Diagnostic accuracy

12 studies were identified and included in the evidence review. 10 studies used biopsy as the reference standard whilst 2 studies used x-ray. All 12 studies reported sensitivity for myeloma. Only 6 reported specificity (due to a lack of people without myeloma in the other 6 studies). The data can be seen in Tables 3.1 and 3.2. Some studies reported high sensitivity with MRI and TC99MIBI bone scan, however there was considerable heterogeneity in sensitivity and specificity estimates. This could be related to the differences in techniques and diagnostic criteria used in the individual studies.

Patient acceptability, Radiation exposure

We did not find evidence for these outcomes.

1 ***Table 3.1: diagnostic accuracy of various imaging methods compared to the reference standard biopsy***

Index tests	study	Myeloma prevalence	TP	FN	FP	TN	sensitivity	specificity	PPV	NPV
MRI	Whole body (WB) MRI (Cascini et al., 2013)	100%	22	0	NR	NR	100%	-	-	-
	WB MRI (Erten et al., 2007)	100%	11	2	NR	NR	85%	-	-	-
	WB MRI - focal lesions (Kloth, 2014)	75%	259	150	33	105	63%	76%	87%	41%
	WB MRI – any bone marrow infiltration (Kloth, 2014)	75%	251	158	53	85	61%	62%	83%	35%
	Spinal MRI STIR (Myslivecek et al., 2008)	79%	38	3	0	11	93%	100%	100%	79%
	Spinal MRI T1 w.i. (Myslivecek et al., 2008)	79%	38	3	6	5	93%	45%	86%	63%
	Spinal MRI SI - b1000 image (Dutoit, 2014)	41%	55	9	45	46	86%	51%	55%	84%
	Spinal MRI ADC_{1000} value (Dutoit, 2014)	41%	48	16	61	30	75%	33%	44%	65%
FDG PET/CT	Cascini et al., 2013	100%	18	4	NR	NR	82%	-	-	-
	Sager et al., 2011	100%	29	3	NR	NR	90%	-	-	-
x-ray bone survey	Sohn et al., 2002	100%	14	8	NR	NR	64%	-	-	-
	Alper et al., 2003	100%	18	2	NR	NR	90%	-	-	-
	Alexandrakis et al, 2001	100%	26	2	NR	NR	93%	-	-	-
TC99MIBI bone scan	Myslivecek et al., 2008	79%	39	2	0	11	95%	100%	100%	85%
	Svaldi et al., 2001	66%	58	0	2	28	100%	93%	97%	100%
	Alexandrakis et al, 2001	100%	22	6	NR	NR	79%	-	-	-
	Alper et al., 2003	100%	20	0	NR	NR	100%	-	-	-
	Erten et al., 2007	100%	17	1	NR	NR	94%	-	-	-
TC99MDP bone scan	Sohn et al., 2002	100%	11	11	NR	NR	50%	-	-	-
	Alexandrakis et al, 2001	100%	15	13	NR	NR	54%	-	-	-
	Alper et al., 2003	100%	15	5	NR	NR	75%	-	-	-
Bone marrow immunoscintigraphy (BMIS) using technetium-99m-labelled AGA	Sohn et al., 2002	100%	18	4	NR	NR	82%	-	-	-

2

Table 3.2: diagnostic accuracy of various imaging methods compared to the reference standard x-ray

Index tests	study	Myeloma prevalence	TP	FN	FP	TN	sensitivity	specificity	PPV	NPV
TC99MIBI	Catalano et al., 1999	100%	7	3	3	10	70%	77%	70%	77%
FDG-PET CT	Zamagni et al., 2007	100%	12	4	21	9	75%	30%	36%	69%

TP: true positive, FN: false negative, FP: false positive, TN: true negative, PPV: positive predictive value, NPV: negative predictive value, NR: not reported

Study quality

The QUADAS-2 assessment tool was used to evaluate risk of bias in the studies (Figures 3.1 and 3.2). Generally there was a low risk of bias across the studies and the studies were found to be applicable to the review question. For some of the studies the risk of bias is unclear due to under-reporting in some studies of the timing of the index and reference tests and whether they were interpreted blind to each other's results.

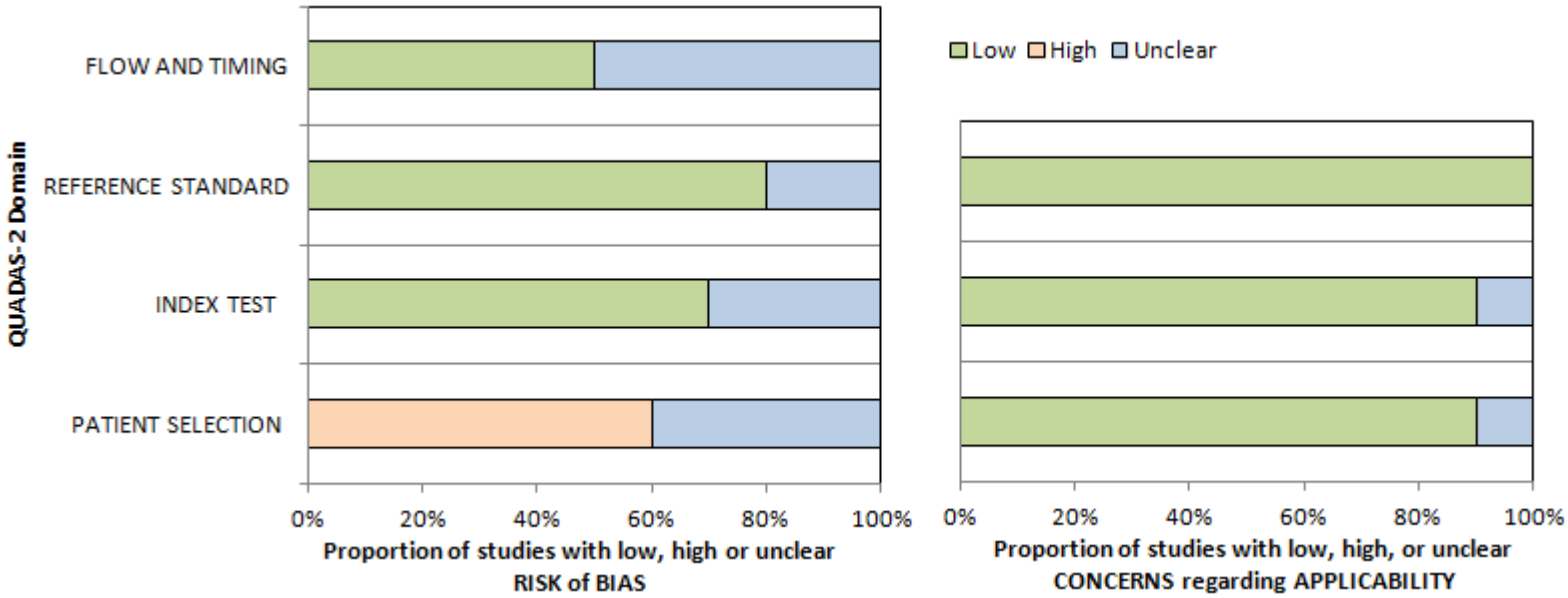
There was most uncertainty in the patient selection methods: many studies did not report this. Some studies were considered to have a high risk of bias in the patient selection category as the population did not include controls i.e. patients without myeloma.

Figure 3.1: Risk of bias and applicability for individual studies

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Alexandrakis et al., 2001	☹	?	☺	?	☺	☺	☺
Alper et al., 2003	☹	☺	☺	☺	☺	☺	☺
Cascini et al., 2013	☹	☺	☺	☺	☺	☺	☺
Catalano et al., 1999	?	☺	☺	?	☺	☺	☺
Dutoit et al., 2014	?	☺	☺	☺	☺	☺	☺
Erten et al., 2007	☹	☺	☺	?	☺	☺	☺
Kloth et all, 2014	?	☺	☺	?	☺	☺	☺
Myslivecek et al., 2008	?	?	?	?	?	?	☺
Sager et al., 2011	☹	☺	☺	☺	☺	☺	☺
Sohn et al., 2002	☹	☺	☺	☺	☺	☺	☺
Svaldi et al., 2001	?	?	?	?	☺	☺	☺
Zamagni et al., 2007	?	☺	☺	☺	☺	☺	☺

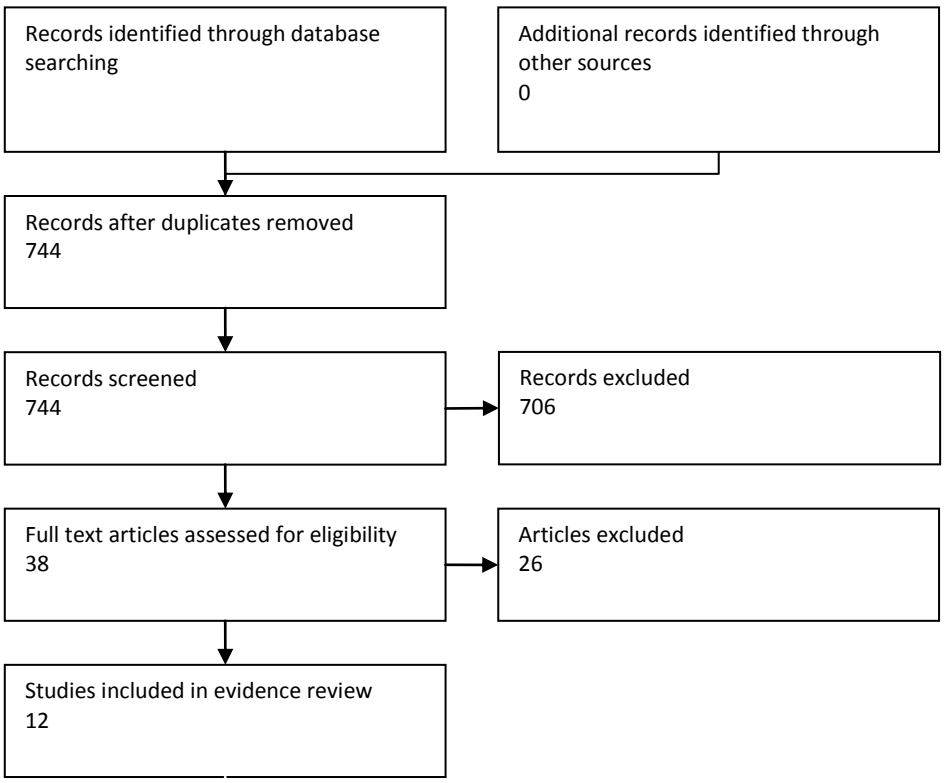
☺ Low Risk ☹ High Risk ? Unclear Risk

Figure 3.2: Risk of bias and applicability across studies



Search Results

Figure 3.3: Screening results



Evidence table

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Alexandrakis et al, 2001

Greece</td>
<td>28 consecutive patients with histologically and cytologically diagnosed myeloma
Male: 15, female: 13
Median age: 65 years
(range: 35-87)</td>
<td>• TC99MIBI (whole-body anterior and posterior scan)

• TC99 MDP (whole-body anterior and posterior scan)

• x-ray bone survey</td>
<td>• bone marrow aspiration and trephine biopsy</td>
<td>
<table>
<tr><th></th><th>x-ray positive</th><th>x-ray negative</th></tr>
<tr><td>Biopsy positive</td><td>26</td><td>2</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>Biopsy positive</td><td>22</td><td>6</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>TC99 MDP positive</th><th>TC99 MDP negative</th></tr>
<tr><td>Biopsy positive</td><td>15</td><td>13</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>x-ray</th><th>TC99 MIBI</th><th>TC99 MDP</th></tr>
<tr><td>sensitivity</td><td>92.8%</td><td>78.5%</td><td>53.5%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Risk of bias in patient selection. Only diagnosed patients included. No negative biopsy patients so unable to determine specificity

• Timing of reference standard unclear and unclear if index tests interpreted blinded to reference standard results</td>
</tr>
<tr>
<td>Alper et al., 2003

Turkey</td>
<td>20 consecutive patients with advanced stage myeloma at diagnosis
Male: 16, female: 4
Mean age: 62 years
(range: 41-80)</td>
<td>• TC99MIBI (whole-body anterior and posterior scan)

• TC99 MDP bone scintigraphy (whole-body)

• skeletal survey</td>
<td>• (standard criteria (Durie and Salmon, 1975))</td>
<td>
<table>
<tr><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>20</td><td>0</td></tr>
</table>
<table>
<tr><th>TC99 MDP positive</th><th>TC99 MDP negative</th></tr>
<tr><td>15</td><td>5</td></tr>
</table>
<table>
<tr><th>skeletal survey positive</th><th>skeletal survey negative</th></tr>
<tr><td>18</td><td>2</td></tr>
</table>
<table>
<tr><th></th><th>TC99MIBI</th><th>TC99 MDP</th><th>skeletal survey</th></tr>
<tr><td>sensitivity</td><td>100%</td><td>75%</td><td>90%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Risk of bias in patient selection. Only diagnosed patients included. No negative biopsy patients so unable to determine specificity

• No information reported on how myeloma diagnosis was done i.e., what was the reference standard. Paper states ‘ the staging of the disease was performed using standard criteria (durie and salmon, 1975)’</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Cascini et al., 2013

Italy</td>
<td>Prospective enrolment of all patients with a diagnosis of myeloma referred to the diagnostic imaging department. Patients were enrolled provided they had not been previously subjected to any therapy.

consecutive newly diagnosed patients (n=22)
Male: 10, female: 12
Age range: 48-83 years</td>
<td>• whole body MRI
(Head to toe.
T1 weighted STIR images.
No intravenous paramagnetic contrast material used)

• FDG PET/CT
(whole body scan from head to toe)</td>
<td>• bone marrow aspirate or biopsy</td>
<td>
<table>
<tr><th></th><th>MRI positive</th><th>MRI negative</th></tr>
<tr><td>Biopsy positive</td><td>22</td><td>0</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>FDG PET/CT positive</th><th>FDG PET/CT negative</th></tr>
<tr><td>Biopsy positive</td><td>18</td><td>4</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>Whole body MRI</th><th>FDG PET/CT</th></tr>
<tr><td>sensitivity</td><td>100%</td><td>82%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Risk of bias in patient selection. Only diagnosed patients included. No negative biopsy patients so unable to determine specificity.</td>
</tr>
<tr>
<td>Catalano et al., 1999

Italy</td>
<td>55 consecutive patients with an immune prolifertive disorder (46 myeloma, 3 solitary plasmacytoma, 6 MGUS)
Male: 34, female: 21
Mean age: 61.6 years
(range: 30-87)

23 untreated myeloma patients</td>
<td>• TC99MIBI
(anterior and posterior whole-body scans)</td>
<td>• skeletal x-ray</td>
<td>
<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>x-ray positive</td><td>7</td><td>3</td></tr>
<tr><td>x-ray negative</td><td>3</td><td>10</td></tr>
</table>
<table>
<tr><th></th><th>TC99MIBI</th></tr>
<tr><td>sensitivity</td><td>70%</td></tr>
<tr><td>specificity</td><td>77%</td></tr>
<tr><td>PPV</td><td>70%</td></tr>
<tr><td>NPV</td><td>77%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Dutoit wt al, 2014

Belgium</td>
<td>155 patients with MGUS, SMM or MM</td>
<td>SE-MRI of the thoracolumbar spine
DWI-MRI of the thoracolumbar spine</td>
<td>Biopsy (within one month of MRI)</td>
<td>
<table>
<tr><th>MRI – SI on b1000 images</th><th>MM</th><th>SMM or MGUS</th></tr>
<tr><td>≥ 16.75 aU</td><td>55</td><td>45</td></tr>
<tr><td><16.75 aU</td><td>9</td><td>46</td></tr>
</table>
Sensitivity 86%, specificity 51%

<table>
<tr><th>MRI – ADC1000 value</th><th>MM</th><th>SMM or MGUS</th></tr>
<tr><td>≥ 1.93X10^{-4} mm^2/s</td><td>48</td><td>61</td></tr>
<tr><td><1.93X10^{-4} mm^2/s</td><td>16</td><td>30</td></tr>
</table>
Sensitivity 75%, specificity 33%
</td>
<td>Blinded interpretation of MRI</td>
</tr>
<tr>
<td>Erten et al., 2007

Turkey</td>
<td>24 patients with myeloma
Male: 14 Female: 10
mean age: :57.7 ± 1.6 years (range 41-70 years)</td>
<td>• TC99MIBI
(dynamic scintigraphy was recorded starting on a bolus injection of 740MBq TC99MIBI. Lumbar spinal and pelvic images were obtained just after the injection. Static images were then recorded on the pelvis, femoral region, chest and shoulders. Then anterior and posterior whole body scans and static images of femur and equivocal sites were obtained)

• MRI
(imaging protocol consisted of T1-weighted spin-echo images and T2 weighted images which were obtained in axial, coronal and sagittal planes. Other sequences included T2 weighted gradient-echo, STIR, T2 weighted fast spin-echo and fat saturated echo)</td>
<td>• Durie-salmon staging system and bone marrow biopsy</td>
<td>From the 24 myeloma patients included in the study 18 were newly diagnosed patients.
All 18 had TC99MIBI scan. 13 also had MRI.

<table>
<tr><th></th><th>TC99 MIBI positive</th><th>TC99 MIBI negative</th></tr>
<tr><td>Biopsy positive</td><td>17</td><td>1</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
13 patients had MRI:
<table>
<tr><th></th><th>MRI positive</th><th>MRI negative</th></tr>
<tr><td>Biopsy positive</td><td>11</td><td>2</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>TC99MIBI</th><th>MRI</th></tr>
<tr><td>sensitivity</td><td>94%</td><td>85%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Risk of bias in patient selection. Only diagnosed patients included. No negative biopsy patients so unable to determine specificity.</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Kloth et al 2014,

Germany</td>
<td>547 patients with newly diagnosed monoclonal plasma cell disease. Myeloma (N=252), smouldering myeloma (157) and MGUS (N=138).</td>
<td>Whole body MRI</td>
<td>IMWG criteria 2003</td>
<td>Diagnostic accuracy for MM or SMM versus MGUS

<table>
<tr><th>MRI: any bone marrow infiltration</th><th>MM or SMM</th><th>MGUS</th></tr>
<tr><td>Yes</td><td>251</td><td>53</td></tr>
<tr><td>No</td><td>158</td><td>85</td></tr>
</table>
Sensitivity 61%, 62%

<table>
<tr><th>MRI: focal lesions</th><th>MM or SMM</th><th>MGUS</th></tr>
<tr><td>Yes</td><td>259</td><td>33</td></tr>
<tr><td>No</td><td>150</td><td>105</td></tr>
</table>
Sensitivity 63%, 76%</td>
<td></td>
</tr>
<tr>
<td>Myslivecek et al., 2008

Czech Republic</td>
<td>52 consecutive patients
Male: 35, female: 17
Median age: 61 years</td>
<td>• TC99MIBI scintigraphy
(anterior and posterior whole-body scans were obtained 10mins after IV administration of 740MBq (20mCi) ^{99m}Tc-MIBI)

• MRI
(MRI of Th and LS spine, T1 w.i. and STIR in the sagittal plane were performed)</td>
<td>• bone marrow biopsy</td>
<td>MGUS n=5
Stage I n=6
Stage II and III n=41

<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>Biopsy positive</td><td>39</td><td>2</td></tr>
<tr><td>Biopsy negative</td><td>0</td><td>11</td></tr>
</table>

<table>
<tr><th>MRI STIR</th><th>MRI positive</th><th>MRI negative</th></tr>
<tr><td>Biopsy positive</td><td>38</td><td>3</td></tr>
<tr><td>Biopsy negative</td><td>0</td><td>11</td></tr>
</table>

<table>
<tr><th>MRI T1 w.i.</th><th>MRI positive</th><th>MRI negative</th></tr>
<tr><td>Biopsy positive</td><td>38</td><td>3</td></tr>
<tr><td>Biopsy negative</td><td>6</td><td>5</td></tr>
</table>
6 patients with stage 1 myeloma had negative TC99MIBI and negative MRI STIR but were positive in MRI T1 w.i.

<table>
<tr><th></th><th>TC99MIBI</th><th>MRI STIR</th><th>MRI T1 w.i.</th></tr>
<tr><td>sensitivity</td><td>95%</td><td>93%</td><td>93%</td></tr>
<tr><td>specificity</td><td>100%</td><td>100%</td><td>45%</td></tr>
<tr><td>PPV</td><td>100%</td><td>100%</td><td>86%</td></tr>
<tr><td>NPV</td><td>85%</td><td>79%%</td><td>63%</td></tr>
</table></td>
<td>**Limitations:**
• Single centre study

• Limited details on study population so unclear if all patients newly diagnosed (not on treatment)

• Timing of reference standard unclear and unclear if index tests interpreted blinded to reference standard results</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Sager et al., 2011

Turkey</td>
<td>Retrospective analysis of 42 myeloma patients with FGD-PET CT imaging
Male: 27, female: 15
Mean age: 58.6 years
(range 22-87 years)
32 patients were referred for initial diagnosis and 10 were referred for assessment of therapy response.</td>
<td>• FGF PET/CT</td>
<td>• bone marrow biopsy</td>
<td>Patients referred at Initial diagnosis:
<table>
<tr><th></th><th>FDG PET-CT positive</th><th>FDG PET-CTI negative</th></tr>
<tr><td>Biopsy positive</td><td>29</td><td>3</td></tr>
<tr><td>Biopsy negative</td><td>0</td><td>0</td></tr>
</table>
Sensitivity of FGF PET/CT in detecting bone marrow involvement at initial diagnosis was 90%.</td>
<td>Limitations:
• Single centre study

• Small sample size

• Limited details on study population. Risk of bias as retrospective review of myeloma patients.
No negative biopsy patients so unable to determine specificity.</td>
</tr>
<tr>
<td>Sohn et al., 2002

South Korea</td>
<td>Twenty-two newly diagnosed myeloma patients
Male: 15, female: 7
Mean age: 57 years
(range 44-70 years)</td>
<td>•bone marrow immunoscintigraphy (BMIS) using technetium-99m-labelled AGA
(Whole-body planar imaging. Tomographic imaging was also acquired if a suspicious lesion was found on planar BMIS images)

• Skeletal radiography
(Skeletal radiographs were obtained of the skull, thoracic spine, lumbar spine, pelvis, chest and proximal sites of both upper and lower extremities)

• Tc- 99mTc-methylene diphosphonate (MDP) bone scan
(Whole-body bone imaging)</td>
<td>• bone marrow biopsy</td>
<td>
<table>
<tr><th></th><th>BMIS positive</th><th>BMIS negative</th></tr>
<tr><td>Biopsy positive</td><td>18</td><td>4</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>Skeletal radiography positive</th><th>Skeletal radiography negative</th></tr>
<tr><td>Biopsy positive</td><td>14</td><td>8</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>Bone scan positive</th><th>Bone scan negative</th></tr>
<tr><td>Biopsy positive</td><td>11</td><td>11</td></tr>
<tr><td>Biopsy negative</td><td>NR</td><td>NR</td></tr>
</table>
<table>
<tr><th></th><th>BMIS</th><th>Skeletal radiography</th><th>Bone scan</th></tr>
<tr><td>Sensitivity</td><td>82%</td><td>64%</td><td>50%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Limited details on study population. Risk of bias as retrospective review of myeloma patients.
No negative biopsy patients so unable to determine specificity</td>
</tr>
<tr>
<td>Svaldi et al., 2001

Italy</td>
<td>A total of 88 MIBI scans were carried out :
20 in MGUS
10 in nonhematological tumors

58 in 46 myeloma patients
Male: 24, female: 22
Median age: 56.5 years
(range 28.5-85.7 years)
15 patients at diagnosis</td>
<td>• TC99MIBI
(anterior and posterior whole-body scans)</td>
<td>• bone marrow biopsy</td>
<td>All stage II and III myeloma were positive at diagnosis.
Therefore the sensitivity of the MIBI scan at diagnosis was 100%.
Specificity was 93% (from the 30 patients not affected by myeloma 28 had a negative scan)
<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>biopsy positive</td><td>58</td><td>0</td></tr>
<tr><td>biopsy negative</td><td>2</td><td>28</td></tr>
</table>
<table>
<tr><th></th><th>TC99MIBI</th></tr>
<tr><td>sensitivity</td><td>100%</td></tr>
<tr><td>specificity</td><td>93%</td></tr>
<tr><td>PPV</td><td>97%</td></tr>
</table>
</td>
<td>Limitations:
• Single centre study

• Small sample size

• Limited details on study population</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table><tr><td>NPV</td><td>100%</td></tr></table></td><td></td></tr>
<tr><td>Zamagni et al., 2007

Italy</td><td>46 consecutive patients with newly diagnosed myeloma
Male: 30, female: 16
Median age: 55 years
(range: 42-65)</td><td>• FDG PET-CT
(Whole-body (including skull, upper limbs and femora)</td><td>• WBXR
(WBXR survey included plain radiographs of the skull, spine, pelvis, ribs, femora and humeri)</td><td><table><tr><th></th><th>FDG PET-CT positive</th><th>FDG PET-CT negative</th></tr><tr><td>WBXR positive</td><td>12</td><td>4</td></tr><tr><td>WBXR negative</td><td>21</td><td>9</td></tr></table>
<table><tr><th></th><th>FDG PET-CT</th></tr><tr><td>sensitivity</td><td>75%</td></tr><tr><td>specificity</td><td>30%</td></tr><tr><td>PPV</td><td>36%</td></tr><tr><td>NPV</td><td>69%</td></tr></table></td><td>Limitations:
• Single centre study

• Small sample size</td></tr>
</table>

1
2

References of included studies

1. Alexandrakis, M. G., Kyriakou, D. S., Passam, F., Koukouraki, S. & Karkavitsas, N. (2001) Value of Tc-99m sestamibi scintigraphy in the detection of bone lesions in multiple myeloma: comparison with Tc-99m methylene diphosphonate. *Annals of Hematology,* 80: 349-353.
2. Alper, E., Gurel, M., Evrensel, T., Ozkocaman, V., Akbunar, T. & Demiray, M. (2003) 99mTc-MIBI scintigraphy in untreated stage III multiple myeloma: comparison with X-ray skeletal survey and bone scintigraphy. *Nuclear Medicine Communications,* 24: 537-542.
3. Cascini, G. L., Falcone, C., Console, D., Restuccia, A., Rossi, M., Parlati, A. & Tamburrini, O. (2013) Whole-body MRI and PET/CT in multiple myeloma patients during staging and after treatment: personal experience in a longitudinal study. *Radiologia Medica,* 118: 930-948.
4. Catalano, L., Pace, L., Califano, C., Pinto, A. M., Renzo, A., Gennaro, F., Vecchio, S., Fonti, R., Salvatore, M. & Rotoli, B. (1999) Detection of focal myeloma lesions by technetium-99m-sestaMIBI scintigraphy. *Haematologica,* 84: 119-124.
5. Dutoit JC, Vanderkerken MA, & Anthonissen (2014). The diagnostic value of SE MRI and DWI of the spine in patients with monoclonal gammopathy of undetermined significance, smouldering myeloma and multiple myeloma. European Radiology, 24, 2754-2765.
6. Erten, N., Saka, B., Berberoglu, K., Turkmen, C., Unal, S., Bakir, B., Yekeler, E. & Besisik, S. K. (2007) Technetium-99m 2-methoxy-isobutyl-isonitrile uptake scintigraphy in detection of the bone marrow infiltration in multiple myeloma: correlation with MRI and other prognostic factors. *Annals of Hematology,* 86: 805-813.
7. Kloth, J. K. (2014). Appearance of monoclonal plasma cell diseases in whole-body magnetic resonance imaging and correlation with parameters of disease activity. International Journal of Cancer, 135, 2380-2386.
8. Myslivecek, M., Nekula, J., Bacovsky, J., Scudla, V., Koranda, P. & Kaminek, M. (2008) Multiple myeloma: predictive value of Tc-99m MIBI scintigraphy and MRI in its diagnosis and therapy. *Nuclear Medicine Review,* 11: 12-16.
9. Sager, S., Ergul, N., Ciftci, H., Cetin, G., Guner, S. I. & Cermik, T. F. (2011) The value of FDG PET/CT in the initial staging and bone marrow involvement of patients with multiple myeloma. *Skeletal Radiology,* 40: 843-847.
10. Sohn, S. K., Ahn, B. C., Lee, S. W., Kim, D. H., Chun, K. A., Kim, J. G., Park, S. H., Song, H. S., Lee, B. & Lee, J. (2002) Bone marrow immunoscintigraphy using technetium-99m anti-granulocyte antibody in multiple myeloma. *European Journal of Nuclear Medicine & Molecular Imaging,* 29: 591-596.
11. Svaldi, M., Tappa, C., Gebert, U., Bettini, D., Fabris, P., Franzelin, F., Osele, L. & Mitterer, M. (2001) Technetium-99m-sestamibi scintigraphy: an alternative approach for diagnosis and follow-up of active myeloma lesions after high-dose chemotherapy and autologous stem cell transplantation. *Annals of Hematology,* 80: 393-397.
12. Zamagni, E., Nanni, C., Patriarca, F., Englaro, E., Castellucci, P., Geatti, O., Tosi, P., Tacchetti, P., Cangini, D., Perrone, G., Ceccolini, M., Brioli, A., Buttignol, S., Fanin, R., Salizzoni, E., Baccarani, M., Fanti, S. & Cavo, M. (2007) A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. *Haematologica,* 92: 50-55.

Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. D'Sa, S., Abildgaard, N., Tighe, J., Shaw, P. & Hall-Craggs, M. (2007) Guidelines for the use of imaging in the management of myeloma. *British Journal of Haematology,* 137: 49-63.	Expert review.
2. Dimopoulos, M., Terpos, E., Comenzo, R. L., Tosi, P., Beksac, M., Sezer, O., Siegel, D., Lokhorst, H., Kumar,	Expert review.

S., Rajkumar, S. V., Niesvizky, R., Moulopoulos, L. A., Durie, B. G. & IMWG. (2009) International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. [Review] [123 refs]. *Leukemia,* 23: 1545-1556.	
3. Dutoit, J. C., Vanderkerken, M. A. & Verstraete, K. L. (2013) Value of whole body MRI and dynamic contrast enhanced MRI in the diagnosis, follow-up and evaluation of disease activity and extent in multiple myeloma. *European Journal of Radiology,* 82: 1444-1452.	Outcomes not relevant to PICO – study examines the extent of bone marrow invasion and doesn't look at diagnostic accuracy.
4. Gleeson, T. G., Moriarty, J., Shortt, C. P., Gleeson, J. P., Fitzpatrick, P., Byrne, B., McHugh, J., O'Connell, M., O'Gorman, P. & Eustace, S. J. (2009) Accuracy of whole-body low-dose multidetector CT (WBLDCT) versus skeletal survey in the detection of myelomatous lesions, and correlation of disease distribution with whole-body MRI (WBMRI). *Skeletal Radiology,* 38: 225-236.	Mixed population: patients referred for initial investigation of suspected plasma cell dyscrasia or those being restaged following therapy. 19 initial evaluation scans, and 20 restaging scans. Data reported for whole population. No data just on initial scans at diagnosis.
5. Horger, M., Claussen, C. D., Bross, B. U., Vonthein, R., Trabold, T., Heuschmid, M. & Pfannenberg, C. (2005) Whole-body low-dose multidetector row-CT in the diagnosis of multiple myeloma: an alternative to conventional radiography. *European.journal of radiology,* 54: 289-297.	Study not relevant to PICO. Aim of study was to establish an optimised whole-body low dose multidetector row-CT protocol.
6. Hung, G. U., Tsai, C. C., Tsai, S. C. & Lin, W. Y. (2005) Comparison of Tc-99m sestamibi and F-18 FDG-PET in the assessment of multiple myeloma. *Anticancer Research,* 25: 4737-4741.	Not imaging at diagnosis. FDG-PET without CT.
7. Hur, J., Yoon, C. S., Ryu, Y. H., Yun, M. J. & Suh, J. S. (2008) Comparative study of fluorodeoxyglucose positron emission tomography and magnetic resonance imaging for the detection of spinal bone marrow infiltration in untreated patients with multiple myeloma. *Acta Radiologica,* 49: 427-435.	Not diagnosis study but study of spinal bone marrow infiltration. FDG-PET without CT. No reference standard.
8. Hur, J., Yoon, C. S., Ryu, Y. H., Yun, M. J. & Suh, J. S. (2007) Efficacy of multidetector row computed tomography of the spine in patients with multiple myeloma: comparison with magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography. *Journal of Computer Assisted Tomography,* 31: 342-347.	10 patients with myeloma stage 3 underwent MDCT and MRI of the spine and FDG-PET. Not diagnosis study but study of spinal bone marrow infiltration. FDG-PET without CT No reference standard.
9. Ippolito, D., Besostri, V., Bonaffini, P. A., Rossini, F., Di, L. A. & Sironi, S. (2013) Diagnostic value of whole-body low-dose computed tomography (WBLDCT) in bone lesions detection in patients with multiple myeloma (MM). *European Journal of Radiology,* 82: 2322-2327.	Study was evaluation of feasibility of a low dose scan. No data on diagnostic accuracy or other outcomes listed in PICO.
10. Lu, Y. Y., Chen, J. H., Lin, W. Y., Liang, J. A., Wang, H. Y., Tsai, S. C. & Kao, C. H. (2012) FDG PET or PET/CT for detecting intramedullary and extramedullary lesions in multiple Myeloma: a systematic review and meta-analysis. [Review]. *Clinical Nuclear Medicine,* 37: 833-837.	Meta-analysis includes older studies on FDG PET without CT. Also not specific to diagnosis – includes studies on staging and/or recurrence.
11. Mele, A., Offidani, M., Visani, G., Marconi, M., Cambioli, F., Nonni, M., Catarini, M., Brianzoni, E., Berbellini, A., Ascoli, G., Brunori, M., Agostini, V., Corvatta, L., Isidori, A., Spinelli, A., Gradari, M. & Leoni, P. (2007) Technetium-99m sestamibi scintigraphy is sensitive and specific for the staging and the follow-up of patients with multiple myeloma:	Imaging not specific to diagnosis.

a multicentre study on 397 scans. *British Journal of Haematology,* 136: 729-735.	
12. Mirzaei S., F. (2003) Comparison of Technetium-99m-MIBI imaging with MRI for detection of spine involvement in patients with multiple myeloma. *BMC Nuclear Medicine,* 3: -4.	Imaging not specific to diagnosis. Not diagnosis study but study of spinal bone marrow infiltration.
13. Nanni, C., Zamagni, E., Cavo, M., Rubello, D., Tacchetti, P., Pettinato, C., Farsad, M., Castellucci, P., Ambrosini, V., Montini, G. C., Al-Nahhas, A., Franchi, R. & Fanti, S. (2007) 11C-choline vs. 18F-FDG PET/CT in assessing bone involvement in patients with multiple myeloma. *World Journal of Surgical Oncology,* 5: 68.	Imaging not at diagnosis
14. Nishiyama, Y., Yamamoto, Y., Nagai, M., Satoh, K. & Ohkawa, M. (2003) Comparative whole-body ^{201}Tl and bone scintigraphies for the detection of bone marrow involvement in multiple myeloma. *Nuclear medicine communications,* 24: 977-986.	^{201}Tl-chloride scintigraphy not in PICO.
15. Nishiyama, Y., Tateishi, U., Shizukuishi, K., Shishikura, A., Yamazaki, E., Shibata, H., Yoneyama, T., Ishigatsubo, Y. & Inoue, T. (2013) Role of 18F-fluoride PET/CT in the assessment of multiple myeloma: initial experience. *Annals of Nuclear Medicine,* 27: 78-83.	Not specific to imaging at diagnosis: 7 patients, 2 of which had received chemotherapy.
16. Okasaki, M. (2015). Comparison of (11)C-4'-thiothymidine, (11)C-methionine, and (18)F-FDG PET/CT for the detection of active lesions of multiple myeloma. Annals of Nuclear Medicine, 29, 224-232.	Most not newly diagnosed
17. Regelink, J. C., Minnema, M. C., Terpos, E., Kamphuis, M. H., Raijmakers, P. G., Pieters-van den Bos IC, Heggelman, B. G., Nievelstein, R. J., Otten, R. H., van Lammeren-Venema, D., Zijlstra, J. M., Arens, A. I., de Rooy, J. W., Hoekstra, O. S., Raymakers, R., Sonneveld, P., Ostelo, R. W. & Zweegman, S. (2013) Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. *British Journal of Haematology,* 162: 50-61.	Systematic review analysing methodology, diagnostic accuracy and detection rate of CT, FGF-PET, FDG-PET-CT and MRI in comparison to WBXR or CT as an alternative reference test for biopsy. Many studies not valid for our question: PET without CT, not specific to diagnosis, not assessment of diagnostic accuracy. Individual studies assessed independently for their relevance to the question and inclusion in the evidence review.
18. Sachpekidis, C. (2015). 18F-FDG Dynamic PET/CT in Patients with Multiple Myeloma: Patterns of Tracer Uptake and Correlation With Bone Marrow Plasma Cell Infiltration Rate. Clinical Nuclear Medicine, 40, e300-e307.	No diagnostic threshold reported.
19. Schirrmeister, H., Bommer, M., Buck, A. K., Muller, S., Messer, P., Bunjes, D., Dohner, H., Bergmann, L. & Reske, S. N. (2002) Initial results in the assessment of multiple myeloma using 18F-FDG PET. *European Journal of Nuclear Medicine & Molecular Imaging,* 29: 361-366.	FDG-PET without CT
20. Shortt, C. P., Gleeson, T. G., Breen, K. A., McHugh, J., O'Connell, M. J., O'Gorman, P. J. & Eustace, S. J. (2009) Whole-Body MRI versus PET in assessment of multiple myeloma disease activity. *AJR,* American Journal of Roentgenology. 192: 980-986.	Imaging not used for diagnosis but to assess disease activity. All patients had begun some form of chemotherapy before PET/CT and MRI.
21. Song, I. C., Kim, J. N., Choi, Y. S., Ryu, H., Lee, M. W., Lee, H. J. et al. (2014). Diagnostic and Prognostic Implications of Spine Magnetic Resonance Imaging at Diagnosis in Patients with Multiple Myeloma. Cancer Res.Treat..	Reference standard not reported
22. Surov, A. (2014). Non-osseous incidental findings in low-dose whole-body CT in patients with multiple myeloma. British Journal of Radiology, 87, 20140185.	Incidental findings (not myeloma related disease)

23. Villa, G., Balleari, E., Carletto, M., Grosso, M., Clavio, M., Piccardo, A., Rebella, L., Tommasi, L., Morbelli, S., Peschiera, F., Gobbi, M. & Ghio, R. (2005) Staging and therapy monitoring of multiple myeloma by 99mTc-sestamibi scintigraphy: a five year single center experience. *Journal of Experimental & Clinical Cancer Research,* 24: 355-361.	Not specific to imaging at diagnosis
24. Weng WW, Dong MJ, & Zhang (2014). A systematic review of MRI, scintigraphy, FDG-PET and PET/CT for diagnosis of multiple myeloma related bone disease--which is best? Asian Pacific Journal of Cancer Prevention: Apjcp, 15, 9879-9884.	Sytematic review but inappropriate analysis (univariate meta-analysis of sensitivity and specificity)
25. Wight, J., Morris, E., Stillwell, A., Grant, B., Lai, H. C., & Irving, I. (2015). Screening whole spine Magnetic Resonance Imaging (MRI) in multiple myeloma. Intern.Med.J..	Reference standard not reported
26. Zamagni, E., Nanni, C., Patriarca, F., Englaro, E., Castellucci, P., Geatti, O., Tosi, P., Tacchetti, P., Cangini, D., Perrone, G., Ceccolini, M., Brioli, A., Buttignol, S., Fanin, R., Salizzoni, E., Baccarani, M., Fanti, S. & Cavo, M. (2007) A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. *Haematologica,* 92: 50-55.	No reference standard. Comparison of different imaging methods for the assessment of bone involvement in myeloma patients.

1 **Checklists to identify risk of bias**

Study: Alexandrakis *et al., 2001*		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	28 patients with histologically and cytologically diagnosed myeloma were enrolled into this prospective study between February 1996 and April 1999.	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		No (no controls/patients without myeloma included)
Could the selection of patients have introduced bias?		Risk of bias. Patients with myeloma used in the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability		
Patient characteristics and setting	N=28 Inclusion criteria: patients with histologically and cytologically diagnosed myeloma Exclusion criteria: patients who received any kind of chemotherapy previously. Relapsed patients. Patients with infections and anaemia Clinical setting: secondary/tertiary care. Greece.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**X ray bone survey**
Were the index test results interpreted without knowledge of the results of the reference standard?		unclear
Could the conduct or interpretation of the index test have introduced bias?		unclear risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

Index test	**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?	unclear
Could the conduct or interpretation of the index test have introduced bias?	unclear risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**TC99MDP**
Were the index test results interpreted without knowledge of the results of the reference standard?	unclear
Could the conduct or interpretation of the index test have introduced bias?	unclear risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	TC99MDP done 72 hours after TC99MIBI. Unclear when x rays and reference standard biopsy done.
Was there an appropriate interval between index test and reference standard?	unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk of bias
Comments	n/a

1

2

Study: Alper *et al., 2003*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Twenty previously untreated patients with stage III myeloma
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No (no controls/patients without myeloma included)
Could the selection of patients have introduced bias?	Risk of bias. Patients with myeloma used in the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability	
Patient characteristics and setting	N= 20 Inclusion criteria: previously untreated newly diagnosed patients with stage III myeloma Exclusion criteria: anaemic patients with high reticulocyte counts

	Clinical setting: secondary/tertiary care. Turkey.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Index test		**TC99MDP**
Were the index test results interpreted without knowledge of the results of the reference standard?		yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Index test		**Skeletal survey**
Were the index test results interpreted without knowledge of the results of the reference standard?		yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**Not reported – standard criteria (durie and salmon 1975)**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	TC99MDP was done within 2-7 days of TC99MIBI. Skeletal survey was done within 2 weeks of TC99MIBI. Timing of reference standard unclear.	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

1

Study: *Cascini et al., 2013*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Prospective enrolment of all patients with a diagnosis of myeloma referred to the diagnostic imaging department.

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No (no controls/patients without myeloma included)
Could the selection of patients have introduced bias?	Risk of bias. Patients with myeloma used in the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability	
Patient characteristics and setting	N=22 Inclusion criteria: patients with newly diagnosed myeloma that had FDG-PET CT, MRI and bone biopsy Exclusion criteria: previously subjected to any therapy Clinical setting: secondary/tertiary care. Italy.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**FGF-PET CT**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**Whole body MRI**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow aspirate or biopsy**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The 2 index tests were done within 2 weeks of each other. The reference standard was done at least 15 days before imaging.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk of bias
Comments	n/a

1

1

Study: Catalano et al., 1999		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	23 previously untreated myeloma patients	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		unclear
Could the selection of patients have introduced bias?		Unclear risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N= 23 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**xray**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	unclear	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Unclear risk of bias
Comments	n/a	

2

3

Study: *Erten et al., 2007*		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	myeloma patients	
Was a consecutive or random sample of patients enrolled?		unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		No (no controls/patients without myeloma

	included)
Could the selection of patients have introduced bias?	Risk of bias. Patients with myeloma used in the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability	
Patient characteristics and setting	N= 18 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Turkey.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**MRI**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**Durie and Salmon staging system and bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	unclear
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk of bias
Comments	n/a

1

2

Study: *Myslivecek et al., 2008*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Not reported

Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	Unclear risk of bias
B. Concerns regarding applicability	
Patient characteristics and setting	N=52 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Czech Republic.
Are there concerns that the included patients and setting do not match the review question?	Unclear concern - unclear if all patients newly diagnosed (not on treatment)
INDEX TEST	
A. Risk of bias	
Index test	**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?	unclear
Could the conduct or interpretation of the index test have introduced bias?	unclear risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	unclear concern
Index test	**MRI**
Were the index test results interpreted without knowledge of the results of the reference standard?	unclear
Could the conduct or interpretation of the index test have introduced bias?	unclear risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	unclear concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**WBXR survey and bone marrow plasma cell count**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The 2 index tests were done within 14 days of each other but it is not reported when the reference standard was done.
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk of bias
Comments	n/a

1

2

Study: *Sager et al., 2011*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Retrospective review of patients with myeloma that had FDG-PET/CT imaging.

Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No (no controls/patients without myeloma included)
Could the selection of patients have introduced bias?	Risk of bias. Patients with myeloma used in the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability	
Patient characteristics and setting	N=32 Inclusion criteria: not reported. Exclusion criteria: not reported. Clinical setting: secondary/tertiary care. Turkey.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**FGF PET/CT**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	The index test was done within 2 weeks after the reference standard was done.
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk of bias
Comments	n/a

1

2

Study: *Sohn et al., 2002*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Newly diagnosed myeloma patients
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	No (no controls/patients without myeloma included)
Could the selection of patients have introduced bias?	Risk of bias. Patients with myeloma used in

	the study. Not patients with suspected myeloma, so no negative biopsy samples to measure specificity.
B. Concerns regarding applicability	
Patient characteristics and setting	N=22 Inclusion criteria: not reported. Exclusion criteria: not reported. Clinical setting: secondary/tertiary care. South Korea.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**bone marrow immunoscintigraphy (BMIS) using technetium-99m-labelled AGA**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**Skeletal radiography**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**Tc- 99mTc-methylene diphosphonate (MDP) bone scan**
Were the index test results interpreted without knowledge of the results of the reference standard?	yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	Tests for each patient were completed within 2 weeks
Was there an appropriate interval between index test and reference standard?	Yes
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk of bias

Comments	n/a

1

2

Study: *Svaldi et al., 2001*		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	Patients that had TC99MIBI scan	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclear risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=15 myeloma patients at diagnosis Inclusion criteria: Unclear. Exclusion criteria: Unclear. Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		unclear
Could the conduct or interpretation of the index test have introduced bias?		unclear risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**bone marrow biopsy**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?		unclear risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	unclear	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		unclear risk of bias
Comments	n/a	

3

4

Study: *Zamagni et al., 2007*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	Newly diagnosed myeloma patients

Was a consecutive or random sample of patients enrolled?		yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclearrisk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=46 myeloma patients at diagnosis Inclusion criteria: Unclear. Exclusion criteria: Unclear. Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**FDG-PET-CT**
Were the index test results interpreted without knowledge of the results of the reference standard?		yes
Could the conduct or interpretation of the index test have introduced bias?		low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**XBXR**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	FDG PET-CT was performed within 2 weeks of WBXR	
Was there an appropriate interval between index test and reference standard?		yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		low risk of bias
Comments	n/a	
Study: *Dutoit et al, 2014*		
PATIENT SELECTION		
A. risk of bias		
Patient sampling		
Was a consecutive or random sample of patients enrolled?		
Was a case-control design avoided?		
Did the study avoid inappropriate exclusions?		
Could the selection of patients have introduced bias?		
B. Concerns regarding applicability		
Patient characteristics and setting		
Are there concerns that the included patients and setting do not match the review question?		
INDEX TEST		
A. Risk of bias		
Index test		
Were the index test results interpreted without knowledge of		

the results of the reference standard?	
Could the conduct or interpretation of the index test have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	
Were the reference standard results interpreted without knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	
FLOW AND TIMING	
A. risk of bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	
Did all patients receive the same reference standard?	
Were all patients included in the analysis?	
Could the patient flow have introduced bias?	
Comments	n/a

1

2

Study: *Kloth et al 2014*	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	
Was a consecutive or random sample of patients enrolled?	
Was a case-control design avoided?	
Did the study avoid inappropriate exclusions?	
Could the selection of patients have introduced bias?	
B. Concerns regarding applicability	
Patient characteristics and setting	
Are there concerns that the included patients and setting do not match the review question?	
INDEX TEST	
A. Risk of bias	
Index test	
Were the index test results interpreted without knowledge of the results of the reference standard?	
Could the conduct or interpretation of the index test have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**bone marrow biopsy**
Is the reference standard likely to correctly classify the target condition?	

Were the reference standard results interpreted without knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	
FLOW AND TIMING	
A. risk of bias	
Flow and timing	
Was there an appropriate interval between index test and reference standard?	
Did all patients receive the same reference standard?	
Were all patients included in the analysis?	
Could the patient flow have introduced bias?	
Comments	n/a

1

2

Imaging for people with newly diagnosed myeloma

Review Question

What is the most effective imaging to guide treatment decisions in patients with newly diagnosed myeloma?

Question in PICO format

Population	Index test(s)	Comparator	Outcomes
Patients with newly diagnosed myeloma including the following subgroups: - Non-secretory - Asymptomatic - Symptomatic - Extra-medullary plasmacytoma - Multiple plasmacytomas	• MRI (spinal and whole body [WB]) • Multiparametric MRI • Diffusion weighted [DW] MRI • Dynamic contrast MRI • CT (including low dose [LD]) • FDG-PET/CT • Skeletal survey	Each other	• Patient acceptability (e.g., claustrophobia, anxiety over procedure, clinical exclusions) • Diagnostic yield • Incremental upstaging • Radiation exposure/risk of second primary cancers • Prognostic accuracy for PFS and OS • Skeletal-related events

Evidence statement

Imaging results

11 studies were identified and included in the evidence review. None of the studies employed a reference standard to verify the imaging results. The studies showed that:

- CT identified more lesions than radiography (3 studies [Kröpil et al., 2008; Princewill et al., 2013; Razek et al., 2013], N = 108; low quality; Tables 3.3 and 3.4) and was also associated with a higher radiation exposure than radiography (2 studies [Kröpil et al., 2008; Princewill et al., 2013], N = 80; low quality; Table 3.15);
- MRI identified more lesions than radiography (1 study [Wolf et al., 2014], N = 119; low quality; Tables 3.5 to 3.7);
- MRI and CT each identified more lesions than radiography (1 study, N = 18 [Mahnken et al., 2002]; low quality; Tables 3.8 and 3.9);
- PET-CT identified more lesions than radiography and an equivalent number of lesions to MRI in half of the included patients with more and less lesions detected, respectively, in the other two quarters of patients, compared to MRI (1 study [Nanni et al., 2006], N = 28; low quality);
- MRI identified more regions affected by myeloma than CT (1 study [Baur-Melnyk et al., 2008], N = 41; low quality; Table 3.10);
- WB-MRI identified more extensive disease than axial skeleton MRI (1 study [Bäuerle et al., 2009], N = 73; low quality; Tables 3.11-3.12)
- MRI identified a different pattern of disease than PET-CT (3 studies [Fonti et al., 2008; Lin et al., 2014; Spinnato et al., 2012], N = 239; low quality; Tables 3.13-3.14)

Results

Outcomes:

Diagnostic yield, incremental upstaging, and skeletal events (by test comparisons):

1. **<u>Radiograph versus CT: Kröpil et al. (2008), Princewill et al. (2013), and Razek et al. (2013)</u>**

1 Table 3.3: Radiograph versus CT

	Kröpil et al., 2008			Princewill et al., 2013			Razek et al., 2013		
	WB-MDCT	**CR**	**p-value**	**Skeletal survey**	**WB-CT**	**P-value**	**WB-MDCT positive**	**CR positive**	**p-value**
Anatomical region									
Anatomical bony region involvement total							98	55	0.001
Mean number of affected regions							3.39	1.96	
Mean number of lesions							~ 9.25	~16.32	
Total skeleton									
- No lesions (N = 0)	257	402	NS/NR						
- Single lesion	57	25							
- 2-4 lesions	70	32							
- > 4 lesions	120	63							
- Small lesion (< 3 mm)	33	8	NR						
Medium lesion (< 10 mm)	79	65	NR						
- Large lesion (> 10 mm)	135	47	NR						
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	150 59 26 92 177	50 46 49 163 214	NR NR NS/NR NR NR						
Vertebral column									
Skull							16	10	0.1
Spine							22	9	0.001
Fracture of spine							4	2	
- No lesions (N = 0)	15	72	p < 0.01						
- Single lesion	11	5							
- 2-4 lesions	15	4							
- > 4 lesions	43	6							
- Small lesion (< 3 mm)	12	0	NR						
Medium lesion (< 10 mm)	20	7	NR						
- Large lesion (> 10 mm)	37	8	NR						
Diagnostic confidence: - Definitely osteolysis	47 15 3	4 5 14	NR NR p <						

	Kröpil et al., 2008			Princewill et al., 2013			Razek et al., 2013		
	WB-MDCT	**CR**	**p-value**	**Skeletal survey**	**WB-CT**	**P-value**	**WB-MDCT positive**	**CR positive**	**p-value**
- Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	4 15	35 29	0.02 NR NR						
Pelvic skeleton							13	7	0.09
- No lesions (N = 0)	51	92	p < 0.01						
- Single lesion	12	5							
- 2-4 lesions	12	5							
- > 4 lesions	37	14							
- Small lesion (< 3 mm)	6	4	NR						
Medium lesion (< 10 mm)	11	9	NR						
- Large lesion (> 10 mm)	44	11	NR						
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	 46 11 2 6 47	 10 9 18 40 39	 NR NR p < 0.001 NR NR						
Thoracic cage							17	7	0.006
- No lesions (N = 0)	102	145	p < 0.01						
- Single lesion	20	4							
- 2-4 lesions	14	11							
- > 4 lesions	26	14							
- Small lesion (< 3 mm)	7	0	NR						
Medium lesion (< 10 mm)	24	23	NR						
- Large lesion (> 10 mm)	29	6	NR						
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no	 31 13 9 15 100	 11 12 12 54 85	 NR NR NS/NR NR NR						

	Kröpil et al., 2008			**Princewill et al., 2013**			**Razek et al., 2013**		
	WB-MDCT	**CR**	**p-value**	**Skeletal survey**	**WB-CT**	**P-value**	**WB-MDCT positive**	**CR positive**	**p-value**
osteolysis - Definitely no osteolysis									
Extremities									
Upper extremities							14	10	0.28
Lower extremities							16	12	0.5
- No lesions (N = 0)	66	69	NS/NR						
- Single lesion	11	9							
- 2-4 lesions	23	12							
- > 4 lesions	12	26							
- Small lesion (< 3 mm)	7	3	NR						
Medium lesion (< 10 mm)	16	22	NR						
- Large lesion (> 10 mm)	23	22	NR						
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	18 17 11 66 0	23 18 4 22 49	NR NR NS NR NR						
Extraosseous findings **- extramedullary**	9 1								
Hyper-attenuating medullary lesions: Focal							6		
Hyper-attenuating medullary lesions: Diffuse marrow involvement							3		
Extra-osseous lesions							Pleural effusion (3); pulmonary infiltrates (2); hepatic lesions (2); lymphadenopathy (1);		

	Kröpil et al., 2008			Princewill et al., 2013			Razek et al., 2013		
	WB-MDCT	**CR**	**p-value**	**Skeletal survey**	**WB-CT**	**P-value**	**WB-MDCT positive**	**CR positive**	**p-value**
							para- and intraspinal soft tissue mass with spinal cord compression (2)		
Total number of lytic lesions				248	968	p < 0.001			
Total number of skull lesions				86	94	p = 0.02			
Total number of spine lesions				49	241	p < 0.001			
Total number of rib lesions				2	102	p < 0.001			
Total number of sternal lesions				1	120	p < 0.001			
Total number of flat bone lesions				36	240	p < 0.001			
Total number of long bone lesions				74	171	p < 0.001			
Stage: **I** **II** **III**							 1 15 12	 8 16 4	

Table 3.4: Radiograph versus CT: Extra results from Princewill et al. (2013): WB-CT versus skeletal survey

Patients with no lesions detected by either test	9/51
Patients with more lesions detected by WB-CT than skeletal survey	39/42 (i.e., 51-9 w/o lesions)
Patients with more lesions detected by skeletal survey than WB-CT	3/42 (i.e., 51-9 w/o lesions)
Patients with new osteolytic lesions missed on skeletal survey, but detected on WB-CT	8
Patients with upstaged disease (overall)	31/51
Patients upstaged from stage I-II based on WB-CT	13/51
Patients upstaged from stage I-III based on WB-CT	9/51
Patients upstaged from stage II-III based on WB-CT	9/51
Patients with no overall change in stage of disease (WB-CT and skeletal survey)	20/51

Razek et al. (2013): WB-MDCT versus conventional skeletal radiography

- Upstaging: 14 patients were upstaged as WB-MDCT revealed more extensive disease than CR: Stage I to II: N = 6; stage I to III: N = 1; stage II to III: N = 7 (significant difference in stage between WB-MDCT and CR, p = 0.002).
- Due to upstaging in 7 patients, the medical treatment plan changed (N = 4 were candidates for stem cell transplant, and N = 3 were not).

2. Radiograph versus MRI: Wolf et al. (2013)

Table 3.5: Radiograph versus WB-MRI: Wolf et al. (2013): Theoretical change in staging

	Projection radiography	WB-MRI	P-value
No focal lesions (no of patients)	95	76	
Focal lesions (no of patients)	24	43	p < 0.001
- Axial (no of patients)	4	11	
- Extraaxial (no of patients)	14	12	
- Axial (intra-osseous and corticalis exceeding)	Not reported	Not reported	p < 0.001
- Axial (intra-osseous)	Not reported	Not reported	p < 0.001
- Axial (corticalis exceeding)	Not reported	Not reported	p = 0.02
- Extra-axial (intra-osseous and corticalis exceeding)	Not reported	Not reported	p < 0.001
- Extraaxial (intra-osseous)	Not reported	Not reported	p < 0.001
- Extraaxial (corticalis exceeding)			p = 0.002

Table 3.6: Radiograph versus WB-MRI: Wolf et al. (2013): Stage

	Durie-Salmon	Durie-Salmon PLUS
MGUS	28	40
I	44	7
II	8	52
III	36	20
Plasmacytoma	3	0

Table 3.7: Radiograph versus WB-MRI: Wolf et al. (2013): Theoretical change in staging and treatment based on Durie-Salmon PLUS

	Durie-Salmon
Change in staging:	
- None	36
- Up-staging	38
- Down-staging	45
Change in treatment:	
- None	78
- Treatment indicated	33
- Treatment not indicated	8

3. Radiograph versus MDCT versus MRI: Mahnken et al. (2002)

Table 3.8: Radiograph versus MDCT versus MRI (all thoracic and lumbar spine; CT and radiograph also pelvis): Mahnken et al. (2002): 325 vertebrae assessed in 18 patients:

	Radiography	MDCT	MRI	Matches in all 3 imaging modalities (N = 226)
Normal bone	118	94	101	84
Diffuse osteopenia with microlacunae and trabecular disruption	154	117	224 abnormal	104
Lacunae > 5 mm, and permeation of cortical bone	13	45		4

Nodular lesions > 1 cm	40	69		34
Number of vertebral fractures	72	86	62	
Number of vertebrae considered at risk	6	12	9	

- Divergent imaging finding between MD-CT and MR imaging would have lead to under-staging of 5 patients if using MRI exclusively, whereas if using MRI and skeletal radiography would lead to understaging 3 patients

Table 3.9: Radiograph versus MDCT versus MRI (all thoracic and lumbar spine; CT and radiograph also pelvis): Mahnken et al. (2002): 180 pelvic areas assessed in 18 patients):

	Radiography	**MDCT**
Normal bone	100	74
Diffuse osteopenia with microlacunae and trabecular disruption	43	34
Lacunae > 5 mm, and permeation of cortical bone	16	38
Nodular lesions > 1 cm	21	34

All lesions detected on radiography were also detected on MD-CT.

4. Radiograph versus MRI versus PET-CT: Nanni et al. (2006)

Nanni et al. (2006): 18F-FDG PET-CT (skull to femora, incl) versus spinal-pelvic MRI versus WB-xray

18F-FDG PET-CT versus WB-Xray:
- More bone lesions detected by PET-CT than WB-XR: 16/28 patients
- Equivalent findings between the two tests: 12/28 patients (4 had no lesions, and 8 had ≥ lesions)

18F-FDG PET-CT versus MRI:
- More lesions detected by PET-CT than MRI: 7/28 patients (all located outside the MRI FOV)
- Equivalent findings between the two tests: 14/28 patients (4 had no lesions, and 8 had ≥ lesions)
- Fewer pathological findings detected by PET-CT than MRI: 7/28 patients.

5. CT versus MRI: Baur-Melnyk et al. (2008)

Table 3.10: WB-MDCT versus WB-MRI: Baur-Melnyk et al. (2008)

	WB-MDCT	**WB-MRI**	**p-value**
No involvement	19	15	
Regions* affected by myeloma	462	975	p < 0.001
Focal disease	9	13	
Combined focal and diffuse		13	
Multifocal (> 20) disease		20	
Pure diffuse disease		1	
Stage# I	25	21	p < 0.001
Stage II	7	2	
Stage III	9	18	

* The skeleton was divided into 61 regions; # Durie and Salmon PLUS

Baur-Melnyk et al. (2008): WB-MDCT versus WB-MRI
- Concordant findings between WB-MDCT and WB-MRI: No involvement (N = 15), involvement (N = 4, all focal).
- Dis-concordant findings between WB-MDCT and WB-MRI: More extensive disease on WB-MRI than on WB-MDCT (N =21; 7 with focal disease, 13 combined diffuse and focal, and 1 diffuse); more extensive disease on WB-MDCT than on WB-MRI (N =1). Four patients were stage I on WB-MDCT and stage II (N = 2) or stage III (N = 2) on WB-MRI.

6. MRI versus WB-MRI: Bäuerle et al. (2009)

Table 3.11: Axial skeleton MRI versus WB-MRI: Bäuerle et al. (2009): Distribution of lesions (not split by type of MRI test, so main message to take away of probably how many are within the axial skeleton and how many outside it)

Located in axial skeleton only: **- No of patients** **- No of lesions**	 9 25
Located in extraaxial skeleton only: **- No of patients** **- No of lesions**	 7 21
Located in axial and extraaxial: **- No of patients** **- No of lesions**	 26 395
No lesions (no of patients)	31
Bone involvement (no of patients): **- Axial skeleton: In bone** **- Axial skeleton: Violating bone** **- Total**	 33 15 35
Bone involvement (no of lesions): **- Axial skeleton: In bone** **- Axial skeleton: Violating bone** **- Total**	 214 24 238
Bone involvement (no of patients): **- Extraaxial skeleton: In bone** **- Extraaxial skeleton: Violating bone** **- Total**	 33 13 33
Bone involvement (no of lesions): **- Extraaxial skeleton: In bone** **- Extraaxial skeleton: Violating bone** **- Total**	 185 18 203

Table 3.12: Axial skeleton MRI versus WB-MRI: Bäuerle et al. (2009): Durie-Salmon PLUS stage by test

	Axial skeleton MRI	**WB-MRI**
MGUS	4	0
IA	37	40
IB	17	14
II	11	19
III	4	6

7. MRI versus PET-CT: Fonti et al. (2008), Lin et al. (2014) and Spinnato et al. (2012)

Table 3.13: 18F-FDG PET-CT versus MRI

	Fonti et al. (2008) All data			**Lin et al. (2014)**		
	WB-18F-FDG PET-CT	**MRI, spine and pelvis**	**p-value**	**18F-FDG PET-CT**	**WB-MRI**	**p-value**
Normal (no of patients)	1	6				
Diffuse (no of patients)	3	13		6	15: Mild: N = 4 Moderate: N = 8 Severe	Not reported

					: N = 3	
Focal (no of patients)	16	6	p < 0.001	10	13	Not reported
Combined focal and diffuse (no of patients)	13	8	p < 0.001			
Focal lesions **- Spine** **- Pelvis** **- Soft tissue** **- Other**	196 35 40 18 103	51 40 11				
Mean no of focal lesions per patient (SD)	5.94 (9.29)	1.54 (2.45)	p < 0.001			
Durie/Salmon PLIUS stage: **I (total no of lesions)** **II (total number of lesions)** **III**				6 (10) 2 (17) 2	3 (4) 1 (9) 9	Not reported

Table 3.14: 18F-FDG PET-CT versus MRI: Fonti et al. (2008): Only data from spinal and pelvic districts

	18F-FDG PET-CT	**MRI**	**p-value**
Normal (no of patients)	12	6	
Diffuse (no of patients)	6	13	
Focal and focal-diffuse (no of patients)	15	14	p < 0.001
Mean no of focal lesions per patient (SD)	2.27 (4.64)	1.54 (2.45)	Non-significant

Spinnato et al. (2012): WB-18F-FDG PET-CT versus WB-MRI

- In 5/62 patients PET-CT was negative whereas MRI showed mild (N = 3) or moderate (N = 2) diffuse spine involvement.
- In (another) 4/62 patients MRI showed a micronodular pattern with salt-and-pepper appearance of bone marrow, whereas PET was negative with the exception of one patient where CT showed mild and diffuse micronodular bone involvement.
- In 23/62 patients PET-CT detected lesions of the MRI field of view, in 3 of whom MRI was normal on the entire spine and pelvis.
- 12/62 patients with dis-concordant PET-CT and MRI findings were down-staged due to PET-CT (N = 11) or MRI (N = 1) findings.

Radiation exposure

Table 3.15: Radiation exposure

	Baur-Melnyk et al., (2008)	**Kröpil et al. (2008)**		**Princewill et al. (2013)**	
	MDCT	**MDCT**	**CR**	**WB-CT**	**SS**
Effective radiation dose (mSv)	3.95	4.8	1.7	4.1	1.8

				(range 2.2-4.9)	
Thyroid gland - Female patients - Male patients		 7 6.9			
Female breast - Female patients		 5.5			
Liver - Female patients - Male patients		 5 5.1			
Ovaries - Female patients		 4.3			
Testes - Male patients		 5.2			
Bones marrow - Female patients - Male patients		 4.1 3.9			
Skeleton - Female patients - Male patients		 8.7 8.4			
Uterus - Female patients		 4.6			

MDCT = multidetector CT; CR = conventional skeletal survey; SS = skeletal survey

Mahnken et al. (2002):

- "The examination protocol that we used resulted in a cumulative dose of 23.3 mSv (ICRP 26) and 25.5 mSv (ICRP 60) in men and 39.8 mSv (ICRP 26) and 36.6 mSv (ICRP 60) in women, respectively. Effective energy was calculated as 82.4 keV."

Outcomes:

Risk of second primary cancers, patient acceptability, and prognostic accuracy for progression-free survival and overall survival:

We did not find evidence for this outcome.

Study quality

The risk of bias and applicability concerns are summarized in Figure 3.4. A modified version of the QUADAS-2 assessment tool was used to evaluate the risk of bias and applicability concerns in the included studies. It was clear a priori that it would not be likely that any studies included a reference standard, so it was therefore decided not to make this a part of the inclusion criteria, although this strategy naturally means that none of the index/comparator test results were verified. Consequently, it is not possible to know, based on the present evidence, which of the index/comparison tests is better when the results differ between the tests, nor indeed if the results are correct even when they do not differ between the included tests.

In a number of the included studies, it was unclear whether the patient selection was consecutive (Baur-Melnyk et al., 2008; Bäuerle et al, 2009; Fonti et al., 2009; Lin et al., 2014; Mahnken et al., 2002; Spinnato et al., 2012) and in one study it was clear that it was not (Wolf et al., 2014; high risk) whereas in the remainder patient selection was consecutive and therefore considered at low risk of bias (Kröpil et al, 2008; Nanni et al., 2006; Princewill et al., 2013, Razek et al., 2013).

The majority of the studies employed blinded assessment of the index and comparator tests, that is, the results were blinded, at least, to those of the other imaging tests, and were therefore considered at low risk whereas the remaining four studies did not employ blinded reading of the index and comparator test results and,

consequently, these studies were rated at high risk of bias (Baur-Melnyk et al., 2008; Kröpil et al, 2008; Mahnken et al., 2002; Nanni et al., 2006).

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX/ COMPARATOR TESTS	REFERENCE STANDARD	TIME INTERVAL BETWEEN TESTS	PATIENT POPULATION	INDEX/ COMPARATOR TESTS	REFERENCE STANDARD
Baur-Melnyk et al., 2008	?	☹	X	☺	☺	☺	X
Bäuerle et al, 2009	?	☺	X	☺	☺	☺	X
Fonti et al., 2008	?	☺	X	☺	☺	☺	X
Kröpil et al, 2008	☺	☹	X	?	☺	☺	X
Lin et al., 2014	?	☺	X	☺	?	☺	X
Mahnken et al., 2002	?	☹	X	☺	?	☺	X
Nanni et al., 2006	☺	☹	X	☺	☺	☺	X
Princewill et al.,	☺	☺	X	☺	?	☺	X

The time interval between the index and comparator tests was acceptable in all but two of the included studies where it was unclear (Kröpil et al, 2008; Wolf et al., 2014).

Generally the studies were found to be applicable to the review question in terms of the index/comparator tests employed and, for the most part, the populations. However, the applicability of the populations of four studies was unclear (Lin et al., 2014; Mahnken et al., 2002; Princewill et al, 2013; and Wolf et al., 2014) as these populations seemed to either be subject to excessive exclusions (for the present purposes: Lin et al., 2014), consist of a narrow range of patients (i.e., all stage III who may or may not have been treated, Mahnken et al., 2002) or be a mix of patients only some of whom are applicable to the current question (Princewell et al., 2013; Wolf et al., 2014).
The small sample sizes of all the included studies should also be noted as a clear limitation.

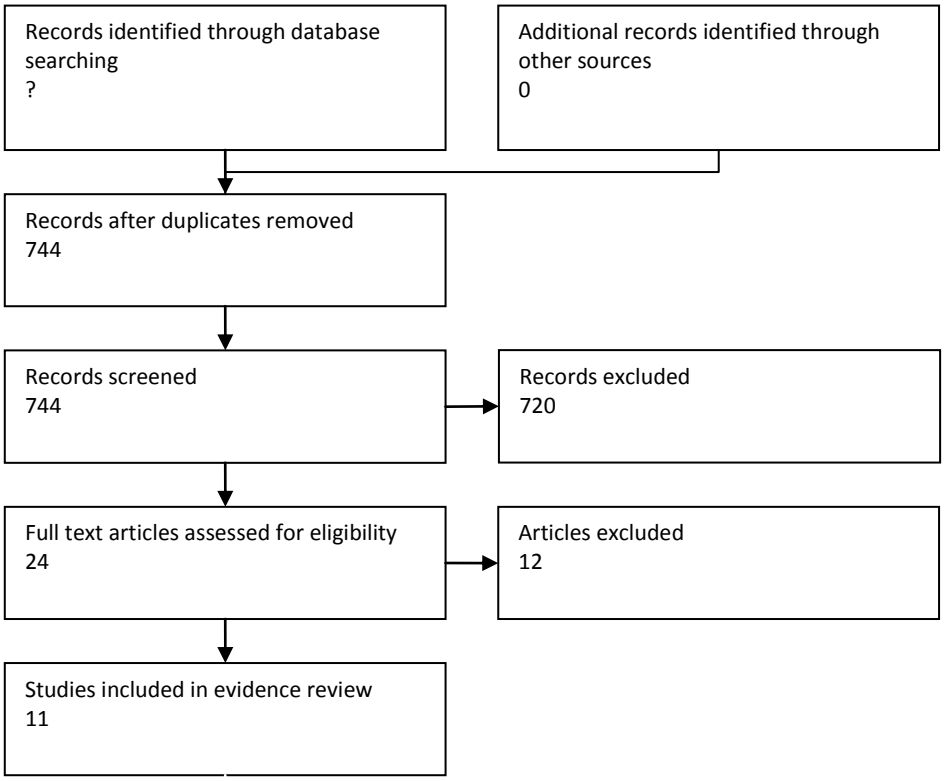
Figure 3.4: Risk of bias and applicability for individual studies

2013							
Razek et al., 2013	☺	☺	X	☺	☺	☺	X
Spinnato et al., 2012	?	☺	X	☺	☺	☺	X
Wolf et al., 2014	☹	☺	X	?	?	☺	X

☺Low Risk ☹High Risk ? Unclear risk X No reference standard, i.e., no verification of the index/comparator test results

Search Results

Figure 3.5: Screening results



Evidence tables

Baur-Melnyk et al, 2008

Population: 41 patients with newly diagnosed multiple myeloma (iliac crest bone marrow biopsy): 15 males, 26 females; mean (range) age: 61 (39-88) years; IgG- (N = 20), IgA- (N = 7), Bence Jones (N = 13), extramedullary plasmacytoma (N = 1); Germany.

Index test: WB-multidetector [MD] CT: Skull to knees on Siemens SOMATOM sensation 16 or 64.

Mean interval (range) between WB-MRI and WB-MDCT: 30 (1-42) day

Image analysis performed by 2 expert radiologists in consensus.

Comparator test: WB-MRI: T1/STIR "The MRI examinations were performed on a 1.5-T system (Symphony or Avanto, Siemens".

Image analysis performed by 2 expert radiologists in consensus.

Results:

	WB-MDCT	**WB-MRI**	**p-value**
No involvement	19	15	
Regions* affected by myeloma	462	975	p < 0.001
Focal disease	9	13	
Combined focal and diffuse		13	
Multifocal (> 20) disease		20	
Pure diffuse disease		1	
Stage# I **Stage II** **Stage III**	25 7 9	21 2 18	p < 0.001

* The skeleton was divided into 61 regions; # Durie and Salmon PLUS

- Concordant findings between WB-MDCT and WB-MRI: No involvement (N = 15), involvement (N = 4, all focal).
- Dis-concordant findings between WB-MDCT and WB-MRI: More extensive disease on WB-MRI than on WB-MDCT (N =21; 7 with focal disease, 13 combined diffuse and focal, and 1 diffuse); more extensive disease on WB-MDCT than on WB-MRI (N =1). Four patients were stage I on WB-MDCT and stage II (N = 2) or stage III (N = 2) on WB-MRI.

- Mean effective dose of CT = 3.95 mSv

Additional comments:

Study quality:

- Prospective study
- Patient selection unclear if consecutive.

- Applicable population
- Non-blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard
- Acceptable time interval between index and comparator tests
- Small sample size

Bäuerle et al, 2009

Population: 73 patients with untreated multiple myeloma (Durie-Salmon stages I-III)with no previous chemotherapy aged > 18 years and WHO status ≥ 2: N = 73, 42 males, 31 females; N = 35 with stage I (median [range] age = 54 [31-74] years) and 38 patients with stages II-III (median [range] age = 60 [27-80] years); Germany
Exclusions: Contraindications to MRI.

Index test: Axial skeleton MRI: "standard contrast-enhanced MR imaging of the axial skeleton (spine and sacral bone)", "MR imaging of the axial skeleton was performed as accompanying morphologic imaging within a study of dynamic contrast-enhanced MR imaging in patients with plasma cell disorders." T1-weighted Spin-Echo, T2-weighted STIR, postcontrast T1-weighted Fat saturated TSE of the axial skeleton alone (including cervical, thoracic, and lumbar spine and sacral bone) on a 1.5T-imager (Symphony, Siemens).

Interval between WB-MRI and axial skeleton MRI: Within 30 days.

Image analysis performed by 2 radiologists with 4 and 5 years experiences, respectively, in consensus, blinded to diagnosis.

Comparator test: WB-MRI: T1-weighted TSE, T2-weighted STIR and T2*-weighted 2D FLASH of the axial and appendicular skeleton, but not the distal parts of the arms and calvesor the feet (depending on the height of the patients, on a 1.5-T imager (Avanto, Siemens).

Image analysis performed by 2 radiologists with 4 and 5 years experiences, respectively, in consensus, blinded to diagnosis.

Results:

Distribution of lesions (not split by type of MRI test, so main message to take away of probably how many are within the axial skeleton and how many outside it)

Located in axial skeleton only: **- No of patients** **- No of lesions**	 9 25
Located in extraaxial skeleton only: **- No of patients** **- No of lesions**	 7 21
Located in axial and extraaxial: **- No of patients** **- No of lesions**	 26 395
No lesions (no of patients)	31
Bone involvement (no of patients):	

- Axial skeleton: In bone	33
- Axial skeleton: Violating bone	15
- Total	35
Bone involvement (no of lesions):	
- Axial skeleton: In bone	214
- Axial skeleton: Violating bone	24
- Total	238
Bone involvement (no of patients):	
- Extraaxial skeleton: In bone	33
- Extraaxial skeleton: Violating bone	13
- Total	33
Bone involvement (no of lesions):	
- Extraaxial skeleton: In bone	185
- Extraaxial skeleton: Violating bone	18
- Total	203

Durie-Salmon PLUS stage by test

	Axial skeleton MRI	**WB-MRI**
MGUS	4	0
IA	37	40
IB	17	14
II	11	19
III	4	6

Additional comments:

Study quality:

- Retrospective study
- Patient selection unclear if consecutive.
- Applicable population.
- Blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard.
- Acceptable time interval between index and comparator tests
- Small sample size

Fonti et al, 2008

Population: 33 patients with newly diagnosed multiple myeloma: 22 males, 11 females; mean (SD) age: 64 (12) years; Italy.

Index test: WB-18F-FDG PET-CT: From base of skull to feet on GE Healthcare Discovery LS8.

Interval between MRI and WB-18F-FDG PET-CT: Within 10 days

Image analysis performed by 2 expert radiologists in consensus, blinded to other imaging results and clinical information.

Comparator test: MRI of spine and pelvis: T1- and T2 weighted gadopentetate dimeglumine-enhanced MRI examinations on a 1.5-T Phillips Achieva.

Image analysis performed by 2 independent nuclear medicine physicians or 2 independent radiologists, blinded to other imaging results.

Results:

All data

	WB-18F-FDG PET-CT	**MRI, spine and pelvis**	**p-value**
Normal (no of patients)	1	6	
Diffuse (no of patients)	3	13	
Focal (no of patients)	16	6	p < 0.001
Combined focal and diffuse (no of patients)	13	8	p < 0.001
Focal lesions **- Spine** **- Pelvis** **- Soft tissue** **- Other**	196 35 40 18 103	51 40 11	
Mean no of focal lesions per patient (SD)	5.94 (9.29)	1.54 (2.45)	p < 0.001

Only data from spinal and pelvic districts

	18F-FDG PET-CT	**MRI**	**p-value**
Normal (no of patients)	12	6	
Diffuse (no of patients)	6	13	
Focal and focal-diffuse (no of patients)	15	14	
Mean no of focal lesions per patient (SD)	2.27 (4.64)	1.54 (2.45)	Non-significant

Additional comments:

Study quality:

- Prospective study
- Patient selection unclear if consecutive.

- Applicable population
- Blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard
- Acceptable time interval between index and comparator tests
- Small sample size

Kröpil et al, 2008

Population: 29 consecutive patients with a clinical diagnosis of multiple myeloma (stage I to III according to the criteria of Durie and Salmon): 16 males, 13 females; mean (range) age: 57 (44-73) years; Germany.
Exclusions: Aged < 40 years, severe claustrophobia, inability to remain in supine position for a few minutes.

Index test: WB-multidetector [MD] CT: Base of skull to knee joints on Siemens SOMATOM sensation Cardiac 64; Non-contrast enhanced.

Mean interval (range) between CR and WB-MDCT: Not reported

Image analysis performed by 2 radiologists in consensus. Skeleton divided into six anatomical regions: Base of the skull, vertebral column, pelvic skeleton, thoracic cage, and extremities, which were each evaluated for lytic marrow lesions.

Comparator test: Conventional skeletal radiography (CR): "A skeletal survey was obtained by CR according to the Parisian Pattern using a digital X-ray unit (Axiom Aristos, Siemens".

Image analysis performed by 2 radiologists in consensus

Results:

Nineteen skeletal areas were examined (it is not clear what the numbers reflect in the case of "No lesions (N = 0)".

	WB-MDCT	**CR**	**p-value**
Anatomical region			
Total skeleton			
- No lesions (N = 0)	257	402	NS/NR
- Single lesion	57	25	
- 2-4 lesions	70	32	
- > 4 lesions	120	63	
- Small lesion (< 3 mm)	33	8	NR
Medium lesion (< 10 mm)	79	65	NR
- Large lesion (> 10 mm)	135	47	NR
Diagnostic confidence:			
- Definitely osteolysis	150	50	NR
- Probably osteolysis	59	46	NR

- Uncertain findings	26	49	NS/NR
- Probably no osteolysis	92	163	NR
- Definitely no osteolysis	177	214	NR
Vertebral column			
- No lesions (N = 0)	15	72	p < 0.01
- Single lesion	11	5	
- 2-4 lesions	15	4	
- > 4 lesions	43	6	
- Small lesion (< 3 mm)	12	0	NR
Medium lesion (< 10 mm)	20	7	NR
- Large lesion (> 10 mm)	37	8	NR
Diagnostic confidence:			
- Definitely osteolysis	47	4	NR
- Probably osteolysis	15	5	NR
- Uncertain findings	3	14	p < 0.02
- Probably no osteolysis	4	35	NR
- Definitely no osteolysis	15	29	NR
Pelvic skeleton			
- No lesions (N = 0)	51	92	p < 0.01
- Single lesion	12	5	
- 2-4 lesions	12	5	
- > 4 lesions	37	14	
- Small lesion (< 3 mm)	6	4	NR
Medium lesion (< 10 mm)	11	9	NR
- Large lesion (> 10 mm)	44	11	NR
Diagnostic confidence:			
- Definitely osteolysis	46	10	NR
- Probably osteolysis	11	9	NR
- Uncertain findings	2	18	p <
- Probably no osteolysis	6	40	0.001
- Definitely no osteolysis	47	39	NR
			NR
Thoracic cage			
- No lesions (N = 0)	102	145	p < 0.01
- Single lesion	20	4	
- 2-4 lesions	14	11	

- > 4 lesions	26	14	
- Small lesion (< 3 mm)	7	0	NR
Medium lesion (< 10 mm)	24	23	NR
- Large lesion (> 10 mm)	29	6	NR
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	 31 13 9 15 100	 11 12 12 54 85	 NR NR NS/NR NR NR
Extremities			
- No lesions (N = 0)	66	69	NS/NR
- Single lesion	11	9	
- 2-4 lesions	23	12	
- > 4 lesions	12	26	
- Small lesion (< 3 mm)	7	3	NR
Medium lesion (< 10 mm)	16	22	NR
- Large lesion (> 10 mm)	23	22	NR
Diagnostic confidence: - Definitely osteolysis - Probably osteolysis - Uncertain findings - Probably no osteolysis - Definitely no osteolysis	 18 17 11 66 0	 23 18 4 22 49	 NR NR NS NR NR
Extraosseous findings **- extramedullary**	9 1		
Effective radiation dose (mSv)	4.8	1.7	
Thyroid gland - Female patients - Male patients	 7 6.9		
Female breast - Female patients	 5.5		
Liver - Female patients - Male patients	 5 5.1		
Ovaries			

- Female patients	4.3		
Testes - Male patients	5.2		
Bones marrow - Female patients - Male patients	4.1 3.9		
Skeleton - Female patients - Male patients	8.7 8.4		
Uterus - Female patients	4.6		

NR = not reported; NS = not significant

Additional comments:

Study quality:

- Prospective study
- Patient selection ok (consecutive)
- Applicable population
- Non-blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard
- Unclear time interval between index and comparator tests
- Small sample size

Lin et al, 2014

Population: 15 patients with newly diagnosed untreated multiple myeloma with an indication for systemic treatment: 10 males, 5 females; mean (range) age: 58 (48-69) years; Taiwan/China

Exclusions: Concurrent active malignancy other than multiple myeloma, contraindications to MRI and/or to the use of gadolinium-based contrast agents (incl a glomerular filtration rate < 30 mL/min).

Index test: 18F-FDG PET-CT: From vertex to mid-thighs on Siemens Biograph mCT lutetium oxyorthosilicate, LSO.

Interval between WB-MRI and 18F-FDG PET-CT: Within a mean (range) of 1.6 (1-4) days.

Image analysis performed by 2 nuclear medicine physicians in consensus, blinded to the clinical data and MRI results.

Comparator test: WB-MRI: T1- and T2 weighted gadopentetate dimeglumine-enhanced MRI examinations on a 32-channel 3-TMR system (Magnetom Trio, Siemens).

Image analysis performed by 1 radiologist, blinded clinical data except age and PET-CT results.

Results:

All data

	18F-FDG PET-CT	WB-MRI	p-value
Diffuse (no of patients)	6	15: Mild: N = 4 Moderate: N = 8 Severe: N = 3	Not reported
Focal (no of patients): **Durie/Salmon PLUS stage:** **I (total no of lesions)** **II (total number of lesions)** **III**	10 6 (10) 2 (17) 2	13 3 (4) 1 (9) 9	Not reported

Additional comments:

Study quality:

- Prospective study
- Patient selection unclear if consecutive.
- Unclear if applicable population as 25 other patients were excluded due to no end-organ damage therefore requiring no therapy (3), treatment already initiated (5), renal impairment (13), and unwillingness to enter the study (4).
- Blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard although bone marrow examinations revealed that all 15 patients had diffuse myeloma involvement.
- Acceptable time interval between index and comparator tests
- Small sample size

Mahnken et al, 2002

Population: 18 patients with multiple myeloma stage III (Durie-Salmon): 14 males, 4 females; mean (range) age: 67.8 (50-81) years; Germany

Index test: Multi-detector (MD) CT: Thoracic and lumbar spine (incl the sacrum) and the pelvis on Siemens Somatom Volume Zoom.

Interval between the three tests: All performed within 2 weeks.

Image analysis performed by 2 radiologists in consensus.

Comparator test: MRI: Thoracic and lumbar spine (incl the sacrum) fat-suppressed short tau inversion recovery- images, T1-weighted spin-echo images, and T2-weighted turbo spin-echo images; gadopentetate dimeglumine-enhanced MRI examinations on a 0.5-T Phillips Gyroscan T5 NT.

Comparator test: Radiography: Thoracic and lumbar spine (incl the sacrum) and the pelvis. No further information reported.

Unclearly reported, but image analysis may have been performed by 2 radiologists in consensus.

Results:

325 vertebrae assessed in 18 patients:

	Radiography	**MDCT**	**MRI**	**Matches in all 3 imaging modalities (N = 226)**
Normal bone	118	94	101	84
Diffuse osteopenia with microlacunae and trabecular disruption	154	117	224 abnormal	104
Lacunae > 5 mm, and permeation of cortical bone	13	45		4
Nodular lesions > 1 cm	40	69		34
Number of vertebral fractures	72	86	62	
Number of vertebrae considered at risk	6	12	9	

- Divergent imaging finding sbetween MD-CT and MR imaging would have lead to under-staging of 5 patients if using MRI exclusively, whereas if using MRI and skeletal radiography would lead to understaging 3 patients

180 pelvic areas assessed in 18 patients:

	Radiography	**MDCT**
Normal bone	100	74
Diffuse osteopenia with microlacunae and trabecular disruption	43	34
Lacunae > 5 mm, and permeation of cortical bone	16	38
Nodular lesions > 1 cm	21	34

All lesions detected on radiography were also detected on MD-CT.

- "The examination protocol that we used resulted in a cumulative dose of 23.3 mSv (ICRP 26) and 25.5 mSv (ICRP 60) in men and 39.8 mSv (ICRP 26) and 36.6 mSv (ICRP 60) in women, respectively. Effective energy was calculated as 82.4 keV."

Additional comments:

Study quality:

- Prospective study
- Patient selection unclear if consecutive.
- Unclear if applicable population as all stage III and not reported if they had already been treated.
- Not blinded index and comparator test interpretation
- Index test and comparator applicable

- No verification of imaging results/no gold standard.
- Acceptable time interval between index and comparator tests
- Small sample size

Nanni et al, 2006

Population: 28 patients with newly diagnosed, symptomatic, untreated multiple myeloma who had been referred to the authors' PET Centre by the Haematology Unit of the authors' hospital: 21 males, 7 females; mean (SD; range) age: 55 (9; 35-74) years; Italy.
Index test: 18F-FDG PET-CT: Skull, upper limbs and femora on a dedicated PET/CT tomography (GE Discovery). Interval between the three tests: All performed within 1 month of each other. Image analysis: "Each PET/CT scan was read by two nuclear medicine physicians in consensus, blinded to the WB-XR and MRI results.
Comparator test 1: Spinal-pelvic MRI: T1- and T2 weighted gadolinium chelate-enhanced MRI examinations. No further information reported. Image analysis: "MRI studies were reviewed by 2 radiologists." No further information reported. Comparator test 2: WB-XR: Skull, spine, pelvis, ribs, femora and humeri. No further information reported. Image analysis: No information reported.
Results: 18F-FDG PET-CT versus WB-XR: - More bone lesions detected by PET-CT than WB-XR: 16/28 patients - Equivalent findings between the two tests: 12/28 patients (4 had no lesions, and 8 had ≥ lesions) 18F-FDG PET-CT versus MRI: - More lesions detected by PET-CT than MRI: 7/28 patients (all located outside the MRI FOV) - Equivalent findings between the two tests: 14/28 patients (4 had no lesions, and 8 had ≥ lesions) - Fewer pathological findings detected by PET-CT than MRI: 7/28 patients.
Additional comments: **Study quality:** - (Probably) Prospective study - Patient selection consecutive. - Applicable population although all described as "symptomatic". - Not all index and comparator test interpretation blinded - Index test and comparator applicable - No verification of imaging results/no gold standard. - Acceptable time interval between index and comparator tests - Small sample size

1 **Princewill et al, 2013**

Population: 51 patients with a confirmed diagnosis (made on the basis of illiaccrest bone biopsy and abnormal laboratory parameters) of multiple myeloma who had a PET/CT and radiographic survey done within 90 days of each other: 27 males, 24 females, mean (range) age = 56 (35-73) years; USA. *39 of the patients underwent imaging at their initial evaluation and 12 patients had imaging done for restaging.*
Exclusions: None listed.

Index test: Radiographic skeletal survey: Skeletal radiographs of the skull; spine; ribs; pelvis; bilateral humeri, forearms, femurs and lower legs using computed radiography.

Interval between WB-MRI and projection radiography: Max 90 days (average = 26 days).

Image analysis performed independently by 2 radiologists with disagreements of lesions ≥ 8 mm resolved by consensus (lesions < 8 mm were discounted due to poor inter observer agreement), blinded to other imaging results. Focal intramedullary lesions evident on CT, without cortical or trabecular bone destruction, were not included since they had no skeletal survey counterpart.

Comparator test: WB-CT: "The CT component of the PET/CT was used as a surrogate for a dedicated stand-alone whole body CT exam." Low-dose CT images from skull base to the thigh on a Phillips Gemini 16 PET/CT system.

Image analysis performed independently by 2 radiologists with disagreements of lesions ≥ 8 mm resolved by consensus (lesions < 8 mm were discounted due to poor inter observer agreement), blinded to other imaging results.

Results:

Patients with no lesions detected by either test	9/51
Patients with more lesions detected by WB-CT than skeletal survey	39/42 (i.e., 51-9 w/o lesions)
Patients with more lesions detected by skeletal survey than WB-CT	3/42 (i.e., 51-9 w/o lesions)
Patients with new osteolytic lesions missed on skeletal survey, but detected on WB-CT	8
Patients with upstaged disease (overall)	31/51
Patients upstaged from stage I-II based on WB-CT	13/51
Patients upstaged from stage I-III based on WB-CT	9/51
Patients upstaged from stage II-III based on WB-CT	9/51
Patients with no overall change in stage of disease (WB-CT and skeletal survey)	20/51

	Skeletal survey	**WB-CT**	**P-value**
Total number of lytic lesions	248	968	$p < 0.001$
Total number of skull lesions	86	94	$p = 0.02$
Total number of spine lesions	49	241	$p < 0.001$
Total number of rib lesions	2	102	$p < 0.001$
Total number of sternal lesions	1	120	$p < 0.001$

Total number of flat bone lesions	36	240	p < 0.001
Total number of long bone lesions	74	171	p < 0.001
Effective radiation dose per patient	1.8 mSv	4.1 (range 2.2-4.9) mSv	

Additional comments:

Study quality:

- Retrospective study
- Patient selection consecutive.
- Partially applicable population (39 of the patients underwent imaging at their initial evaluation and 12 patients had imaging done for restaging).
- Blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard.
- Acceptable time interval between index and comparator tests
- Small sample size

Razek et al, 2013

Population: 28 consecutive patients with pathologically confirmed (iliac-crest bone marrow biopsy) newly diagnosed , untreated multiple myeloma: 19 males, 9 females; mean (range) age: 60 (51-73) years; Egypt

Index test: WB-multidetector [MD] CT: Top of skull to knee joints on Phillips Brilliance 64

Mean interval (range) between CR and WB-MDCT: 9 (3-16) days

Image analysis performed by 2 radiologists, blinded to each patient's other imaging study, analyzing first skeletal surveys and then CT scans with a time interval of 7-15 days between readings. Disagreements resolved by consensus. Skeleton divided into six anatomical regions: Skull, vertebral column, pelvic bones, thoracic cage, and upper and lower extremities, which were each evaluated for cortical lytic lesions, hyperattenuating medullary lesions, fractures and extraosseous lesions.

Comparator test: Conventional skeletal radiography (CR): Anteriorposterior (AP) and lateral skull, spine, humeri, femora and forearm; posterioranterior (PA)chest and AP pelvis

Results:

Anatomical region	**WB-MDCT positive**	**CR positive**	**p-value**
Skull	16	10	0.1
Spine	22	9	0.001
Pelvic bones	13	7	0.09
Thoracic cage	17	7	0.006
Upper extremities	14	10	0.28
Lower extremities	16	12	0.5
Anatomical bony region involvement total	98	55	0.001

Hyper-attenuating medullary lesions: Focal	6		
Hyper-attenuating medullary lesions: Diffuse marrow involvement	3		
Fracture of spine	4	2	
Extra-osseous lesions	Pleural effusion (3); pulmonary infiltrates (2); hepatic lesions (2); lymphadenopathy (1); para- and intraspinal soft tissue mass with spinal cord compression (2)		
Mean number of affected regions	3.39	1.96	
Mean number of lesions	~ 9.25	~16.32	
Stage: **I** **II** **III**	 1 15 12	 8 16 4	

- Upstaging: 14 patients were upstaged as WB-MDCT revealed more extensive disease than CR: Stage I to II: N = 6; stage I to III: N = 1; stage II to III: N = 7 (significant difference in stage between WB-MDCT and CR, p = 0.002).
- Due to upstaging in 7 patients, the medical treatment plan changed (N = 4 were candidates for stem cell transplant, and N = 3 were not).

Additional comments:

Study quality:

- Prospective study
- Patient selection ok (consecutive)
- Applicable population
- Blinded index and comparator test interpretation
- Index test and comparator applicable
- No verification of imaging results/no gold standard
- Acceptable time interval between index and comparator tests
- Small sample size

Spinnato et al, 2012

Population: 191 patients: 110 males, 81 females; mean (SD; range) age: 61.9 (9.9; 33-81) years; 62/191 patients evaluated at multiple myeloma diagnosis, 58/191 evaluated at the end of therapies and 90/191 during follow-up protocol. Only the data from the first patients evaluated at diagnosis is reported; Italy.

Index test: WB-18F-FDG PET-CT: Including skull, superior limbs and femurs (when lesions were suspected out of these regions the field of view was also focused elsewhere on GE Healthcare Discovery LS.

Interval between WB-MRI and WB-18F-FDG PET-CT: Within 15 days

Image analysis performed by 2 expert radiologists in consensus, blinded to other imaging results and clinical information.
Comparator test: WB-MRI: T1-weighted gadolinium-enhanced MRI examinations on a 1.5-T GE Signa Horizon. Image analysis performed by 2 expert radiologists in consensus, blinded to other imaging results and clinical information.
Results: - In 5/62 patients PET-CT was negative whereas MRI showed mild (N = 3) or moderate (N = 2) diffuse spine involvement. - In (another) 4/62 patients MRI showed a micronodular pattern with salt-and-pepper appearance of bone marrow, whereas PET was negative with the exception of one patient where CT showed mild and diffuse micronodular bone involvement. - In 23/62 patients PET-CT detected lesions of the MRI field of view, in 3 of whom MRI was normal on the entire spine and pelvis. - 12/62 patients with dis-concordant PET-CT and MRI findings were down-staged due to PET-CT (N = 11) or MRI (N = 1) findings.
Additional comments: **Study quality:** - Retrospective study - Patient selection unclear if consecutive. - Applicable population - Blinded index and comparator test interpretation - Index test and comparator applicable - No verification of imaging results/no gold standard - Acceptable time interval between index and comparator tests - Small sample size

Wolf et al, 2014

Population: 119 patients with untreated multiple myeloma of all stages, including MGUS and solitary plasmacytoma: 61 males, 58 females, average (range) age = 57 (20-80) years; Germany Exclusions: Contraindications to MRI (e.g., pacemaker, cochlear implant, claustrophobia).
Index test: Projection radiography: Skeletal radiographs of the head, spine, pelvis, proximal upper and lower extremities on a digital radiograph (AXIOM Aristos MX, Siemens). Interval between WB-MRI and projection radiography: Unclear but max 4 months. Image analysis performed by 2 radiologists in consensus, blinded to any clinical data, and MRI results.
Comparator test: WB-MRI: T1-, T2- and T2*-weighted of head to the lower extremities on a 1.5-T imager (MAGNETOM Avanto, Siemens). Image analysis performed by 2 radiologists in consensus, blinded to any clinical data, and projection radiography results.
Results: **Stage**

	Durie-Salmon	Durie-Salmon PLUS
MGUS	28	40
I	44	7
II	8	52
III	36	20
Plasmacytoma	3	0

Theoretical change in staging and treatment based on Durie-Salmon PLUS

	Durie-Salmon
Change in staging:	
- None	36
- Up-staging	38
- Down-staging	45
Change in treatment:	
- None	78
- Treatment indicated	33
- Treatment not indicated	8

	Projection radiography	WB-MRI	P-value
No focal lesions (no of patients)	95	76	
Focal lesions (no of patients)	24	43	$p < 0.001$
- Axial (no of patients)	4	11	
- Extraaxial (no of patients)	14	12	
- Axial (intra-osseous and corticalis exceeding)	Not reported	Not reported	$p < 0.001$
- Axial (intra-osseous)	Not reported	Not reported	$p < 0.001$
- Axial (corticalis exceeding)	Not reported	Not reported	$p = 0.02$
- Extra-axial (intra-osseous and corticalis exceeding)	Not reported	Not reported	$p < 0.001$
- Extraaxial (intra-osseous)	Not reported	Not reported	$p < 0.001$
- Extraaxial (corticalis exceeding)	Not reported	Not reported	$p = 0.002$

Additional comments:

Study quality:

- Retrospective study
- Patient selection not consecutive.
- Partially applicable population (24% MGUS based on Durie-Salmon criteria [laboratory parameters and projection radiography).
- Blinded index and comparator test interpretation
- Index test and comparator applicable

- No verification of imaging results/no gold standard.
- Unclear time interval between index and comparator tests
- Small sample size

1

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11. Wolf, M. B., Murray, F., Kilk, K., Hillengass, J., Delorme, S., Heiss, C., Neben, K., Goldschmidt, H., Kauczor, H. U. & Weber, M. A. (2014) Sensitivity of whole-body CT and MRI versus projection radiography in the detection of osteolyses in patients with monoclonal plasma cell disease. *European Journal of Radiology,* 83: 1222-1230.

Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. Boutry, N., Dutouquet, B., Leleu, X., Vieillard, M. H., Duhamel, A. & Cotten, A. (2013) Low-dose biplanar skeletal survey versus digital skeletal survey in multiple myeloma. *European Radiology,* 23: 2236-2245.	Population not in PICO: 35/56 patients had relapsed myeloma
2. Breyer, R. J., III, Mulligan, M. E., Smith, S. E., Line, B. R. & Badros, A. Z. (2006) Comparison of imaging with FDG PET/CT with other imaging modalities in myeloma. *Skeletal Radiology,* 35: 632-640.	Population not in PICO: Average duration of disease 30 months (range 6 months-11 years)
3. Caers, J., Withofs, N., Hillengass, J., Simoni, P., Zamagni, E., Hustinx, R. & Beguin, Y. (2014) The role of positron emission tomography-computed	Expert review

tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. *Haematologica,* 99: 629-637.	
4. Dinter, D. J., Neff, W. K., Klaus, J., Bohm, C., Hastka, J., Weiss, C., Schoenberg, S. O. & Metzgeroth, G. (2009) Comparison of whole-body MR imaging and conventional X-ray examination in patients with multiple myeloma and implications for therapy. *Annals of Hematology,* 88: 457-464.	Population not in PICO: "most patients had initially already been treated with conventional chemotherapy….. or high-dose chemotherapy with stem cell transplantation."
5. Fonti, R. (2015). 18F-FDG PET/CT, 99mTc-MIBI, and MRI in the prediction of outcome of patients with multiple myeloma: a comparative study. Clinical Nuclear Medicine, 40, 303-308.	Comparator (99Tc-MIBI) not in PICO – MRI results not reported.
6. Gleeson, T. G., Moriarty, J., Shortt, C. P., Gleeson, J. P., Fitzpatrick, P., Byrne, B., McHugh, J., O'Connell, M., O'Gorman, P. & Eustace, S. J. (2009) Accuracy of whole-body low-dose multidetector CT (WBLDCT) versus skeletal survey in the detection of myelomatous lesions, and correlation of disease distribution with whole-body MRI (WBMRI). *Skeletal Radiology,* 38: 225-236.	Population not in PICO: 20/39 patients had restaging scans
7. Hillner, B. E., Siegel, B. A., Shields, A. F., Liu, D., Gareen, I. F., Hunt, E. & Coleman, R. E. (2008) Relationship between cancer type and impact of PET and PET/CT on intended management: findings of the national oncologic PET registry. *Journal of Nuclear Medicine,* 49: 1928-1935.	Outcomes not in PICO. Unclear what PET is compared to.
8. Mai, E. K. (2015). A magnetic resonance imaging-based prognostic scoring system to predict outcome in transplant-eligible patients with multiple myeloma. Haematologica, 100, 818-825	No comparator test, MRI only.
9. Merz, M. (2014). Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia, 28, 1902-1908.	
10. Narquin, S., Ingrand, P., Azais, I., Delwail, V., Vialle, R., Boucecbi, S. & Tasu, J. P. (2013) Comparison of whole-body diffusion MRI and conventional radiological assessment in the staging of myeloma. *Diagnostic and Interventional Imaging,* 94: 629-636.	Mixed population with only 14/27 patients having newly diagnosed multiple myeloma
11. Song MK, Chung JS, Lee JJ, Lee JH, Song IC, Lee SM et al. (2015). Risk stratification model in elderly patients with multiple myeloma: clinical role of magnetic resonance imaging combined with international staging system and cytogenetic abnormalities. Acta Haematologica, 134, 7-16	No comparator test, MRI only.
12. Squillaci, E., Bolacchi, F., Altobelli, S.,	Unclear whether patients (N=36) were newly

	Franceschini, L., Bergamini, A., Cantonetti, M. et al. (2015). Pre-treatment staging of multiple myeloma patients: comparison of whole-body diffusion weighted imaging with whole-body T1-weighted contrast-enhanced imaging. Acta Radiologica, 56, 733-738.	diagnosed.

1

2

Chapter 4: Smouldering myeloma

Review Question:
What are the most effective primary management strategies (including observation) for patients with asymptomatic myeloma?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients diagnosed asymptomatic myeloma	• Treatment intervention immediately ○ Chemotherapy ○ Thalidomide based regimens ○ Bortezomib based regimes ○ Lenalidomide based regimens ○ bisphosphonates	observation (deferred treatment until progression of the disease)	• disease-related mortality • Overall survival • Progression free survival • Progression to symptomatic myeloma • Prevention of renal failure • HRQOL • Patient acceptability • Adverse events • Skeletal related events

Evidence statements

See Tables 4.1 to 4.3 and Figures 4.1 to 4.8

Overall survival
Low quality evidence from five randomised trials (Mateos et al, 2013; Witzig et al, 2013; Hjorth et al, 1993; Riccardi et al, 2000; D'Arena et al 2011) including 552 patients with asymptomatic myeloma suggests uncertainty about the effect of immediate treatment on overall survival, when compared to treatment deferred until progression (HR 1.00; 95% C.I. 0.71 to 1.40; where HR < 1 favours immediate treatment).

Two trials used immediate treatment with thalidomide plus zoledronate (Witzig et al, 2013) or lenalidomide plus dexamethasone (Mateos et al 2013). Pooling these IMiD trials suggests uncertainty about whether immediate treatment improves overall survival (HR 0.61; 95% C.I. 0.30 to 1.24; where HR < 1 favours immediate treatment), although Mateos et al (2013) did report a significant overall survival benefit with immediate treatment (HR 0.31; 95% C.I. 0.10 to 0.94; where HR < 1 favours immediate treatment).

Progression to symptomatic disease
Low quality evidence from two randomised trials including 187 patients with asymptomatic myeloma (Mateos et al 2013; Witzig et al, 2013) suggests that immediate treatment with an IMiD regimen delays the progression to symptomatic disease (HR 0.36; 95% C.I. 0.23 to 0.55; where HR <

1 favours immediate treatment). In Mateos et al (2013) three year symptomatic progression free survival was around 78% in patients who received immediate treatment compared to 30% in those with deferred treatment.

Low quality evidence from two randomised trials including 340 patients with asymptomatic myeloma (Musto et al 2008; D'Arena et al, 2011) suggests uncertainty about the effect of treatment with bisphosphonates on progression to symptomatic disease when compared to observation alone (HR 0.94; 95% C.I. 0.72 to 1.23; where HR < 1 favours immediate treatment).

Disease progression (including biological progression)

Witzig et al (2013) defined disease progression as increased M-protein level 25% above the lowest level or new bone lesion or plasmacytoma. Using this definition of progression, immediate treatment with lenalidomide plus zoledronate was more effective than treatment with zoledronate alone (HR 0.51; 95% C.I. 0.28 to 0.91).

Skeletal related events

Low quality evidence from two randomised trials including 274 patients with asymptomatic myeloma (D'Arena et al 2011; Musto et al 2008) suggests that immediate treatment with bisphosphonates reduces the risk of skeletal related events compared to observation alone (RR 0.61; 95% C.I. 0.45 to 0.81; where RR<1 favours bisphosphonate treatment). These figures suggest that an additional skeletal related event could be avoided for every ten patients treated with bisphosphonates instead of observation alone.

Low quality evidence from two RCTS (Hjorth et al 1993; Riccardi et al, 2000) including 188 patients with asymptomatic myeloma suggests uncertainty over whether immediate treatment melphalan and prednisone lowers the risk of vertebral compression when compared to deferred treatment (RR 0.19; 95% C.I. 0.02 to 1.60; where RR <1 favours immediate treatment). In these studies no vertebral compression occurred in the immediate treatment whereas 4% of patients in the deferred treatment group experienced vertebral compression.

Treatment related adverse events

Low quality evidence from two randomised trials including 187 patients (Mateos et al 2013; Witzig et al, 2013) suggests uncertainty about whether immediate IMiD treatment is associated with an increased rate of grade 3-4 adverse events (RR 1.70; 95% C.I. 0.60 to 5.06; where RR>1 favours deferred treatment).

Low quality evidence from three randomised trials including 288 patients (Mateos et al, 2013; Hjorth et al, 1993; Riccardi et al 2000) suggests that immediate treatment is associated with an increased risk of a second primary cancer when compared to deferred treatment (RR 4.49; 95% C.I. 1.15 to 17.49; where RR>1 favours deferred treatment).

Osteonecrosis of the jaw occurred in 1.3% of those treated with bisphosphonates (D'Arena et al 2011; Musto et al 2008; Witzig et al, 2013).

Outcomes not reported

HRQOL, patient acceptability, renal failure and disease related mortality were not reported in the trials.

Figure 4.1: Screening results

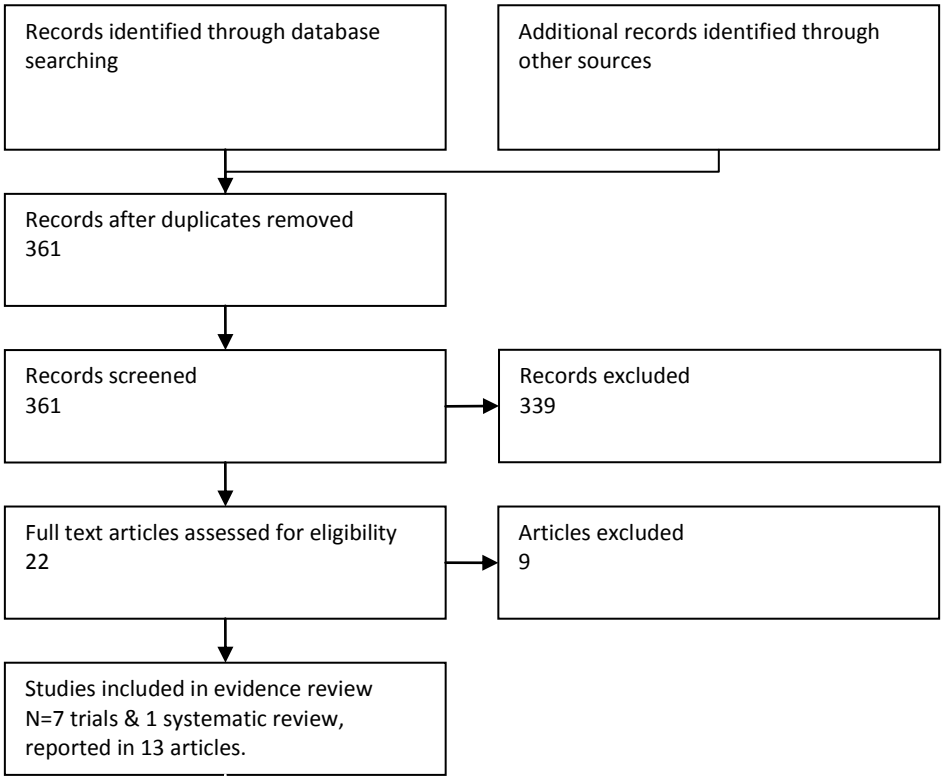


Figure 4.2. Study risk of bias

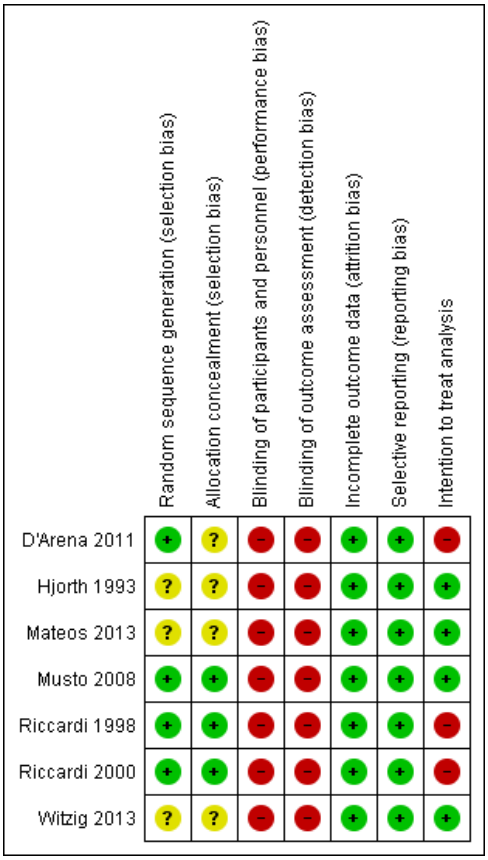


Table 4.1. GRADE profile: immediate IMiD treatment versus deferred treatment for asymptomatic myeloma

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate IMiD treatment	Deferred treatment	Relative (95% CI)	Absolute	
Overall survival (event is death from any cause)											
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	13/92 (14.1%)	22/95 (23.2%)	HR 0.61 (0.3 to 1.24)	-	⊕⊕OO LOW
Time to disease progression (event is progression to symptomatic disease)											
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	39/92 (42.4%)	72/95 (75.8%)	HR 0.31 (0.2 to 0.48)	-	⊕⊕OO LOW
Grade 3 or 4 adverse effects											
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	24/92 (26.1%)	15/95 (15.8%)	RR 1.74 (0.6 to 5.06)	117 more per 1000 (from 63 fewer to 641 more)	⊕⊕OO LOW

[1] Mateos 2013; Witzig 2013

[3] Low number of events

[4] Allocation concealment and sequence generation unclear; no blinding

Table 4.2. GRADE profile for immediate mephalan+prednisone treatment vs deferred treatment for asymptomatic myeloma

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate mephalan+prednisone treatment	Deferred treatment	Relative (95% CI)	Absolute	
Overall survival (event is death from any cause)											
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	58/97 (59.8%)	47/91 (51.6%)	HR 1.39 (0.78 to 2.47)	-	⊕⊕OO LOW
Time to disease progression (event is progression to symptomatic disease)											
1[4]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/72 (6.9%)	34/66 (51.5%)	HR 0.11 (0.05 to 0.24)	-	⊕⊕OO LOW
Acute leukaemia											
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	4/97 (4.1%)	1/93 (1.1%)	RR 3.01 (0.47 to 19.43)	22 more per 1000 (from 6 fewer to 198 more)	⊕⊕OO LOW
Secondary primary cancer											
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	6/82 (7.3%)	1/87 (1.1%)	RR 4.20 (0.71 to 23.57)	41 more per 1000 (from 2 fewer to 291 more)	⊕⊕OO LOW
Vertebral compression											
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/97 (0%)	4/91 (4.4%)	RR 0.19 (0.02 to 1.60)	41 more per 1000 (from 2 fewer to 291 more)	⊕⊕OO LOW

[1] Riccardi 2000; Hjorth 1993
[2] Allocation concealment and sequence generation unclear; no blinding
[3] Low number of events
[4] Riccardi 2000

Table 4.3. GRADE profile for immediate bisphosphonate treatment vs deferred treatment for asymptomatic myeloma.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate bisphosphonate treatment	Deferred treatment	Relative (95% CI)	Absolute	
Overall survival (event is death from any cause)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	none	0/89 (0%)	0/88 (0%)	Not estimable	-	⊕⊕OO LOW
Time to disease progression (event is progression to symptomatic disease)											
2[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	90/170 (52.9%)	90/170 (52.9%)	HR 0.94 (0.72 to 1.23)	-	⊕⊕OO LOW
Skeletal events											
2[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	24/126 (19%)	38/127 (29.9%)	RR 0.64 (0.41 to 0.99)	108 fewer per 1000 (from 3 fewer to 177 fewer)	⊕⊕OO LOW
Osteonecrosis of the jaw											
2[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	2/170 (1.2%)	0/170 (0%)	RR 5.06 (0.25 to 103.83)	12 more per 1000 with bisphosphonates	⊕⊕OO LOW

[1] Not intention-to-treat analysis in D'Arena (2011); no blinding in Musto (2008) or D'Arena (2011)
[2] Number of deaths not reported
[3] Musto 2008, D'Arena 2011
[4] Low number of events

Figure 4.3. Overall survival

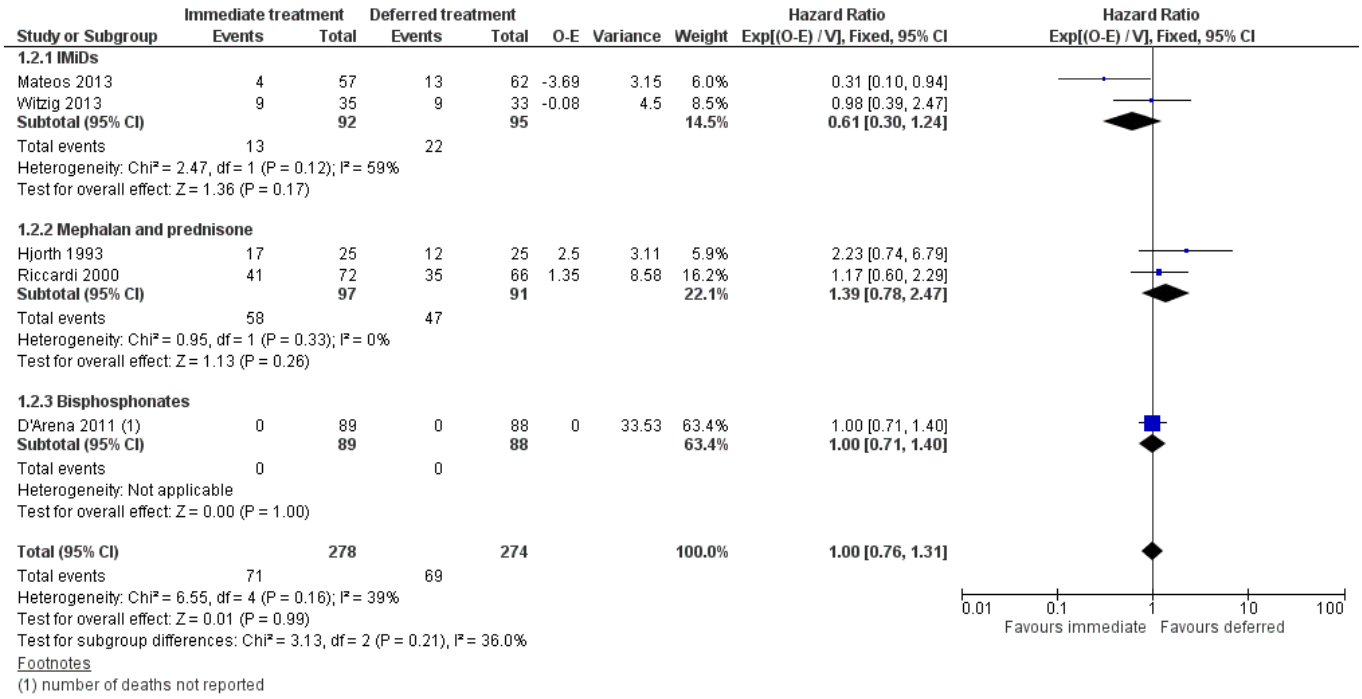


Figure 4.4. Symptomatic progression free survival

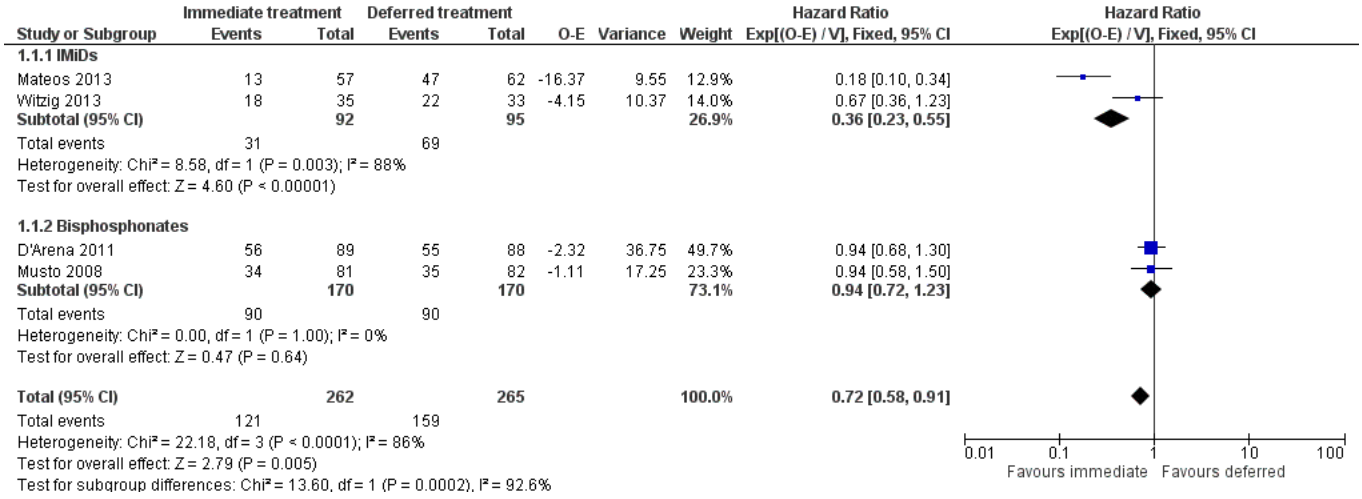


Figure 4.5. Grade 3 or 4 adverse events

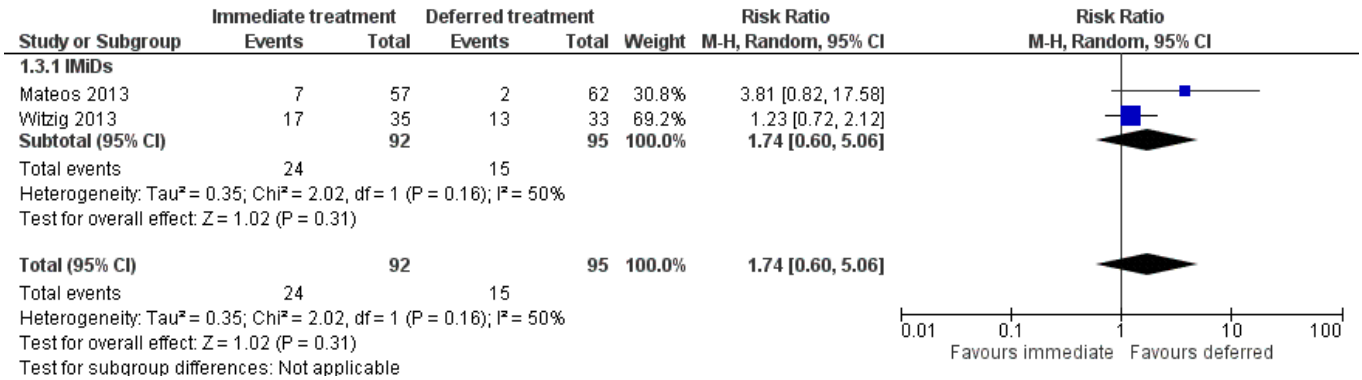


Figure 4.6. Skeletal related events and vertebral compression

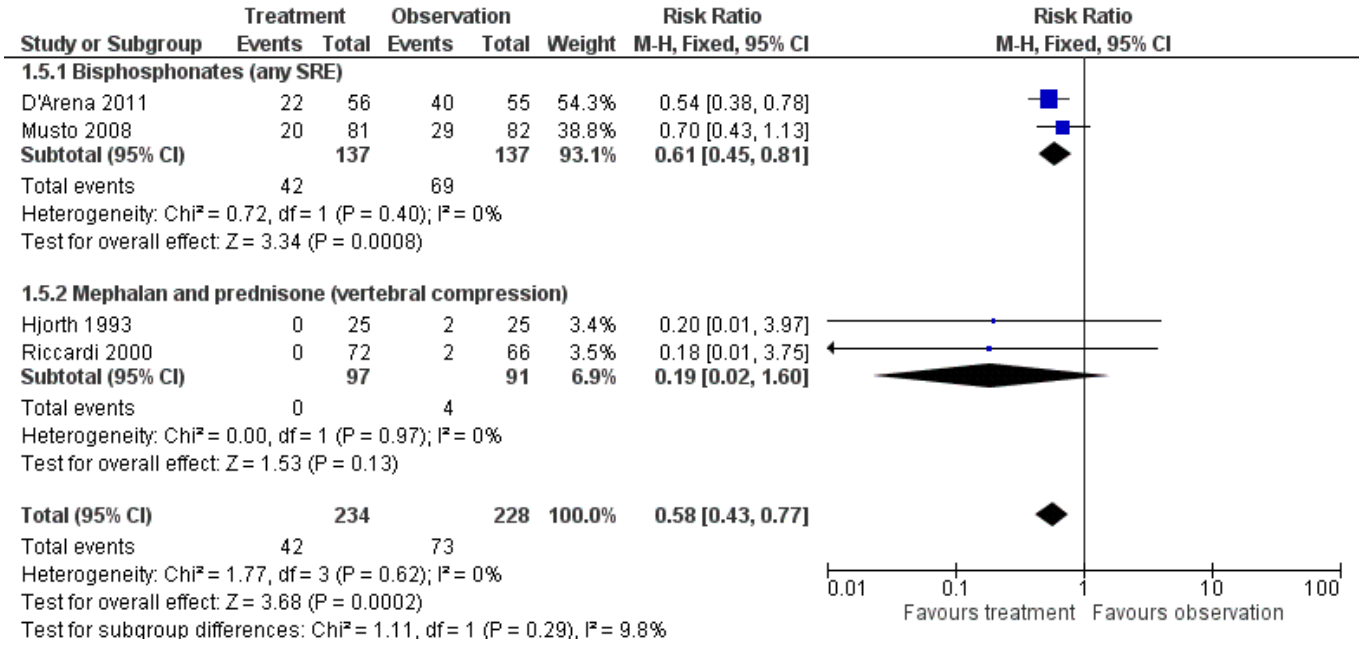


Figure 4.7. Osteonecrosis of the jaw

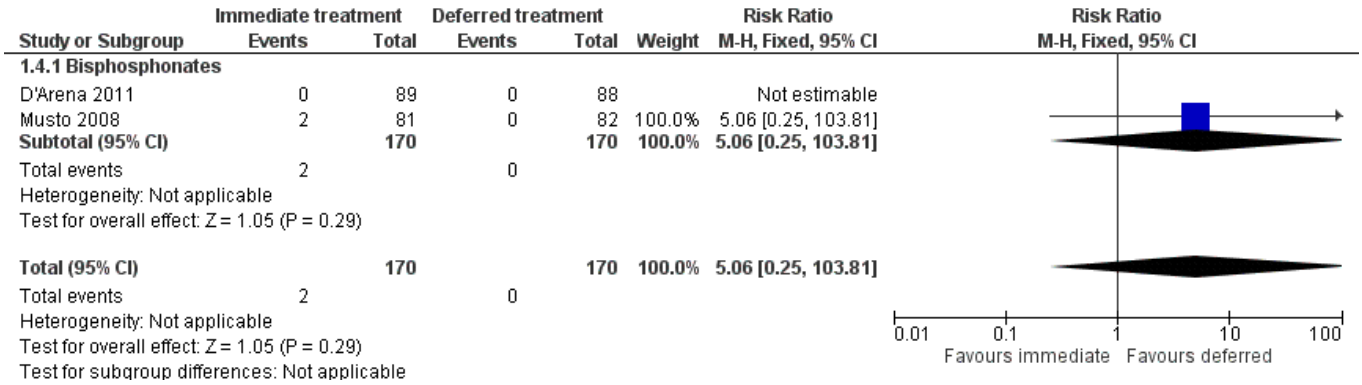
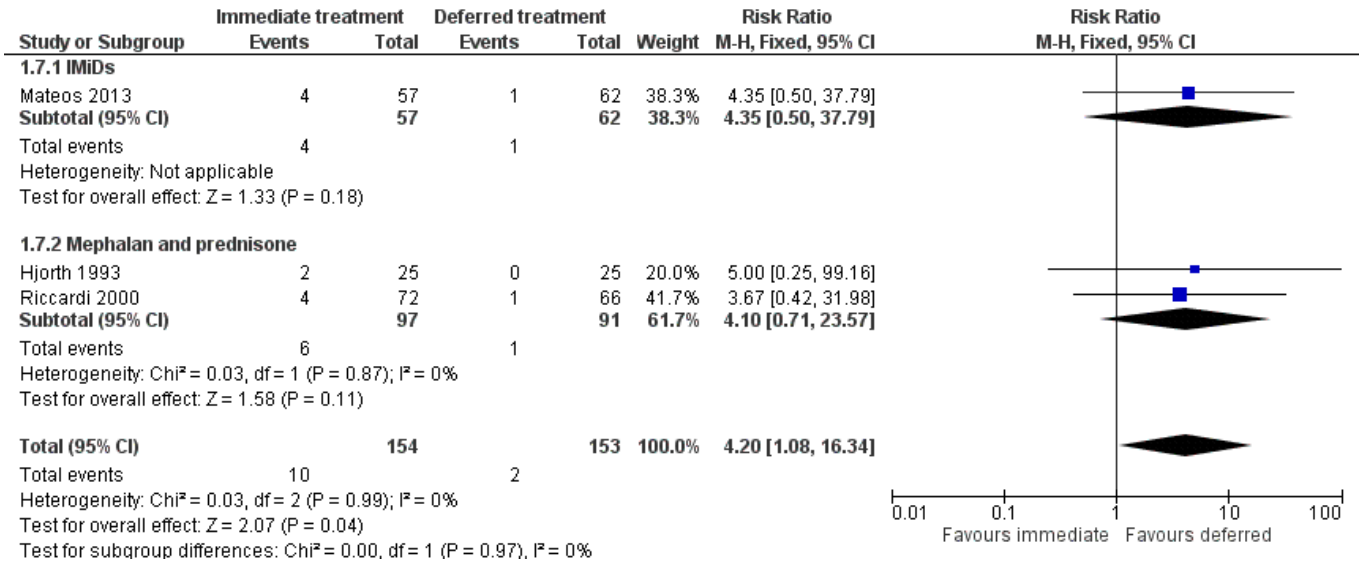


Figure 4.8. Second primary cancer



1

2 **Evidence table**

<table>
<tr><th>Study, country</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th><th>Source of funding</th></tr>
<tr>
<td>Gao (2014) Systematic review, Sweden, Italy, Spain, USA</td>
<td>Patients with smoldering multiple myeloma.
5 RCTs including 449 patients</td>
<td>Immediate versus deferred treatment
• Riccardi (1994; 2000), Hjorth (1993) melphalan + prednisone vs deferred treatment
• Mateos (2013) lenalidomide plus dexamethasone vs deferred treatment
• Witzig (2013) thalidomide + zoledronic acid vs zoledronic acid</td>
<td>See figures 4 to 8.
Progression to symptomatic disease
<table>
<tr><th></th><th>Immediate</th><th>Deferred</th><th></th></tr>
<tr><td>Riccardi 2000</td><td>5/72</td><td>34/66</td><td>N.R.</td></tr>
<tr><td>Mateos (2013)</td><td>13/57</td><td>47/62</td><td>HR 0.18 [0.10 to 0.34]</td></tr>
<tr><td>Witzig (2013)</td><td>18/35</td><td>22/33</td><td>HR 0.67 [0.36 to 1.23]</td></tr>
</table>
Overall survival (event is death from any cause)
<table>
<tr><th></th><th>Immediate</th><th>Deferred</th><th></th></tr>
<tr><td>Hjorth (1993)</td><td>17/25</td><td>12/25</td><td>HR 2.23 [0.74, 6.79]</td></tr>
<tr><td>Riccardi 2000</td><td>41/72</td><td>35/66</td><td>HR 1.17 [0.60, 2.29]</td></tr>
<tr><td>Mateos (2013)</td><td>4/57</td><td>13/62</td><td>HR 0.31 [0.10, 0.94]</td></tr>
<tr><td>Witzig (2013)</td><td>9/35</td><td>9/33</td><td>HR 0.98 [0.30, 1.24]</td></tr>
</table>
Grade 3 - 4 adverse events
<table>
<tr><th></th><th>Immediate</th><th>Deferred</th><th></th></tr>
<tr><td>Mateos (2013)</td><td>7/57</td><td>2/62</td><td>RR 3.81 [0.82, 17.58]</td></tr>
<tr><td>Witzig (2013)</td><td>17/13</td><td>13/33</td><td>RR 1.23 [0.60, 5.06]</td></tr>
</table>
Vertebral compression
<table>
<tr><th></th><th>Immediate</th><th>Deferred</th><th></th></tr>
<tr><td>Hjorth (1993)</td><td>0/25</td><td>2/25</td><td>RR 0.20 [0.01, 3.97]</td></tr>
<tr><td>Riccardi (2000)</td><td>0/72</td><td>2/66</td><td>RR 0.18 [0.01, 3.75]</td></tr>
</table>
Second primary cancer
<table>
<tr><th></th><th>Immediate</th><th>Deferred</th><th></th></tr>
<tr><td>Hjorth (1993)</td><td>0/25</td><td>2/25</td><td>RR 0.20 [0.01, 3.97]</td></tr>
<tr><td>Riccardi (2000)</td><td>0/72</td><td>2/66</td><td>RR 0.18 [0.01, 3.75]</td></tr>
</table>
ONJ occurred in 1/68 patients treated in Witzig et al (2013)</td>
<td>Overall and progression free survival analyses used risk ratios - I have redone them using hazard ratios (taken from survival curves in some cases).

Overlap between Riccardi (1994) and (2000) studies – have used 2000 study only.

See figure 2 for study quality</td>
<td>Riccardi (1994; 2000) AIRC,CNR, IRCCS and MURST grants.
Hjorth (1993) - Gothenburg oncology centre
Mateos (2013) Celgene.
Witzig (2013) Celgene and Novartis</td>
</tr>
</table>

<table>
<tr><th>Study, country</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th><th>Source of funding</th></tr>
<tr><td>D'Arena (2011), Italy</td><td>Patients with asymptomatic myeloma</td><td>Pamidronate versus observation</td><td>
<table>
<tr><th></th><th>Pamidronate</th><th>Observation</th><th></th></tr>
<tr><td>Overall survival</td><td>?/89</td><td>?/88</td><td>HR 1.00 [0.71, 1.40]</td></tr>
<tr><td>progression to symptomatic disease</td><td>56/89</td><td>55/89</td><td>HR 0.94 [0.68 to 1.30]</td></tr>
<tr><td>Skeletal related events</td><td>22/56</td><td>40/55</td><td>RR 0.54 [0.38, 0.78]</td></tr>
<tr><td>Osteonecrosis of the jaw</td><td>0/89</td><td>0/88</td><td>-</td></tr>
</table>
</td><td>See figure 2 for study quality</td><td>Not reported</td></tr>
<tr><td>Musto (2008), Italy</td><td>Patients with asymptomatic myeloma</td><td>Zoledronate versus observation</td><td>
<table>
<tr><th></th><th>Zoledronate</th><th>Observation</th><th></th></tr>
<tr><td>Death from myeloma</td><td>14/36</td><td>15/37</td><td>-</td></tr>
<tr><td>progression to symptomatic disease</td><td>34/81</td><td>35/92</td><td>HR 0.94 [0.58 to 1.50]</td></tr>
<tr><td>Skeletal related events</td><td>20/81</td><td>29/82</td><td>RR 0.70 [0.43, 1.13]</td></tr>
<tr><td>Osteonecrosis of the jaw</td><td>2/81</td><td>0/82</td><td>RR 5.06 [0.25, 103.81]</td></tr>
</table>
</td><td>See figure 2 for study quality</td><td>Not reported. No relevant conflicts of interest.</td></tr>
</table>

References of included studies

1. Gao, M., Yang, G., Tompkins, V. S., Gao, L., Wu, X., Tao, Y. et al. (2014). Early versus deferred treatment for smoldering multiple myeloma: a meta-analysis of randomized, controlled trials. PLoS ONE [Electronic Resource], 9, e109758. **Includes the following trials:**
2. Hjorth, M., Hellquist, L., Holmberg, E., Magnusson, B., Rödjer, S., & Westin, J. (1993). Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden. European.journal of haematology., 50, 95-102.
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4. Mateos, M.-V. (2010). Smoldering multiple myeloma (SMM) at high-risk of progression to symptomatic disease: A phase III, randomized, multicenter trial based on lenalidomide-dexamethasone (Len-Dex) as induction therapy followed by maintenance therapy with len alone vs no treatment. Blood, Conference, 21.
5. Hernandez, J. M. (2011). Effect of treatment with lena / dexa of asymptomatic multiple myeloma at high risk of progression on bone remodeling markers and cytokines related to bone disease. Haematologica, Conference, 130.
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7. Mateos, M. V. (2012). Smoldering multiple myeloma at high-risk of progression to symptomatic disease: A randomized trial of LEN-DEX as induction followed by maintenance therapy with LEN alone vs no treatment. Haematologica, Conference, 114-115.
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10. Riccardi, A., Mora, O., Tinelli, C., Valentini, D., Brugnatelli, S., Spanedda, R. et al. (2000). Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study. British Journal of Cancer, 82, 1254-1260.
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in patients with asymptomatic myeloma.[Erratum appears in Cancer. 2008 Nov 15;113(10):2835]. Cancer, 113, 1588-1595.

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Excluded papers (after checking full text)

Reference	Exclusion reason
16. Alahamdi, M. S. & Tay, J. (2013). Early versus late treatment for smoldering (asymptomatic) multiple myeloma: A systematic review. Journal of clinical.oncology, 31.	Abstract only
17. Horwitz, L. J. (2012). A prospective, randomized, chemoprevention trial of celecoxib for high risk monoclonal gammopathy of undetermined significance and asymptomatic multiple myeloma. Blood, 120.	Includes MGUS
18. Golombick, T., Diamond, T. H., Manoharan, A., & Ramakrishna, R. (2012). Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. American.journal of hematology., 87, 455-460. Golombick, T. (2013). Multiple myeloma precursor disease and curcumin. Clinical Lymphoma, Myeloma and Leukemia, Conference, S168.	Includes MGUS
19. McCloskey, E. V., MacLennan, I. C. M., Drayson, M. T., Chapman, C., Dunn, J., & Kanis, J. A. (1998). A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. British Journal of Haematology, 100, 317-325.	Includes symptomatic myeloma
20. Mhaskar, R. S. (2009). Bisphosphonates in multiple myeloma. a systematic review and meta analysis. Blood, Conference, 22.	Abstract only
21. Vijayakumar, J. (2014). Meta-analysis of pharmacotherapy vs. Observation for management of smoldering multiple myeloma. Blood, Conference, 21.	Abstract only

Chapter 5: Service organisation

Review Question:
What is the optimal configuration of local and regional haematology services for management of myeloma (including access to specialised radiological imaging, radiotherapy services, the management of renal disease, spinal disease and bone disease, clinical trials and supportive & palliative care)?

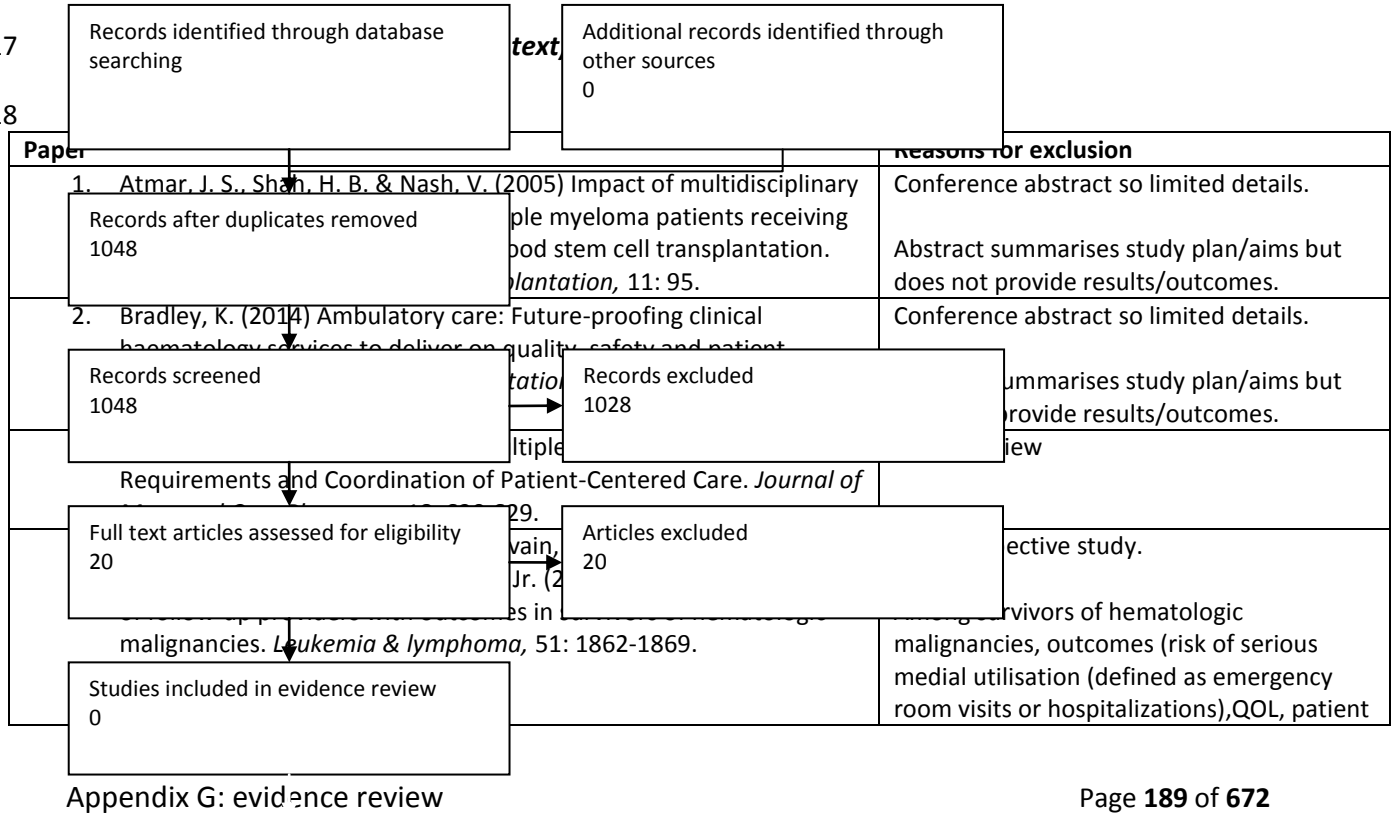
Question in PICO format

Population	Intervention	Comparator	Outcomes
Myeloma patients (Analyse data by centre volume)	Access to an MDT, specialised radiological imaging, radiotherapy services, the management of renal disease, spinal disease and bone disease, clinical trials, transplant services, dental clinic, and supportive & palliative care in one network	Any other service configuration	• Patient-reported outcomes (patient experience) • Travel times • HRQOL • Overall survival • Progression-free survival

Evidence statements
No studies were identified in the literature that examined the configuration of local and regional haematology services for management of myeloma.

Search Results

Figure 5.1: Screening results



Paper	Reasons for exclusion
1. Atmar, J. S., Shah, H. B. & Nash, V. (2005) Impact of multidisciplinary ple myeloma patients receiving od stem cell transplantation. *lantation,* 11: 95.	Conference abstract so limited details. Abstract summarises study plan/aims but does not provide results/outcomes.
2. Bradley, K. (2014) Ambulatory care: Future-proofing clinical *tatio* ltiple Requirements and Coordination of Patient-Centered Care. *Journal of* 29.	Conference abstract so limited details. ummarises study plan/aims but rovide results/outcomes. iew
vain, Jr. (2 malignancies. *Leukemia & lymphoma,* 51: 1862-1869.	ective study. ivors of hematologic malignancies, outcomes (risk of serious medial utilisation (defined as emergency room visits or hospitalizations),QOL, patient

	satisfaction) were not different for survivors who were seen by single or multiple follow-up providers. Information on follow-up provider was obtained from patient questionnaire: 1. Doctor from University of Nebraska Medical Centre (UNMC) 2. Doctor outside UNMC 3. Doctors from both UNMC and outside UNMC No mention of access to specific services. Not specific to myeloma: 6% of patients seen by single providers had myeloma and 14% of patients seen by multiple providers had myeloma.
5. Davies, M. J. (2006) Advancing access to myeloma treatment: administration, side effects, and implications for survival. [Review] [11 refs]. *ONS News,* 21: 11-12.	Expert review. Symposium summary. No discussion of service provision.
6. Gertz, M. A., Ansell, S. M., Dingli, D., Dispenzieri, A., Buadi, F. K., Elliott, M. A., Gastineau, D. A., Hayman, S. R., Hogan, W. J., Inwards, D. J., Johnston, P. B., Kumar, S., Lacy, M. Q., Leung, N., Micallef, I. N., Porrata, L. F., Schafer, B. A., Wolf, R. C. & Litzow, M. R. (2008) Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. *Mayo Clinic Proceedings,* 83: 1131-1138.	Not relevant to PICO – feasibility of outpatient transplant
7. Howell, D. A., Shellens, R., Roman, E., Garry, A. C., Patmore, R. & Howard, M. R. (2011) Haematological malignancy: are patients appropriately referred for specialist palliative and hospice care? A systematic review and meta-analysis of published data. [Review]. *Palliative Medicine,* 25: 630-641.	Not relevant to PICO – study comparing use of palliative care and hospice services in patients with haematological cancers compared to other cancers.
8. Innis-Shelton, R. D. (2014). Access to advanced care and survival in multiple myeloma. Blood, Conference, 21.	Not relevant to PICO
9. Kohlweyer, U., Rohdenburg, S., Reinhardt, H., Hug, S., Metzke, B., Jakobs, D., Burbeck, M., Wider, S., Otte, P., Surlan, I., Schall, H., Urban, J. E., Muller, M., Schmidt, V., Udi, J., Kleber, M. & Engelhardt, M. (2011) Advantages of a 'Center of Clinical Investigations, Optimization, Standardization & Safety (CIO)' as a central unit for Hematology & Oncology departments for clinical studies, chemotherapy management, and cancer registry assessments - Freiburg (UKF) experience. *Onkologie,* 34: 129.	Conference abstract so limited details. Not relevant to PICO – not service provision for patients.
10. Lipe, B. C., Lansigan, F., Gui, J. & Meehan, K. (2012) Bone marrow transplant for multiple myeloma: impact of distance from the transplant center. *Clinical Advances in Hematology & Oncology,* 10: 28-32.	Not relevant to PICO – retrospective analysis (US study) of 77 myeloma patients to investigate possible disparities in survival, based on the distance a patient lives from a transplant centre.
11. Paul, C. L., Hall, A. E., Carey, M. L., Cameron, E. C. & Clinton-McHarg, T. (2013) Access to care and impacts of cancer on daily life: do they differ for metropolitan versus regional hematological cancer survivors? *Journal of Rural Health,* 29 Suppl 1: s43-s50.	Not relevant to PICO – questionnaire sent to haematological cancer patients (in Australia) to document experiences in relation to the barriers to accessing care and associated financial and social impacts of the disease.
12. Ragon, B. K., Clifton, C., Chen, H., Savani, B. N., Engelhardt, B. G.,	Not relevant to PICO – retrospective

Kassim, A. A., Vaughan, L. A., Lucid, C. & Jagasia, M. (2014) Geographic distance is not associated with inferior outcome when using long-term transplant clinic strategy. *Biology of Blood & Marrow Transplantation,* 20: 53-57.	analysis (US study) to examine prognostic factors (including distance from transplant centre) for survival following stem cell transplant. Mixed population.
13. Rao, K., Darrington, D. L., Schumacher, J. J., Devetten, M., Vose, J. M. & Loberiza, F. R. (2007) Disparity in survival outcome after hematopoietic stem cell transplantation for hematologic malignancies according to area of primary residence. *Biology of Blood and Marrow Transplantation,* 13: 1508-1514.	Not relevant to PICO – retrospective analysis (US study) of 2006 haematological cancer patients to investigate possible disparities in survival, based on whether the patient lived in a rural or urban area.
14. Rios, R. (2013) The impact of the type of hospital on survival of multiple myeloma patients: The MICORE study. *Revista Clinica Espanola,* 213: 330-335.	Spanish retrospective study to analyse whether there are differences in survival of myeloma patients treated in community hospitals (n=175) vs. university hospital (n=256). No mention of access to specific services.
15. Saunders CL, Abel GA, & Lyratzopoulos (2015). Inequalities in reported cancer patient experience by socio-demographic characteristic and cancer site: evidence from respondents to the English Cancer Patient Experience Survey. European Journal of Cancer Care, 24, 85-98.	Not relevant to PICO
16. Short, M. & Bloodworth, C. (2015). An audit showing the effect of modern myeloma treatments on service delivery: How will day units cope with the increase in demand in the future? British Journal of Haematology, 169, 96.	Not relevant to PICO – does not compare service models.
17. Sinacola, A., Waller, M., Murphy, M. & Tholouli, E. (2008) The myeloma patient pathway: a multi-disciplinary team approach from diagnosis to stem cell transplantation. *Bone marrow transplantation,* 41: S351.	Conference abstract so limited details. Development of patient pathway. No outcomes reported.
18. Sive, J. (2012) Hotel-based ambulatory care for complex cancer patients: A review of the University College London Hospital experience. *Leukemia and Lymphoma,* 53: 2397-2404.	Not relevant to PICO – review/audit of one centres experience of using a hotel-based ambulatory care unit.
19. Takita, M., Tanaka, Y., Matsumura, T., Kishi, Y., Kodama, Y., Nishimura, T., Goto, T., Nagai, M. & Kami, M. (2009) Regional social system for specialized medical care in hematologic malignancies: a pilot study. *Rural & Remote Health,* 9: 1106-1Sep.	Not relevant to PICO – pilot study in Japan reporting on regional medical supply and demand for patients with haematological cancer.
20. Underhill, C., Koschel, A., Szer, J., Steer, C., Clarke, K., Grigg, A., Juneja, S., Stella, D., Francis, H. & Josselyn, K. (2010) Mentoring in the management of hematological malignancies. *Asia-Pacific Journal of Clinical Oncology,* 6: 28-34.	Not relevant to PICO – mentoring of health professionals

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Chapter 6: Managing newly diagnosed myeloma

First-line treatment

First autologous stem cell transplantation

Review Question:
Which patients with newly diagnosed myeloma should be considered for autologous stem cell transplantation?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients with newly diagnosed myeloma grouped according to - Age - Fragility/weakness - Comorbidities (charlson score, ACE-27, FACT-BMT) - Renal impairment - Genetic abnormalities - Response depth	Autologous stem cell transplant	no further treatment comparator treatment (e.g. lesser intensity)	• Health related quality of life • Overall survival • Progression free survival • Treatment related mortality • Treatment related morbidity • Patient/carer/family acceptability • Later effects • TWiST

Evidence Statements

See Figures 6.1 to 6.9 and Tables 6.1 to 6.7 below.

Age

Overall survival
Low quality evidence, from an individual patient meta-analysis (Levy et al, 2005) of three randomised trials (Attal et al, 1996; Fermand et al, 1998 and Fermand et al 1999; N=575), suggests that the effectiveness of high dose therapy with autologous stem cell transplant (HDT-ASCT) compared to standard dose treatment (SDT) is similar in younger and older age groups. There was no significant interaction between age (< 60 years versus 60 to 65 years) and the relative effectiveness of HDT-ASCT and SDT (P=0.96). For patients aged 60 to 65 years the hazard ratio for all cause mortality for HDT-ASCT versus SDT was 0.91 (95% C.I. 0.63 to 1.31; where HR < 1 favours HDT-ASCT), for patients younger than 60 years the hazard ratio was 0.90 (95% C.I. 0.72 to 1.12; where HR < 1 favours HDT-ASCT).

Seven randomised trials looked at age as a prognostic factor for overall survival but only two of these trials found age (Bladé et al 1996 and Sonneveld et al 2007) to be an independent prognostic factor. In Bladé et al (1996) the 56 to 70 year old age group were at higher risk of all cause mortality

compared to those younger than 56 years: HR 1.87 [95%C.I. 1.12 to 3.19]. In Sonneveld et al (2007), each additional year in age was associated with an increased risk of overall mortality: HR 1.04 [95%C.I. 1.02 to 1.07].

Progression free survival

Moderate quality evidence from nine randomized trials including 2474 patients, suggests progression free survival is better with HDT-ASCT, regardless of the age entry criteria used in the trial. For HDT-ASCT versus SDT, the HR for disease progression was 0.78 (95%C.I. 0.71 to 0.86; where HR <1 favours HDT-SCT). In only one of the nine trials was progression free survival significantly worse with autologous stem cell transplant (Facon et al, 2007), this was a trial in older patients (aged 65 to 75 years) comparing reduced intensity autologous stem cell transplantation with melphalan, prednisolone and thalidomide.

TWiSTT

Moderate quality evidence from two randomized trials (Fermand et al 1998, 2005) including 375 patients suggests that TWiSTT is 6.93 months longer (95%C.I. 1.61 to 12.26 months longer) with HDT-ASCT than with standard dose chemotherapy, regardless of the age entry criteria used in the trial.

Treatment related mortality

Low quality evidence from six randomized trials including 1588 patients suggests that the risk of treatment related mortality is higher with HDT-ASCT than with standard dose therapy, RR 2.00 [95%C.I. 1.25 to 3.19] where RR <1.0 favours HDT-ASCT. When grouping the trials by their age entry criteria, the highest relative risks of treatment related mortality were seen in trials that included patients aged 70 years or less, however the absolute risk of treatment related mortality with HDT-ASCT in this subgroup was around 4% - lower than the 8% to 10% seen in trials restricted to under 65s or under 55s respectively.

Treatment related morbidity

In patients randomized to receive transplantation in Attal et al (1996) the completion of allocated treatment was related to age, with older patients less likely to undergo transplantation. 12 of 67 patients (18%) aged 60 or less did not undergo transplantation compared to 14 of 33 patients (42%) aged 60-65 years (P=0.01).

Fragility/weakness

Overall survival

Moderate quality evidence suggested a difference in the effectiveness of HDT-ASCT versus standard dose therapy (SDT) according to the trials' performance status (PS) entry criteria (test for subgroup differences, P=0.01). For trials restricted to patients with WHO PS 0 to 2 there was uncertainty about the relative effectiveness of HDT-ASCT and SDT in terms of overall survival (HR = 1.06; 95% C.I. 0.92 to 1.23; HR <1 favours HDT-ASCT). For trials that did not state any PS entry criteria, overall survival was significantly better with HDT-ASCT than SDT (HR = 0.80; 95% C.I. 0.68 to 0.95; HR <1 favours HDT-ASCT). It was unclear, however, what the actual performance status was of the patients in trials not specifying performance status entry criteria.

Disease progression

Moderate quality evidence from nine randomized trials including 2474 patients, suggests a difference in the relative effectiveness of HDT-ASCT and SDT in terms of disease progression according to the performance status entry criteria used in the trial (test for subgroup differences, P<0.0001). For trials restricted to patients with WHO PS 0 to 2 there was uncertainty about the relative effectiveness of HDT-ASCT and SDT in terms of disease progression (HR = 0.93; 95% C.I. 0.82

to 1.05; HR <1 favours HDT-ASCT). For trials that did not state any PS entry criteria, progression free survival was significantly better with HDT-ASCT than SDT (HR = 0.63; 95% C.I. 0.55 to 0.72; HR <1 favours HDT-ASCT). It was unclear, however, what the actual performance status was of the patients in trials not specifying performance status entry criteria.

In only one of these nine trials was progression free survival significantly worse with autologous stem cell transplant (Facon et al, 2007), this was a trial in older patients (aged 65 to 75 years) comparing reduced intensity autologous stem cell transplantation with melphalan, prednisolone and thalidomide. The inclusion of this trial in the WHO PS 0-2 subgroup accounts for the subgroup differences.

Comorbidities (charlson score, ACE-27, FACT-BMT)

No evidence was identified about the influence of comorbidities on the relative effectiveness of high dose therapy or conventional dose therapy.

Renal impairment

Overall survival

Moderate quality evidence, from an individual patient meta-analysis (Levy et al, 2005) of three randomised trials (Attal et al, 1996; Fermand et al, 1998 and Fermand et al 1999; N=575), suggests that the effectiveness of high dose therapy with autologous stem cell transplant (HDT) compared to standard dose treatment (SDT) is similar in high and low creatinine groups. There was no significant interaction between creatinine level (< 120 µmol/L versus ≥ 120 µmol/L) and the relative effectiveness of high dose therapy with autologous stem cell transplant (HDT) and conventional treatment (P=0.72). For patients with creatinine level < 120 µmol/L the hazard ratio for all cause mortality for HDT versus conventional treatment was 0.86 (95% C.I. 0.69 to 1.08; where HR < 1 favours HDT), for patients creatinine level ≥ 120 µmol/L the hazard ratio was 0.94 (95% C.I. 0.65 to 1.12; where HR < 1 favours HDT).

Three randomised trials looked at creatinine as a prognostic factor for overall survival and in two of these trials (Barlogie et al 2006 and Child et al 2003) creatinine level was an independent prognostic factor for overall survival .

Disease progression

Two trials (Barlogie et al 2006 and Child et al 2003) looked at creatinine level as a prognostic factor for disease progression and in one of these trials (Child et al 2003) it was an independent prognostic factor for overall survival .

Genetic abnormalities

One trial (Barlogie et al, 2006) considered deletion of chromosome 13 on FISH as a prognostic factor. FISH del(13) was an independent prognostic factor for both overall survival and disease progression free survival. Compared with others, patients with FISH del(13) had an increased risk of all cause mortality (HR 1.96; 95%C.I. 1.30 to 2.94) and of disease progression (HR 1.48; 95%CI 1.03 to 2.12). No evidence was presented of the relative effectiveness of HDT-ASCT versus SDT within the subgroup of patients with FISH del(13).

Response depth

In Child (2003) the depth of response was associated with overall survival in the HDT-ASCT group – for minimal response median survival was 25.6 months (95% CI 7.0 to 31.3 months), for partial

response median survival was 39.8 months (95% CI 33.8 to 61.4 months) and for complete response median survival was 88.6 months (lower limit of 95% CI 61.4 months),

1 **Table 6.1. GRADE profiles for high dose therapy with autologous stem cell transplant versus standard dose therapy**

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose therapy with AutoSCT	Standard Chemotherapy	Relative (95% CI)	Absolute	
Death from any cause (age < 60 years) (follow-up median 8.67 years)											
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/212 (72.6%)	161/215 (74.9%)	HR 0.896 (0.717 to 1.121)	-	⊕⊕⊕O MODERATE
Death from any cause (age 60 to 65 years) (follow-up median 8.67 years)											
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	57/73 (78.1%)	63/75 (84%)	HR 0.906 (0.626 to 1.311)	-	⊕⊕OO LOW
Death from any cause (performance status not specified) (follow-up median 3.1 to 10 years)											
5[4]	randomised trials	no serious risk of bias	serious[5]	serious[6]	no serious imprecision	none	261/533 (49%)	300/528 (56.8%)	HR 0.80 (0.68 to 0.95)	-	⊕⊕OO LOW
Death from any cause (performance status 0 to 2) (follow-up median 4.7 to 7.7 years)											
4[7]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	374/623 (60%)	353/611 (57.8%)	HR 0.94 (0.84 to 1.05)	-	⊕⊕⊕O MODERATE
Death from any cause (creatinine < 120 µmol/L) (follow-up median 8.67 years)											
3[1]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/217 (71%)	167/226 (73.9%)	HR 0.864 (0.693 to 1.077)	-	⊕⊕⊕O MODERATE
Death from any cause (creatinine ≥ 120 µmol/L) (follow-up median 8.67 years)											
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	57/68 (83.8%)	57/64 (89.1%)	HR 0.935 (0.645 to 1.355)	-	⊕⊕OO LOW
Progression free survival (follow-up median 3.1 to 10 years)											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose therapy with AutoSCT	Standard Chemotherapy	Relative (95% CI)	Absolute	
9[9]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	?/1223	?/1194	HR 0.78 (0.71 to 0.86)	-	⊕⊕⊕O MODERATE
TWiSTT (follow-up median 4.8 to 10 years; Better indicated by higher values)											
2[10]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185	190	-	MD 6.93 months longer (1.61 to 12.26 longer)	⊕⊕⊕O MODERATE
Treatment related mortality (follow-up median 3.1 to 10 years)											
6[11]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	50/796 (6.3%)	25/792 (3.2%)	RR 2.00 (1.25 to 3.19)	32 more per 1000 (from 8 more to 69 more)	⊕⊕OO LOW
Health related quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Treatment related morbidity - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Patient acceptability - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Attal (1996), Fermand (1998), Fermand (2005) - IPD meta analysis by Levy (2005)
[2] Unclear random sequence generation and blinding in all studies
[3] Low number of events
[4] Attal (1996), Child (2003), Fermand (1998), Fermand (2005) and Palumbo (2004)
[5] Unclear random sequence generation and blinding in most studies
[6] Only Child (2003) reported the actual performance status of included patients.
[7] Barlogie (2006), Blade (2005), Facon (2007) and Sonneveld (2007)
[8] No explanation was provided
[9] Attal (1996), Barlogie (2006), Blade (2005), Child (2003), Facon (2007), Fermand (1998), Fermand (2005), Plaumbo (2004) and Sonneveld (2007)
[10] Fermand (1998), Fermand (2005)
[11] Attal (1996), Barlogie (2006), Fermand (1998), Fermand (2005), Palumbo (2004) and Sonneveld (2007)

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2 ***Table 6.2. Study characteristics according to the PICO subgroups***

Study, country	Age	Fragility/weakness	Comorbidities (Charlson score, ACE-27, FACT-BMT)	Renal function	Genetic abnormalities	Response depth
Attal 1996, France, Belgium	Up to 65 years (median 57 HDT, 57 SDT)	-	Excluded abnormal cardiac, liver or renal function,	-	-	
Barlogie 2006 USA	28 to 70 years (median 55 HDT, 54 SDT)	WHO PS 0-2 (or 3-4 if due to myeloma related bone disease)	-	Serum creatinine <2mg/dL	FISH 13 del test	-
Blade 2005, Spain	Up to 70 years (median 57 HDT, 56 SDT)	WHO PS 0 or 2	-	-	-	Responders to induction treatment only
Child 2003, UK and NZ	Up to 65 years (median 55 HDT, 56 SDT)	WHO PS 0-2 (84%) WHO PS 3-4 (15%)	Suitable for HDT	Suitable for HDT	-	-
Facon 2007	65-75 years (median between 65 and 70 years)	WHO PS 0 or 2	Excluded abnormal cardiac, liver or renal function, hepatitis, HIV	Serum creatinine <5mg/dL	-	-
Fermand 1998, France	Up to 56 years (median 48 HDT, 47 SDT)	-	Excluded severely abnormal cardiac, liver or renal function.	Serum creatinine <3.4mg/dL	-	-
Fermand 2005, France	55 to 65 years (median 61 HDT, 60 SDT)	-	Excluded severely abnormal cardiac, liver or renal function.	Serum creatinine <3.4mg/dL		
Palumbo 2004, Italy	50 to 70 years (median 65 HDT, 63 SDT)	-	Excluded abnormal cardiac, liver or renal function, hepatitis, HIV	Serum creatinine <3mg/dL	-	-
Sonneveld 2007, Belgium, Netherlands	32 to 65 years (median 56 HDT, 55 SDT)	WHO PS 0 or 2	Excluded severe cardiac disease	Serum creatinine <2mg/dL	-	-

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4 ***Table 6.3: Evidence tables for RCTs***

Study, country	Study type, period	Population	Subgroup analysis	Intervention	Comparison	Outcomes	Follow-up	Additional comments
Attal 1996, France, Belgium	RCT, 1990-1993	N=200 **Inclusion criteria** Age <65 years, untreated myeloma, DSS II+III **Exclusion criteria** cardiac problems, respiratory disease, abnormal liver function**,** psychiatric disease	**Age, <65, <60** Fragility/weakness, N Comorbidity, N **Renal impairment , Y (not excluded)** Genetics, N **Response depth, Y**	HDT plus autologous stem cell transplant	Conventional dose chemotherapy	Response rate, Overall survival, event free survival, Treatment related mortality	Median 3.1 yrs	Multivariate analysis of prognostic factors: age, DSS, IgG vs other, Hemoglobin level, beta-2-microglobulin level, plasma cells in marrow (%)
Barlogie 2006 USA	RCT,	N=516 **Inclusion criteria** Age ≤ 70 years, untreated symptomatic myeloma, Zubrod performance status of 0-2 (or 3-4 if due to myeloma bone disease) **Exclusion criteria**	**Age ≤ 70** Fragility/weakness, N Comorbidity, N Renal impairment , N	HDT plus autologous stem cell transplant	Conventional dose chemotherapy	Overall survival, progression free survival,	Median 6.3 yrs	Multivariate analysis of prognostic factors: age > 60 years, calcium ≥ 10 mg/dL, creatinine > 2 mg/dL, PLT < 130 X 10^3/μL, B2M > 3.5

Study, country	Study type, period	Population	Subgroup analysis	Intervention	Comparison	Outcomes	Follow-up	Additional comments
		Systolic ejection fraction or carbon dioxide diffusing capacity <50%, active malignant disease within the previous 5 years.	Genetics, N Response depth, N					mg/dL, LDH > 190 U/L, PCLI > 1%
Blade 2005, Spain	RCT, 1994-1999	N=216 **Inclusion criteria** Age <70yrs, untreated symptomatic myeloma, DSS II+III, PS 0 to 2 **Exclusion criteria** No response to initial chemotherapy	**Age, <70** Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N Response depth, N	HDT plus autologous stem cell transplant	Conventional dose chemotherapy	Overall survival, progression free survival, Response,	Median 4.7 yrs	Multivariate analysis of prognostic factors: Age > 56 years, serum albumin level, hemoglobin level, beta-2-microglobulin level, M-protein type (IgA vs others) and treatment arm
Child 2003, UK and NZ	RCT, 1993-2000	N=401 **Inclusion criteria** Age <65yrs, untreated myeloma, meeting MRC criteria for treatment **Exclusion criteria** Not reported (not meeting MRC criteria)	**Age, <65** Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N **Response depth, Y**	HDT plus autologous stem cell transplant	Conventional dose chemotherapy	Overall survival, progression free survival, Treatment related mortality, Response,	Median 3.5 yrs	Multivariate analysis of prognostic factors: age, serum creatinine, haemoglobin level, beta-2-microglobulin level
Facon 2007, France	RCT, 2000-2005	N=447 **Inclusion criteria** Age 65-75yrs (or ineligible for HDT), untreated myeloma, DSS II+III or I high risk **Exclusion criteria** Cardiac problems, abnormal liver function amyloidosis**,** abnormal renal function (creatinine > 5 mg/dl), other cancers, infections with HIV, HepB or HepC	Age, 65-75 Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N Response depth, N	Reduced intensity autologous stem cell transplantation	Melphalan and prednisolone ± thalidomide	Overall survival, Treatment related mortality, Progression free survival, Treatment toxicity (grade 3-4), Response, Second line treatment,		
Fermand 1998, France	RCT, 1990-1995	N=185 **Inclusion criteria** Age <56yrs, untreated symptomatic myeloma **Exclusion criteria** Stage I MM, PFS 3-4, severe cardiac problems, respiratory disease, abnormal liver function**,** abnormal renal function	Age, <56 Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N Response depth, N	HDT and autologous stem cell transplant	Conventional dose therapy (HDT delayed until relapse)	Overall survival, Treatment related mortality TWiSTT Event free survival, Response	Median 4.8 yrs	Analysis of prognostic factors, (treatment, age, salmon-durie, IgA, and β-microglobulin, LDH/ULN)
Fermand 2005, France	RCT,	N=190 **Inclusion criteria** Age 55-65yrs , untreated symptomatic myeloma **Exclusion criteria**	Age, N Fragility/weakness, N Comorbidity, N	HDT and autologous stem cell transplant	Conventional dose therapy	Overall survival, Treatment related mortality TWiSTT	Median 10 years	Analysis of prognostic factors, (treatment, ISS stage, creatinine, calcium, haemoglobin

Study, country	Study type, period	Population	Subgroup analysis	Intervention	Comparison	Outcomes	Follow-up	Additional comments
		Stage I MM, PFS 3-4, severe cardiac problems, respiratory disease, abnormal liver function**,** abnormal renal function	Renal impairment , N Genetics, N Response depth, N			Event free survival, Response		and β-microglobulin)
Palumbo 2004, Italy	RCT, 1997-2000	N=194 **Inclusion criteria** Age 50-70yrs, untreated myeloma **Exclusion criteria** Cardiac problems, respiratory disease, abnormal liver function (serum bilirubin > 2 mg/dl)**,** abnormal renal (creatinine > 3 mg/dl), other cancers, psychiatric or liver disease	Age, 50-70, 65-70 Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N Response depth, N	Melphalan with stem cell support	Oral melphalan and prednisolone (MP)	Overall survival, Disease progression, Early death, Response	Median 3.25 years	Multivariate analysis of prognostic factors: (treatment and β-microglobulin)
Sonneveld 2007, Belgium, Netherlands	RCT, 1995-2000	N=303 **Inclusion criteria** Age 18-65yrs, untreated myeloma **Exclusion criteria** PFS 3-4, severe cardiac problems, respiratory disease, abnormal liver function**,** abnormal renal function	Age, 18-65 Fragility/weakness, N Comorbidity, N Renal impairment , N Genetics, N Response depth, N	VAD then Cyclophosphamide with stem cell support	VAD then Melphalan, G-CSF	Overall survival, Disease progression, EFS Response	Median 7.7 yrs	Multivariate analysis of prognostic factors: (treatment, age, salmon-durie, IgA, and β-microglobulin, LDH/ULN)

1 ***Table 6.4. Details of prognostic models***

Study, country	Population	Factors considered	Independent prognostic factors
Attal 1996, France, Belgium	N=200 **Inclusion criteria** Age <65 years, untreated myeloma, DSS II+III **Exclusion criteria** cardiac problems, respiratory disease, abnormal liver function**,** psychiatric disease	Age, DSS, IgG vs other, Hemoglobin level, beta-2-microglobulin level, plasma cells in marrow (%), treatment group, response to treatment	**OS** beta-2-microglobulin level **EFS** beta-2-microglobulin level, treatment group
Barlogie 2006 USA	N=516 **Inclusion criteria** Age ≤ 70 years, untreated symptomatic myeloma, Zubrod performance status of 0-2 (or 3-4 if due to myeloma bone disease) **Exclusion criteria** Systolic ejection fraction or carbon dioxide diffusing capacity <50%, active malignant disease within the previous 5 years.	Age > 60 years, calcium ≥ 10 mg/dL, creatinine > 2 mg/dL, PLT < 130 X 10^3/μL, B2M > 3.5 mg/dL, LDH > 190 U/L, PCLI > 1%, FISH 13 deletion	**OS** creatinine > 2 mg/dL, PLT < 130 X 10^3/μL, LDH > 190 U/L, PCLI > 1%, FISH 13 deletion **PFS** LDH > 190 U/L, PCLI > 1%, FISH 13 deletion
Blade 2005, Spain	N=216 **Inclusion criteria** Age <70yrs, untreated symptomatic myeloma, DSS II+III, PS 0 to 2 **Exclusion criteria** No response to initial chemotherapy	Age > 56 years, serum albumin level, hemoglobin level, beta-2-microglobulin level, Ig isotype (IgA vs others) and treatment arm	**OS** Age > 56 years, haemoglobin > 100g/L
Child 2003, UK and NZ	N=401 **Inclusion criteria** Age <65yrs, untreated myeloma, meeting MRC criteria for treatment **Exclusion criteria** Not reported (not meeting MRC criteria)	Age, serum creatinine, haemoglobin level, beta-2-microglobulin level	**OS** creatinine > 1.7 mg/dL, haemoglobin **>** 9 g/dL, beta-2-microglobulin level, treatment group **PFS** creatinine > 1.7 mg/dL, haemoglobin **>** 9 g/dL, beta-2-microglobulin level
Fermand 2005, France	N=190 **Inclusion criteria** Age 55-65yrs , untreated symptomatic myeloma **Exclusion criteria** Stage I MM, PFS 3-4, severe cardiac problems, respiratory disease, abnormal liver function**,** abnormal renal function	Age, treatment, ISS stage, creatinine, calcium, haemoglobin and β-microglobulin)	**OS** beta-2-microglobulin level
Palumbo 2004, Italy	N=194 **Inclusion criteria** Age 50-70yrs, untreated myeloma **Exclusion criteria** Cardiac problems, respiratory disease, abnormal liver function (serum bilirubin > 2 mg/dl)**,** abnormal renal (creatinine > 3 mg/dl), other cancers, psychiatric or liver disease	Age, sex, treatment group, Ig isotype, DS stage and beta-2-microglobulin	**OS** Treatment group and beta-2-microglobulin level **EFS** Treatment group and beta-2-microglobulin level
Sonneveld 2007, Belgium,	N=303 **Inclusion criteria** Age 18-65yrs, untreated myeloma	Age, DSS stage, Ig isotype (IgA vs other), beta-2-microglobulin (natural log), LDH/upper normal limit,	**OS** Age (higher), IgA isotype, lower haemoglobin concentration and higher

Study, country	Population	Factors considered	Independent prognostic factors
Netherlands	**Exclusion criteria** PFS 3-4, severe cardiac problems, respiratory disease, abnormal liver function**,** abnormal renal function		LDH/UNL value **EFS** Age (higher), IgA isotype and lower haemoglobin concentration **PFS** Age (higher), IgA isotype, lower haemoglobin concentration and higher LDH/UNL value

1
2
3

Table 6.5. Independent prognostic factors for overall survival in trials of HDT-AutoSCT versus SDT

	Attal	Barlogie	Blade	Child	Fermand	Palumbo	Sonneveld
Age	–	–	✔	–	–	–	✔
Beta-2-microglobulin	✔	–	–	✔	✔	✔	–-
Haemoglobin level	–	–	✔	✔	–		✔
Treatment group	–		–	✔	–	✔	
Immunoglobulin isotype	–		–			–	✔
DS stage	–					–	–
Creatinine		✔		✔	–		
LDH		✔					✔
Albumin		–	–				
Calcium		–			–		
Plasma cell index	–	✔					
IS stage					–		
FISH 13 deletion		✔					
platelets		✔					
Sex						–	

Key: ✔ significant independent prognostic factor, - not significant independent prognostic factors, grey areas indicate the study did not consider the prognostic factor

Table 6.6. Prognostic factors for event free survival in trials of HDT-AutoSCT versus SDT

	Attal	Palumbo	Sonneveld
Age	–	-	✔
Beta-2-microglobulin	✔	✔	-
Haemoglobin level	–-		✔
Treatment group	✔	✔	
Ig isotype	–		✔
DS stage	–	–	–
LDH			✔
Plasma cell index	–		
Sex		–	

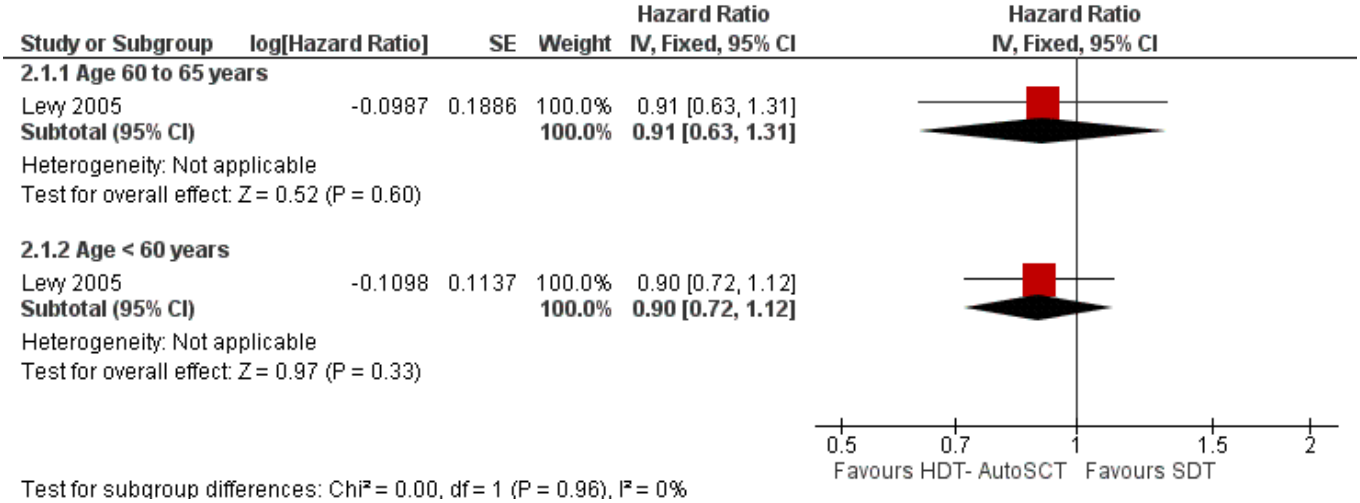
Key: ✔ significant independent prognostic factor, - not significant independent prognostic factors, grey areas indicate the study did not consider the prognostic factor

Table 6.7. Prognostic factors for progression free survival in trials of HDT-AutoSCT versus SDT

	Barlogie	Child	Sonneveld
Age	–	–	✔
Beta-2-microglobulin	–	✔	–
Haemoglobin level	–	✔	–
Treatment group		-	
Ig isotype			✔
DS stage			–
Creatinine	–	✔	
LDH	✔		✔
Albumin	–		
Calcium	–		
Plasma cell index	✔		
IS stage			
FISH 13 deletion	✔		
platelets	–		

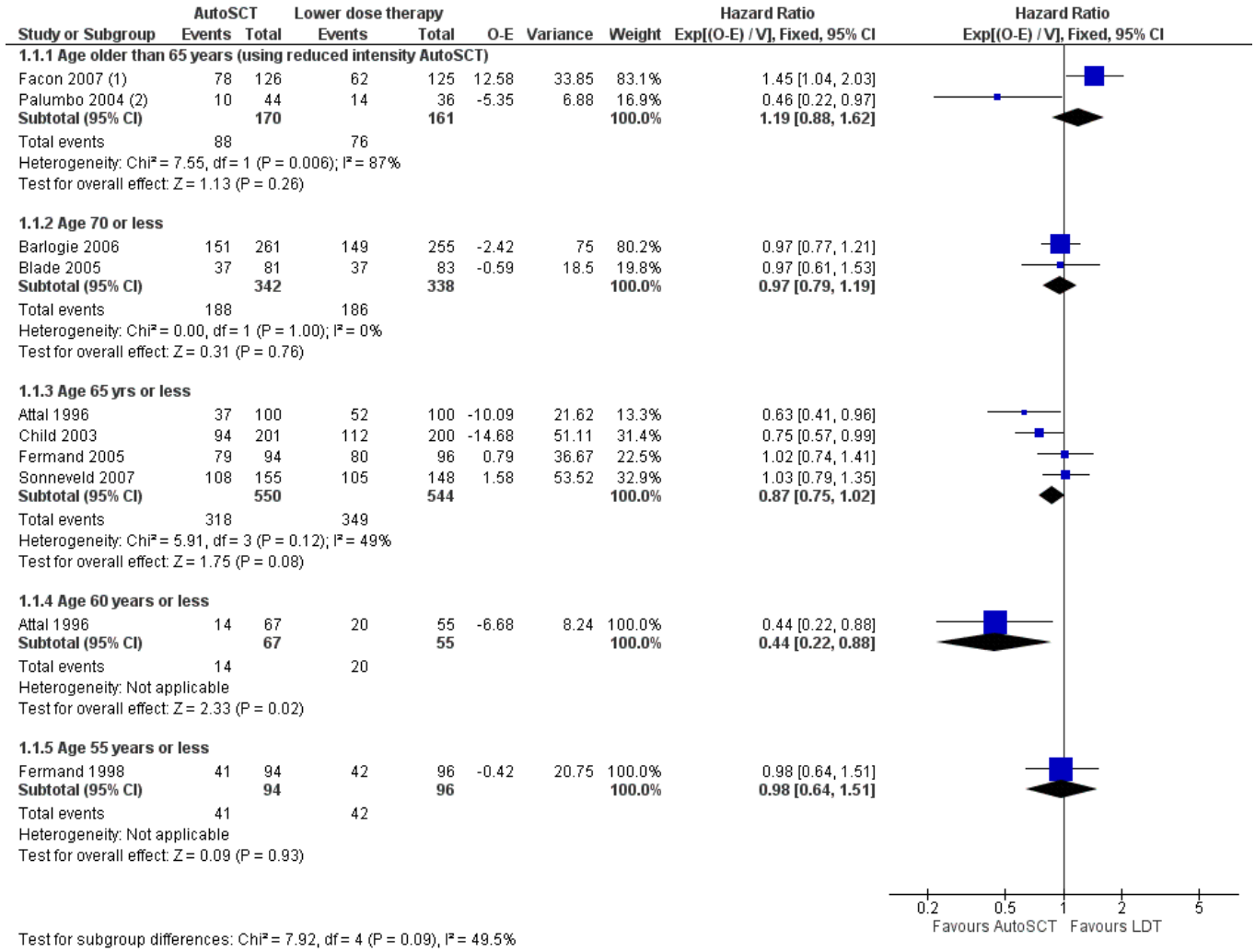
Key: ✔ significant independent prognostic factor, - not significant independent prognostic factors, grey areas indicate the study did not consider the prognostic factor

Figure 6.1. Overall mortality by age group, HDT versus SDT. From Levy (2005) meta-analysis



Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$

Figure 6.2. Overall mortality by trial age entry criteria, HDT versus lower dose therapy.



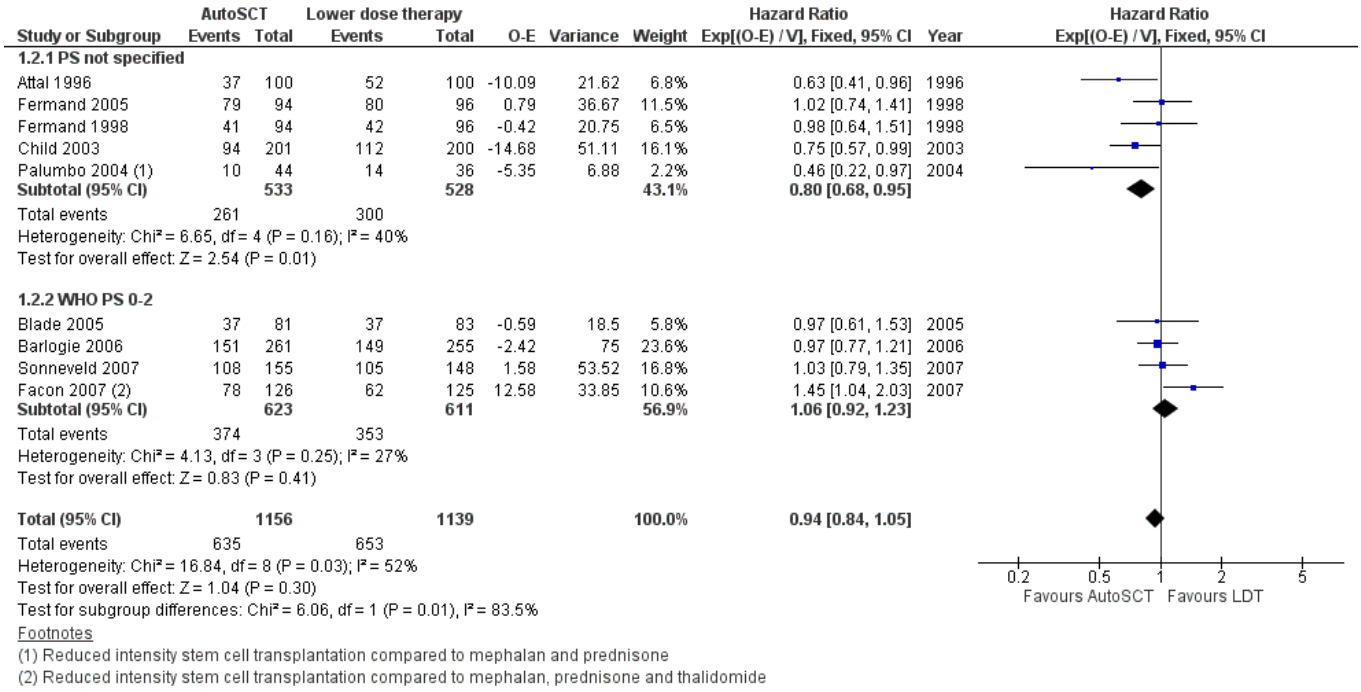
Test for subgroup differences: Chi² = 7.92, df = 4 (P = 0.09), I² = 49.5%

Footnotes

(1) Reduced intensity stem cell transplantation compared to mephalan, prednisone and thalidomide

(2) Reduced intensity stem cell transplantation compared to mephalan and prednisone

Figure 6.3. Overall mortality by trial performance status entry criteria HDT versus lower dose therapy.



Footnotes

(1) Reduced intensity stem cell transplantation compared to mephalan and prednisone

(2) Reduced intensity stem cell transplantation compared to mephalan, prednisone and thalidomide

Figure 6.4. Overall mortality by creatinine group, HDT versus lower dose therapy. From Levy (2005) meta-analysis

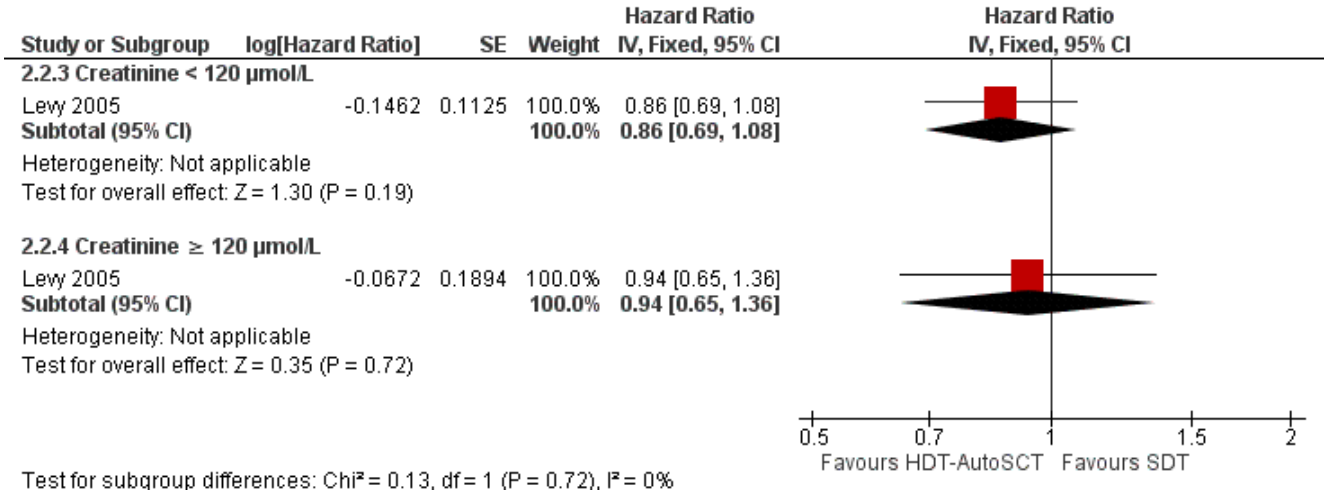


Figure 6.5. Disease progression by trial age entry criteria, HDT versus lower dose therapy (using data from Faussner, 2012)

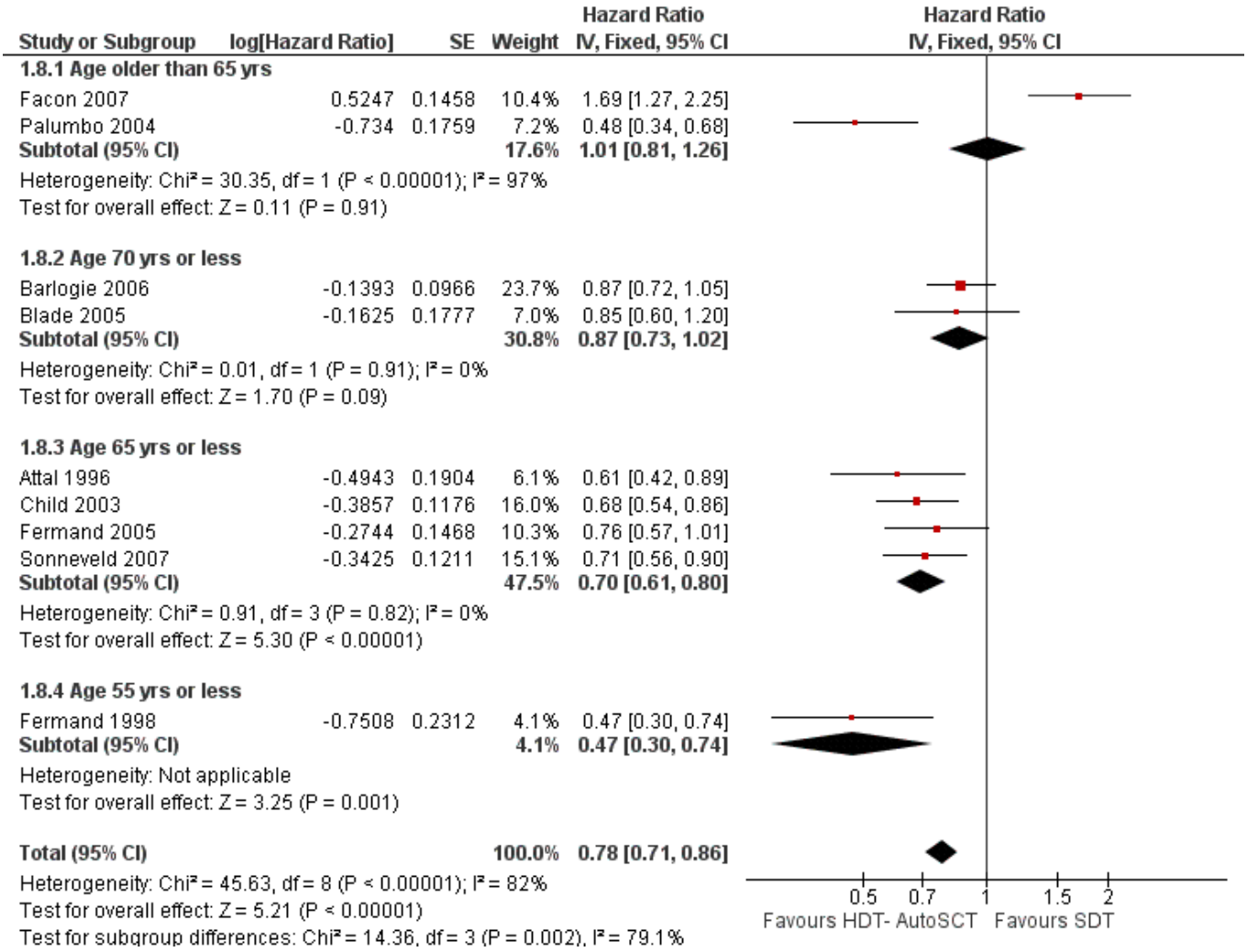


Figure 6.6. Disease progression by trial performance status entry criteria, HDT versus lower dose therapy (using data from Faussner, 2012)

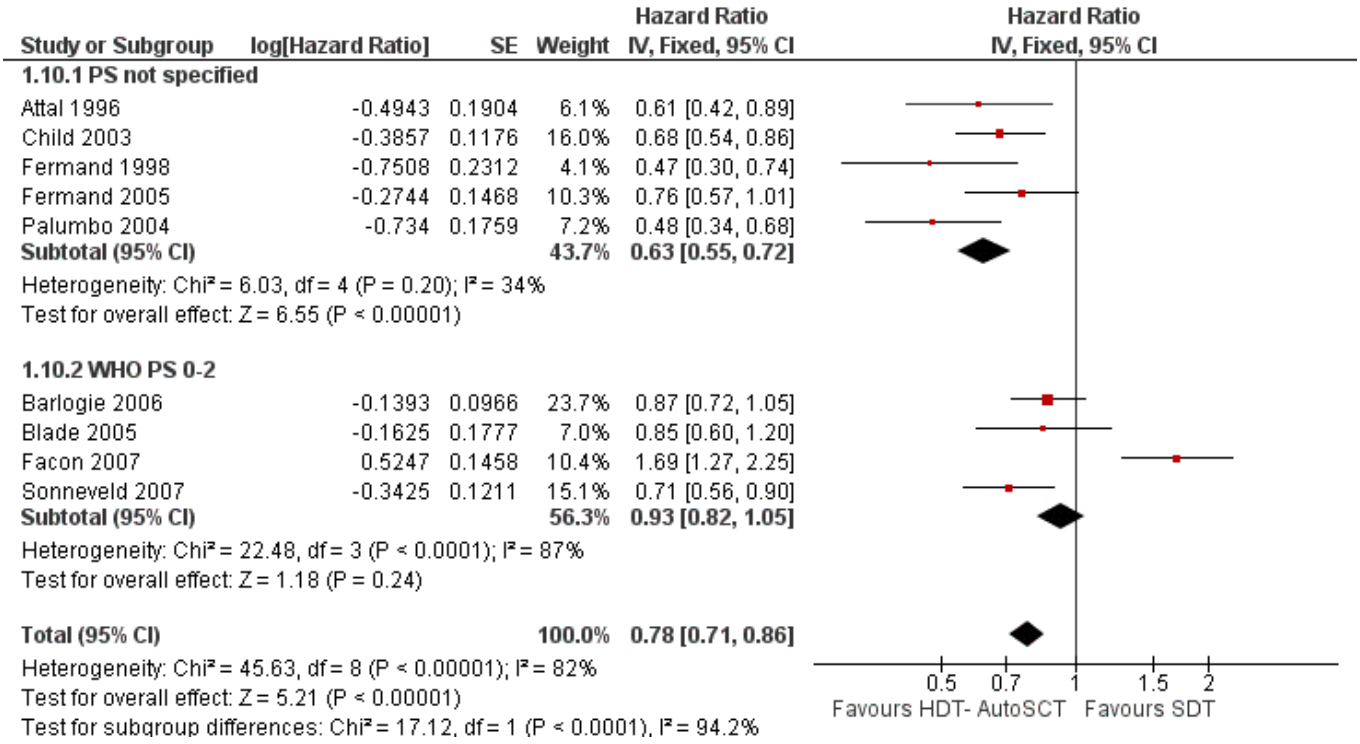


Figure 6.7. TWiSTT (months) by trial age entry criteria, HDT versus lower dose therapy

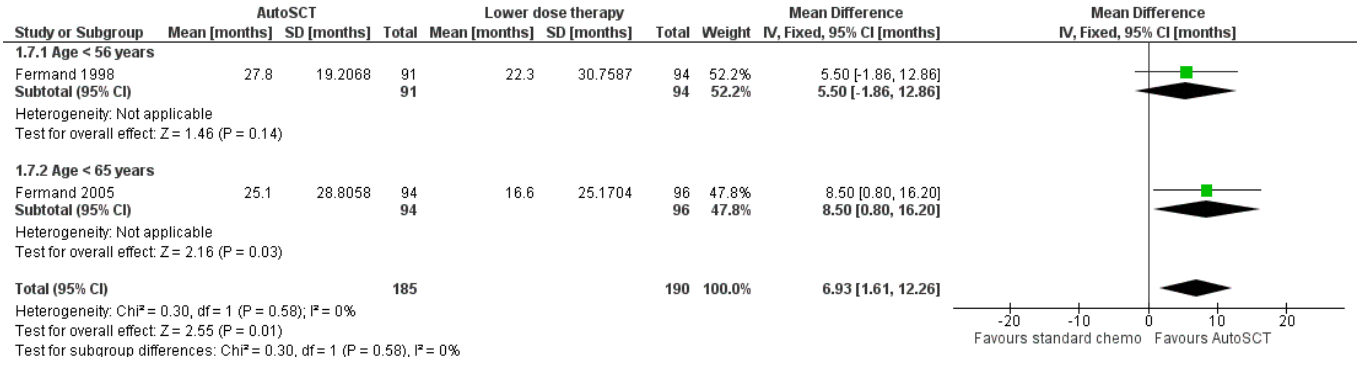


Figure 6.8. Treatment related mortality by trial age entry criteria, HDT versus SDT

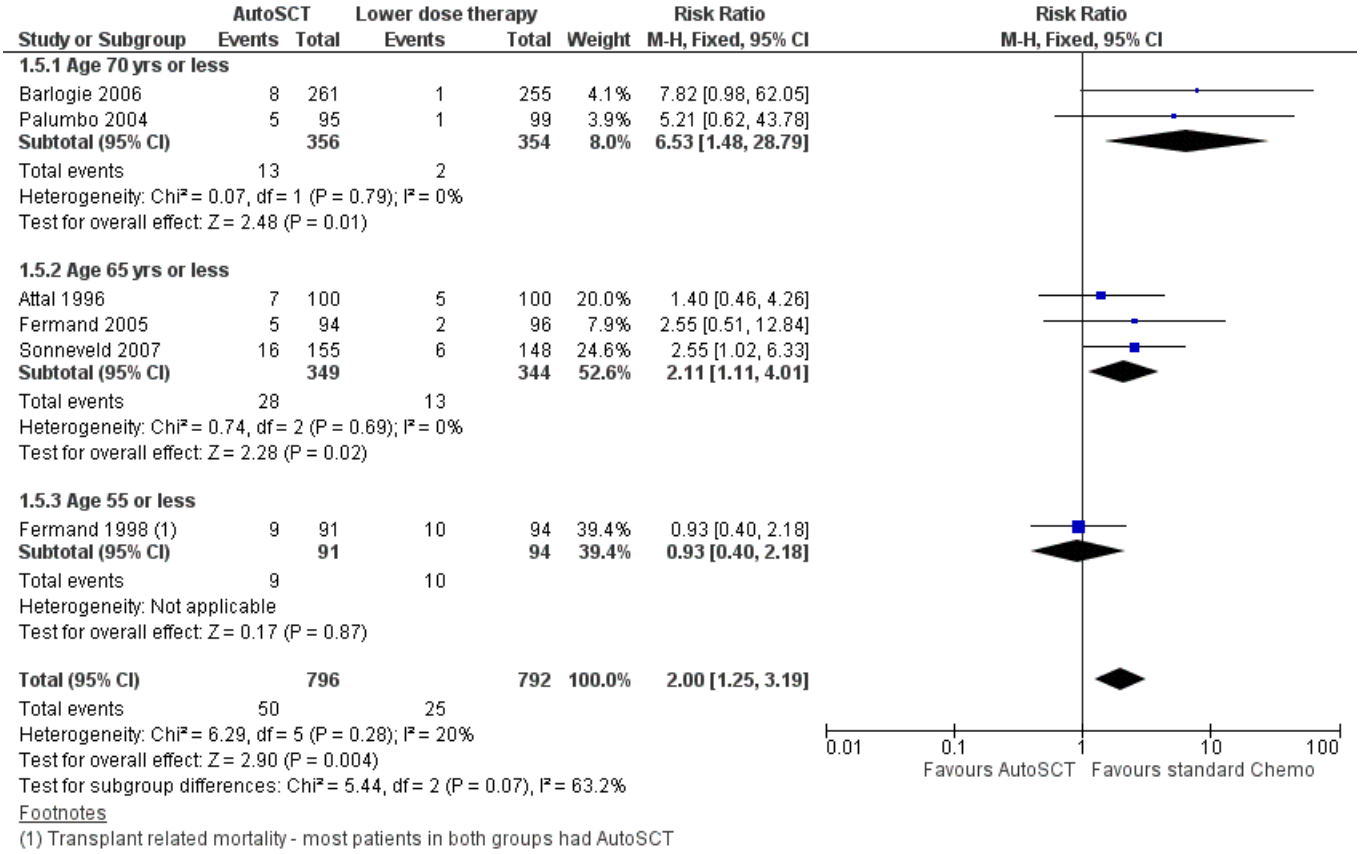


Figure 6.9. Risk of bias summary

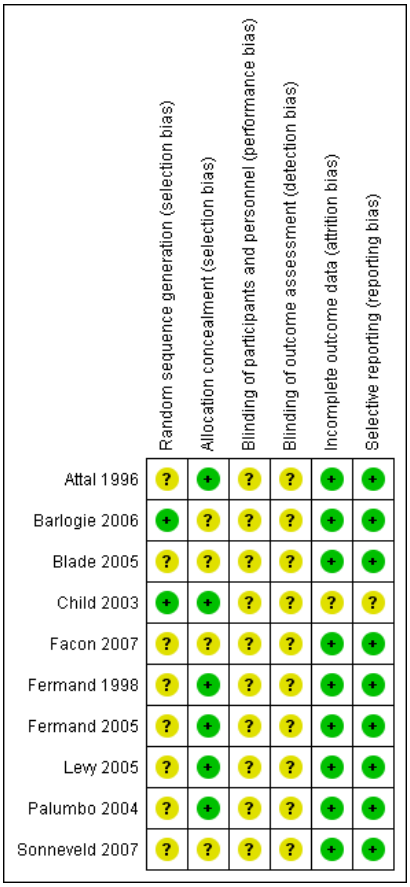
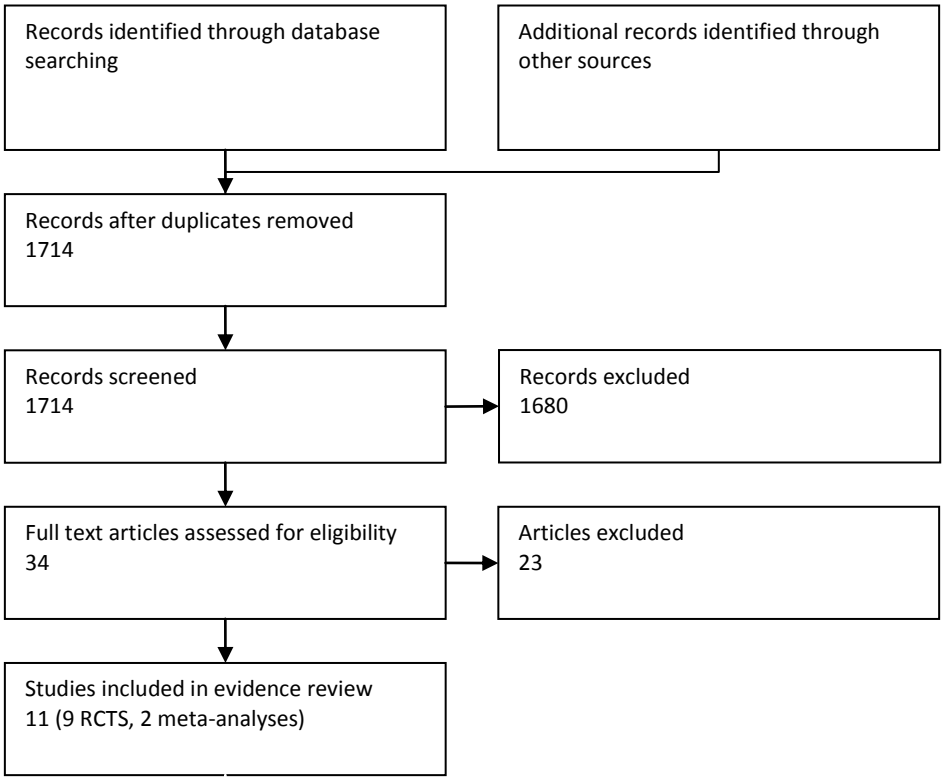


Figure 6.10: Screening results



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Health economic evidence

Myeloma: diagnosis and management of myeloma	**Economic evidence summary**

Topic: Primary disease management for newly diagnosed myeloma, including autologous stem cell transplantation.

Key question: Which patients with newly diagnosed myeloma should be considered for autologous stem cell transplantation?

Population: Patients with newly diagnosed myeloma

Intervention: Autologous stem cell transplant

Comparator: no further treatment, comparator treatment (e.g. lesser intensity).

Outcomes: Health related quality of life, Overall survival, Progression free survival, Treatment related mortality, Treatment related morbidity, Patient/carer/family acceptability, Later effects, TWiST

Summary

- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted from any OECD countries were considered (Guidelines Manual 2014).
- 463 possibly relevant papers were identified. Of these, 11 full papers relating to this topic were obtained for appraisal. Three papers were not relevant to the PICO, one only considered costs and four did not report quality of life based outcomes. Therefore three studies (Gulbrandsen et al 2001, Van Agthoven et al 2004, Corso et al 2013) were included in the current review of published economic evidence for this topic.
- Gulbrandsen et al considered the cost effectiveness of high dose chemotherapy in addition to autologous stem cell transplant versus high dose chemotherapy alone in patients under 60 years of age with newly diagnosed, symptomatic myeloma. The study reported the results in terms of cost per Quality Adjusted Life Year (QALY) gained and considered a Norwegian societal perspective.

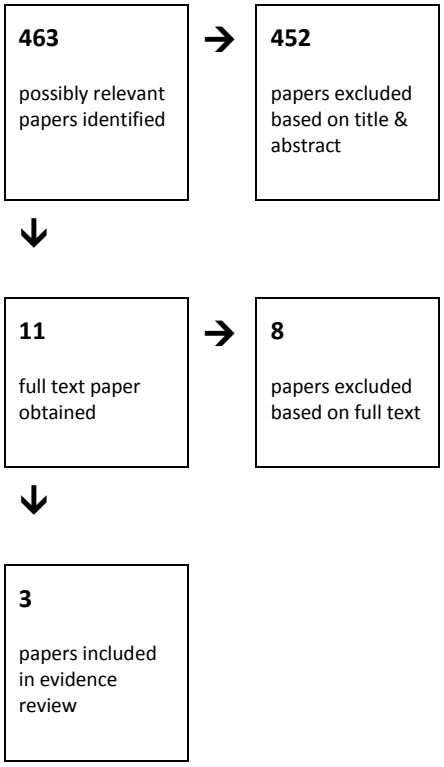
Gulbrandsen et al found the transplant strategy to be both more costly and more effective estimating a cost per QALY of $27,000. This ranged from $6,800 to $40,000 per QALY during sensitivity analysis.

- Gulbrandsen had limited exploration of uncertainty around the parameters and results and did not present a probabilistic sensitivity analysis.
- Corso et al considered the cost effectiveness of high dose chemotherapy with autologous stem cell support versus high dose chemotherapy in previously untreated myeloma patients. The study reported results in terms of cost per QALY gained and considered an Italian health payer perspective. The transplant strategy was found to be both more expensive and more effective leading to a cost per QALY of €44,454.
- There was a lack of transparency in the Corso study around their elicitation of key parameters (in particular utility weights) and the distributions used for parameters in their probabilistic sensitivity analysis. Deterministic sensitivity analyses were not presented.
- van Agthoven considered the cost effectiveness of intensive chemotherapy with stem cell transplant versus intensive chemotherapy alone in patients ≤65 years of age with previously untreated stage II or III A/B myeloma. The study found the transplant strategy to be both more costly and less effective.
- van Agthoven presented limited exploration of uncertainty around their estimate making it difficult to consider the robustness of these conclusions. The study was therefore deemed to have potentially serious limitations.
- Despite all three studies considering similar interventions and comparators it is difficult to meaningfully compare results given the differing range of perspectives taken. All studies though reported significantly higher costs for the transplant strategy than for the non-transplant strategy. The incremental QALYs between the transplant and non-transplant strategies differed widely across all studies ranging from -0.14 to 1.73 QALYs
- All studies were considered only partially applicable to the decision problem. This is because all studies took a perspective other than a NHS+PSS one. Discounting of costs and health outcomes was also inconsistent, with that recommended by NICE. Only one study (van Agthoven et al) elicited changes in 'Health Related Quality of Life' from a representative sample of the general public.

Volume of evidence

- 463 possibly relevant papers were identified. Of these, 11 full papers relating to this topic were obtained for appraisal. Three papers were not relevant to the PICO, one only considered costs and four did not report quality of life based outcomes. Therefore three studies (Gulbrandsen et al 2001, Van Agthoven et al 2004, Corso et al 2013) were included in the current review of published economic evidence for this topic.
- All three studies compared a transplant strategy with a high dose chemotherapy strategy and reported their outcomes in terms of cost per QALY

Selection criteria for included evidence:



- Studies that compare costs and health consequences of interventions were included (i.e. true cost-effectiveness analyses)
- Quality of life based outcomes were used as the measure of effectiveness in at least one of the analyses presented
- Studies conducted in OECD countries were included
- Studies that presented incremental results or presented enough information for incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies not considering a UK NHS+PSS perspective which presented identical or similar economic models to a study which did were excluded

Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations		Corso et al 2013 Gulbrandsen et al 2001 Van Agthoven et al 2004
	Very serious limitations		

- All studies were considered only partially applicable to the decision problem that we are evaluating. This is because all studies did not take a NHS+PSS perspective and discounting was also inconsistent, with that recommended by NICE. Only one study (van Agthoven et al) elicited changes in 'Health Related Quality of Life' from a representative sample of the general public.
- Potentially serious limitations were identified with all studies. All three studies presented inadequate exploration of uncertainty with only one presenting a limited probabilistic sensitivity analysis. Other limitations included the identification and reporting of key parameters.

Reference List

Corso A, Mangiacavalli S, Cocito F et al. (2013) Long Term Evaluation of the Impact of Autologous Peripheral Blood Stem Cell Transplantation in Multiple Myeloma: A Cost-Effectiveness Analysis. **PLoS ONE** 8(9): e75047.

Gulbrandsen, N., Wisløff, F., Nord, E., et al. (2001). 'Cost-utility analysis of high-dose melphalan with autologous blood stem cell support vs. melphalan plus prednisone in patients younger than 60

years with multiple myeloma.' **European Journal of Haematology**, 66, 328-336.

Van Agthoven, M., Segeren, C. M., Buijt, I., et al. (2004). 'A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study. '**European Journal of Cancer**, 40, 1159-1169.

Allogeneic stem cell transplantation

Review Question:

Which patients with myeloma should be considered for allogeneic stem cell transplantation?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients with newly diagnosed myeloma grouped according to - Age - Performance status - Comorbidities (Charlson score, ACE-27) - Renal impairment - Genetic abnormalities (FISH) - ISS - Beta-2 microglobulin Patients with relapsed myeloma grouped according to - Age - Performance status - Comorbidities (Charlson score, ACE-27) - Renal impairment - Genetic abnormalities (FISH) - Time to relapse - Number of relapses - Disease responsiveness (disease that responded or is stable after re-induction therapy)	Allogeneic stem cell transplant - Myeloablative conditioning (MAC) - Non-Myeloablative conditioning (NMA) or reduced intensity conditioned (RIC including auto/allo RIC)	• Chemotherapy • First (in newly diagnosed patients) or second (in relapsed patients) autologous stem cell transplant • no treatment	• Health related quality of life • Overall survival • Progression free survival • Treatment related mortality • Treatment related morbidity • Adverse events • Patient/carer/family acceptability • PROMs

Evidence statements

See Tables 6.8 to 6.15.

Patients with newly diagnosed myeloma

Very low to low quality evidence suggests that outcomes are better (OS and PFS or EFS are longer) following treatment with a tandem approach of autologous-allogeneic stem cell transplant compared to treatment with a tandem autologous-autologous stem cell transplant in newly diagnosed myeloma patients in the following subgroups: patients with del13 (Björkstrand et al., 2011; Gahrton et al., 2013), ISS stage 3 patients (Lokhorst et al., 2012) and chemosensitive patients (Rosinol et al., 2008). Allogeneic transplant was also found to be superior to any other treatment in patients with beta-2-microglobulin (B2M) greater than 3 (Lokhorst et al., 2012).

There was also evidence to the contrary from 2 studies which reported that outcomes were better with tandem autologous stem cell transplant compared to allogeneic transplant in newly diagnosed high risk myeloma patients (Garban et al., 2006; Krishnan et al., 2011). In addition, one study reported no difference in outcomes for the two treatment strategies in high risk patients (Bruno et al., 2007).

Conflicting results between the different studies are unlikely to be due to a true difference in the effect of allogeneic transplant in specific subgroups of patients but more than likely can be explained by differences between studies such as different patient selections, different conditioning regimens, and different GVHD prophylaxis regimen. Variation in the length of follow-up employed in the different studies may also account for the differences in results. The studies of high risk myeloma patients all report better results (longer OS and PFS or EFS) with tandem autologous transplant compared to autologous-allogeneic transplant whereas studies of other population subgroups report better outcomes with autologous-allogeneic transplant. But these studies of high risk patients have shorter follow-up times (24-45 months) compared to the other studies (62-96 months).

No evidence was identified for the outcomes treatment related morbidity, health related quality of life, adverse events, patient/carer/family acceptability and PROMs.

Patients with relapsed myeloma

Low quality evidence from a retrospective analysis suggests that outcomes are worse following treatment with allogeneic stem cell transplant compared to a second autologous stem cell transplant in relapsed patients with Durie-Salmon stage III myeloma. Allotransplant was associated with a higher risk of relapse and treatment failure compared to autologous transplantation (Freytes et al., 2014). Evidence from the same study suggests that there is little difference in outcomes between related and unrelated donor allogeneic transplantation. The 3-year OS of patients who underwent transplant from related donors was 19% compared to 21% in patients whose donors were unrelated. Furthermore the TRM was also similar irrespective of donor type (Freytes et al., 2014).

Moderate quality evidence from studies of allogeneic transplant that reported predictive factors (high quality prognostic factor studies but downgraded as comparative studies are better for answering the review question) suggest that in relapsed myeloma patients undergoing allogeneic transplant B2 microglobulin < 3.3mg/L is predictive of lower NRM and longer PFS and OS (Efebera et al., 2010), a longer interval between auto and relapse is predictive of lower OS (Patriarca et al., 2012), an interval of more than 1 year between the first and the salvage transplant is predictive of longer OS (Qazilbash et al., 2006), previous auto STC is predictive of lower NRM and longer PFS and OS (Efebera et al., 2010), refractory disease is predictive of worse OS and PFS (Shimoni et al., 2010),

disease duration of >5 years is predictive of worse PFS (Shimoni et al., 2010) and SCT from female donor to male recipient is predictive of worse OS and PFS (Shimoni et al., 2010).

No evidence was identified for the outcomes treatment related morbidity, health related quality of life, adverse events, patient/carer/family acceptability and PROMs.

Table 6.8: Predictive factors for allogeneic transplant in relapsed myeloma patients

	Efebera[a]	**Patriarca**[a]	**Qazilbash**[b]	**Shimoni**[a]
B2 microglobulin < 3.3mg/L	Predictive of lower NRM and longer PFS and OS.	n/a	X	n/a
Interval between diagnosis and allo	X	X	n/a	n/a
Interval between auto and allo	X	n/a	Longer interval predictive of longer OS	X
Interval between auto and relapse	n/a	Longer interval predictive of lower OS	n/a	n/a
Previous auto STC	Predictive of lower NRM and longer PFS and OS.	n/a	n/a	X
age	X	n/a	X	X
disease status before SCT (responsive or unresponsive)	n/a	X	X	Refractory disease predictive of worse OS and PFS
Disease duration of >5 years	n/a	n/a	n/a	Predictive of worse PFS
Stem cell source	X	X	n/a	n/a
Donor type (related/unrelated)	X	X	X	X
Donor and recipient gender	n/a	n/a	n/a	SCT from female donor to male recipient predictive of worse OS and PFS
Use of DLI	X	X	n/a	n/a
ATG	n/a	X	n/a	n/a
Immunoglobulin subtype	X	n/a	n/a	n/a
Serum lactate dehydrogenase	X	n/a	n/a	n/a
Serum albumin	X	n/a	X	n/a
Cytogenetic data	n/a	n/a	X	n/a

[a] *Independent predictive factors from multivariate analysis.*
[b] *Results from univariate analysis. Multivariate analysis was not performed due to a small sample size.*
X: Not predictive.
n/a: Factor not investigated or too few numbers of patients to include in analysis.

1 ***Table 6.9: Summary of results in newly diagnosed myeloma patients***

	OS	PFS	EFS	TRM	Relapse/progression
Patients with del13 *Björkstrand et al., 2011;* *Gahrton et al., 2013*	Better with allo than 2nd auto	Better with allo than 2nd auto	n/a	n/a	less with allo than 2nd auto
Patients with ISS stage III *Lokhorst et al., 2012*	Better with allo than 2nd auto	Better with allo than 2nd auto	n/a	n/a	n/a
Patients with B2M greater than 3 *Lokhorst et al., 2012*	Better with allo than other treatment	Better with allo than other treatment	n/a	n/a	n/a
High risk myeloma (patients younger than 65 years, B2M greater than 3, chr13 abnormalities) *Garban et al., 2006*	Better with 2nd auto than allo	n/a	Better with 2nd auto than allo	n/a	n/a
High risk patients (B2M, cytogenetics) *Krishnan et al., 2011*	Better with 2nd auto than allo	Better with allo than 2nd auto	n/a	Higher with allo than 2nd auto	higher with 2nd auto than allo
High risk patients (high B2M and/or chr13 abnormalities) *Bruno et al., 2007*	No difference between auto-allo and tandem auto	n/a	No difference between auto-allo and tandem auto	n/a	n/a
Chemosensitive patients *Rosinol et al., 2008*	Better with allo than 2nd auto	Better with allo than 2nd auto	Better with allo than 2nd auto	Higher with allo than 2nd auto	n/a

2

Table 6.10: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma del13)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
PFS at 96 months											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	63	-	PFS at 96 months was 16% greater in the allo group compared to those in the second auto group	⊕OOO VERY LOW
OS at 96 months											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	63	-	OS at 96 months was 16% greater in the allo group compared to those in the second auto group	⊕OOO VERY LOW

Table 6.11: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who have high risk disease)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
EFS											
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	265	-	One study: HR 0.52 (95%CI: 0.22-1.21). Second study: mean EFS was 3 months longer in patients in the second auto group compared to those in the allo group.	⊕⊕OO LOW
OS											
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	123	265	-	One study: HR 0.34 (95%CI: 0.10-1.18). Second study: mean OS was 12 months longer in patients in the second auto group compared to those in the allo group.	⊕⊕OO LOW
3 yr PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	31	-	3 yr PFS was 3% greater in patients in the second auto group compared to those in the allo group.	⊕OOO VERY LOW
3 yr OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	31	-	3 yr OS was 3% greater in patients in the second auto group compared to those in the allo group.	⊕OOO VERY LOW
3 yr TRM											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	31	-	3 yr TRM was 7% lower in patients in the second auto group compared to those in the allo group.	⊕OOO VERY LOW
relapse/progression at 3 yrs											

1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	29	31	-	Relapse/progression at 3yrs was 4% greater in patients in the second auto group compared to those in the allo group.	⊕OOO VERY LOW

Table 6.12: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who have ISS stage III)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
5yr PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	17	17	-	5 yr PFS was 28% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW
5yr OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	17	17	-	5 yr OS was 23% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW

Table 6.13: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus other treatment in patients with newly diagnosed myeloma who have β2M greater than 3mg/L)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	other treatment	Relative (95% CI)	Absolute	
5yr PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	46	47	-	5 yr PFS was 20% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW
5yr OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	46	47	-	5 yr OS was 17% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW

Table 6.14: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in patients with newly diagnosed myeloma who are chemosensitive)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
CR rate											

1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	25	85	-	CR was 29% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW
median PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	25	85	-	median PFS was 31 months in the second auto group and not reached in the allo group.	⊕OOO VERY LOW
median EFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	25	85	-	median EFS was 6 months greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW
median OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	25	85	-	median OS was 58 months in the second auto group and not reached in the allo group	⊕OOO VERY LOW
TRM											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	Serious[1]	none	25	85	-	TRM was 11% greater in patients in the allo group compared to those in the second auto group.	⊕OOO VERY LOW

[1] *imprecision due to small sample size*

Table 6.15: GRADE profile: Which patients with myeloma should be considered for allogeneic stem cell transplantation (allo versus second auto in relapsed myeloma patients with Durie-Salmon stage III myeloma)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Allo	second auto	Relative (95% CI)	Absolute	
relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	152	137	-	Allotransplant was associated with a high risk of relapse compared to autotransplant (HR 3.05, 95% CI 2.20-4.22)	⊕⊕OO LOW

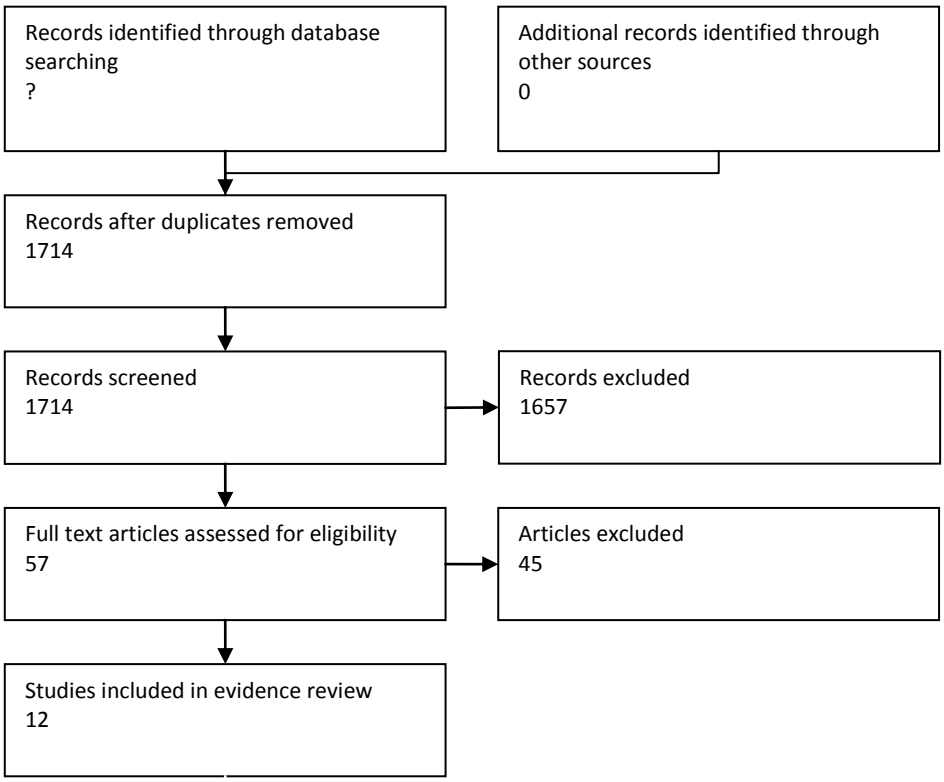
Search Results

Many studies were excluded as even though the outcomes of interest were reported the population was heterogeneous and it was not possible to extract data specifically for newly diagnosed or relapsed patients.

Seven papers were identified that were specific for newly diagnosed patients. They were all prospective studies comparing auto-allo STC (5 RIC and 2 NMA) with second auto STC as part of a tandem procedure in specific sub-groups of patients.

Five papers were identified that were specific for relapsed patients. One study was a retrospective analysis of a multicentre database that compared RIC auto-allo with second auto STC in specific sub-groups of patients and 4 studies were single intervention studies that evaluated prognostic factors for survival

Figure 6.11: Screening result



1 ***Evidence table***

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Björkstrand et al., 2011

Prospective study
Multi-centre

Europe</td>
<td>newly diagnosed

357 patients with myeloma up to age 69 years were enrolled from 2001 to 2005. Patients with an HLA-identical sibling donor were allocated to the auto-allo arm (n =108) and patients without a matched sibling donor were allocated to the auto arm (n =249).

Median time of follow-up after inclusion (i.e., the first ASCT) was 61 months (range, 21 to 91 months) for patients alive at last follow-up.</td>
<td>Of the 108 patients allocated to the auto-allo arm, 91 received an RIC alloSCT

Median time between autograft and allograft was 4.2 months (range, 1.3 to 22.2 months)

65 male, 43 female
Median age 54 (34-66)</td>
<td>Patients without a matched sibling donor received either no further treatment (n=145) or, at the discretion of the centre, a second ASCT as part of a tandem transplantation program (n=104).

146 male, 103 female
Median age 57 (31-69)</td>
<td>Cytogenetic analysis with respect to chromosome 13 deletion was performed in 214 patients by FISH.
<table>
<tr><th></th><th>allo</th><th>2nd auto</th></tr>
<tr><td>Del(13)</td><td>29</td><td>63</td></tr>
<tr><td>no Del(13)</td><td>34</td><td>88</td></tr>
</table>
Del(13)
<table>
<tr><th></th><th>PFS at 60 months (95% CI)</th><th>OS at 60 months (95% CI)</th><th>relapse/ progression risk</th></tr>
<tr><td>allo</td><td>31%
(18% - 53%)</td><td>69%
(54% - 88%)</td><td>55%
(39% - 77%)</td></tr>
<tr><td>2nd auto</td><td>11%
(5% - 22%)</td><td>55%
(44% - 69%)</td><td>86%
(78% - 96%)</td></tr>
<tr><td></td><td>P=.002</td><td>P=.003</td><td>P=.004</td></tr>
</table>
no Del(13)
<table>
<tr><th></th><th>PFS at 60 months (95% CI)</th><th>OS at 60 months (95% CI)</th><th>relapse/ progression risk</th></tr>
<tr><td>allo</td><td>44%
(30% - 64%)</td><td>70%
(56% - 88%)</td><td>39%
(25% - 60%)</td></tr>
<tr><td>2nd auto</td><td>20%
(12% - 32%)</td><td>61%
(51% - 73%)</td><td>76%
(67% - 87%)</td></tr>
<tr><td></td><td>P=.017</td><td>P = .363</td><td>P=.005</td></tr>
</table>
</td>
<td>Although del(13) is not an optimal prognostic marker for outcome, at the time the study was being done this was the only chromosomal aberration that could be adequately analyzed in most centres.
It is still of some value since it is often associated with new and better prognostic chromosomal makers, which indicate poor prognosis (del(17p), t(14;16), t(14;20)).

For update at 96 months see Gahrton et al., 2013.</td>
</tr>
<tr>
<td>Bruno et al., 2007

Prospective
Multicentre

Italy</td>
<td>newly diagnosed

The study enrolled 245 consecutive patients 65 years of age or younger with stage II or III myeloma at five Italian centres.

Of these 245 patients, 199 had siblings, and 162 of the patients who had siblings</td>
<td>Auto-allo transplant (nonmyeloablative)

N=58

30 male, 28 female

Mean age 55 years (34-65)</td>
<td>Tandem auto transplant

N=46

27 male, 19 female

Mean age 55 years (33-63)</td>
<td>The availability of an HLA-identical sibling and, therefore, the possibility of receiving an allograft were significantly associated with longer overall survival (HR 0.35; 95% CI, 0.19- 0.64; P = 0.001)
and event-free survival
(HR, 0.54; 95% CI, 0.35-0.81; P = 0.003).

In a stratified analysis that classified patients with high β2-microglobulin levels or with chromosome 13 abnormalities as being at high risk, the adjusted hazard ratios were 0.34 (95% CI, 0.10 to 1.18) for overall survival and 0.52 (95% CI, 0.22 to 1.21) for event-free survival.</td>
<td></td>
</tr>
</table>

Study	Population	Intervention	Comparator	Results	Additional comments
	underwent HLA typing to determine whether they had potential HLA-identical donors. median follow-up 45 months (range: 21 to 90)				
Efebera et al., 2010 Retrospective analysis Single-centre USA	Relapsed 51 patients with heavily pre-treated relapsed myeloma 27 males, 24 females Median age 51 years (32-65) Median follow-up in surviving patients was 27 months (3–98).	RIC allo STC Median time from diagnosis to allo HCT was 34 months	n/a	Multivariate Factors affecting OS and PFS: Age, Immunoglobulin subtype (IG), serum lactate dehydrogenase (LDH), serum albumin, stem cell source, donor type, use of DLI, interval between diagnosis and allo SCT or interval between auto and allo SCT did not emerge as statistically significant predictors of outcome.	Non-comparative/single intervention study but included as study reports predictive factors.
Freytes et al., 2014 Retrospective analysis of a multicentre database USA	Relapsed The study population comprised of myeloma patients <65 years who had relapsed/progressed after prior autologous transplant and subsequently received NST/RIC allogeneic transplant or a 2nd autotransplant between 1995 and 2008 Median follow-up of NST/RIC survivors is 30 months (range, 2–98 months) and 29 months for patients who underwent a 2nd autotransplant (range, 3–97 months).	152 subjects received NST/RIC (32 from HLA-identical siblings and 120 from HLA-matched unrelated donors 90 male, 62 female median age 53 (32 – 65)	137 subjects received a 2nd autotransplant 84 male, 53 female median age 56 years (28 – 65)	Durie-Salmon stage III. In these patients, allotransplant was associated with a higher risk relapse and treatment-failure compared to autotransplantation (HR 3.05, 95% CI, 2.20–4.22; p = 0.001). Patients who underwent NST/RIC from related and unrelated donors had a similar outcome. The 3-year OS of patients who underwent NST/RIC from related donors was 19% (95% CI: 7–33) compared to patients whose donors were unrelated, 21% (95% C: 14–28). The TRM was also similar irrespective of donor type (HR 1.077, 95% CI 0.75–1.54, p = 0.68).	Major limitations of this study are the absence of cytogenetic data and a paucity of other prognostic factors available in the NST/RIC cohort. 25% of the NST/RIC patients had these data available.

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Gahrton et al., 2013

Update at a median follow-up of 96 months of Björkstrand et al. that prospectively compares auto/RIC allo to auto.

Europe.</td><td>newly diagnosed

See Björkstrand et al

Median time of follow-up after inclusion (i.e., the first ASCT) was 96 months (range, 47 to 127 months) for patients alive at last follow-up.</td><td>See Björkstrand et al</td><td>See Björkstrand et al</td><td>Del(13)
<table><tr><th></th><th>PFS at 96 months (95% CI)</th><th>OS at 96 months (95% CI)</th></tr><tr><td>allo</td><td>21%</td><td>47%</td></tr><tr><td>2nd auto</td><td>5%</td><td>31%</td></tr></table>no Del(13)
<table><tr><th></th><th>PFS at 96 months (95% CI)</th><th>OS at 96 months (95% CI)</th></tr><tr><td>allo</td><td>26%</td><td>55%</td></tr><tr><td>2nd auto</td><td>16%</td><td>46%</td></tr></table>Patients with or without the del(13) abnormality had similar outcome when treated with auto/RIC allo and better outcome than those with auto. This is in contrast to the outcome with auto, which was poorer in patients with the del(13) abnormality than in those without.</td><td>See Björkstrand et al</td></tr>
<tr><td>Garban et al., 2006

Prospective study multicentre

France & Switzerland</td><td>newly diagnosed
284 patients
High risk myeloma: Patients younger than 65 years who had Durie-Salmon stage I (one bone lesion), II, or III myeloma and initial biologic features chr13 deletion (FISH analysis) and B2-microglobulin levels greater than 3 mg

When an HLA-identical sibling donor was identified at diagnosis, the patient was offered dose-reduced allogeneic stem cell transplantation after ASCT.

Patients who had no donor underwent tandem ASCT.

Median follow-up time of</td><td>RIC-Allo SCT (n=65)

32 male, 33 female
Median age 54 (36-65)

46 patients completed the entire program

The median time between diagnosis and ASCT was 153 days (range, 120-226 days), and it was 73 days (range, 44-92 days) between ASCT and dose-reduced allograft.</td><td>Second ASCT (n=219)

114 male, 105 female
Median age 58 (28-65</td><td>Combination of ASCT followed by allogeneic transplant was not superior to tandem ASCT.
OS and EFS – no significant difference.

<table><tr><th></th><th>EFS</th><th>OS</th></tr><tr><td>RIC-Allo</td><td>31.7 months</td><td>35 months</td></tr><tr><td>2nd auto</td><td>35 months</td><td>47.2 months</td></tr><tr><td></td><td>P=0.35</td><td>P=0.07</td></tr></table>There was a trend for better OS for the patients in the tandem transplantation trial than for patients treated with the combination of ASCT followed by mini-allogeneic transplantation.</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td>24 months.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Krishnan et al., 2011

Phase 3 multicentre trial

USA</td><td>newly diagnosed

710 patients with multiple myeloma within 10 months from initiation of induction therapy were classified as standard (SRD) or high risk (HRD) disease based on cytogenetics and beta-2-microglobulin levels. (standard risk : β-2 microglobulin was < 4 mg/L and no deletion of chr 13)

Assignment to auto-allo HCT was based on availability of an HLA-matched sibling donor.

Median follow up of the study population is 40 months (inter-quartile range 38–43 months)</td><td>allogeneic transplant using a non-myeloablative conditioning

standard risk:
n=156
111 male, 78 female
Median age 53 (29-68)

High risk:
N=29
21 male, 16 female
Median age 51 (32-66)</td><td>second autologous transplant

standard risk:
n=366
260 male, 176 female
Median age 55 (22-70)

High risk:
n=31
27 male, 21 female
Median age 57 (32-70)</td><td>Standard risk
<table><tr><th></th><th>3 yr PFS</th><th>3 yr OS</th><th>Relapse/progression at 3 yrs</th><th>3 yr TRM</th></tr><tr><td>allo</td><td>43%
(36% - 51%)</td><td>77%
(72% - 84%)</td><td>46%
(39% - 54%)</td><td>11%
(7% - 16%)</td></tr><tr><td>2nd auto</td><td>46%
(42% - 51%)</td><td>80%
(77% - 84%)</td><td>50%
(46% - 55%)</td><td>4%
(2% - 5%)</td></tr><tr><td></td><td>P=0.671</td><td>P=0.191</td><td>P=0.402</td><td>P<0.001</td></tr></table>High risk
<table><tr><th></th><th>3 yr PFS</th><th>3 yr OS</th><th>Relapse/progression at 3 yrs</th><th>3 yr TRM</th></tr><tr><td>allo</td><td>40%
(47% - 60%)</td><td>59%
(45% - 78%)</td><td>38%
(22% - 54%)</td><td>22%
(8% - 35%)</td></tr><tr><td>2nd auto</td><td>33%
(22% - 50%)</td><td>67%
(54% - 82%)</td><td>57%
(42% - 71%)</td><td>11%
(2% - 19%)</td></tr><tr><td></td><td>P=0.743</td><td>P =0 .460</td><td>P=0.079</td><td>P=0.311</td></tr></table></td><td></td></tr>
<tr><td>Lokhorst et al., 2012

Prospective multicentre study

Netherlands</td><td>Newly diagnosed

donor versus no-donor analysis of patients included in the phase 3 HOVON-50MMtrial.

266 patients having received an autologous-SCT fulfilled the criteria to be included, 138 patients without an HLA-identical sibling donor and 122 patients with a donor

Median follow-up of 77 months.</td><td>donor
n=122
71 male, 51 female
Median age 54 (32-65)

99 allo-RIC
15 maintenance
8 no treatment

Median time between auto and allo was 3.9 months</td><td>no donor
n=138
93 male, 45 female
Median age 54 (30-65)

97 patients started with maintenance
3 high dose melphan
41 no treatment</td><td>ISS stage III
<table><tr><th></th><th>5-year PFS</th><th>5-year OS</th></tr><tr><td>Maintenance of second HDM</td><td>41%</td><td>65%</td></tr><tr><td>Second auto n=17</td><td>13%</td><td>42%</td></tr><tr><td></td><td>P=0.17</td><td>P=0.55</td></tr></table>B2M great than 3 mg/L
<table><tr><th></th><th>5-year PFS</th><th>5-year OS</th></tr><tr><td>Allo SCT n=46</td><td>35%</td><td>59%</td></tr><tr><td>Other treatment n=47</td><td>15%</td><td>42%</td></tr><tr><td></td><td>P=0.13</td><td>P=0.31</td></tr></table></td><td>Among the 260 patients included in this analysis, there were 224 (86%) with conventional karyotyping data available. However, only 23 patients had del(13/13q), of whom only 10 received an allo-SCT. These numbers are too small to draw any conclusion.</td></tr>
</table>

Study	Population	Intervention	Comparator	Results	Additional comments
				In the subgroup of donor-patients who actually received an allo-SCT, higher age was significantly associated with worse PFS (HR = 1.04, 95% CI = 1.01-1.07, *P* = .02) and OS (HR = 1.05, 95% CI = 1.01-1.09, *P* = .01)	
Patriarca et al., 2012 Retrospective analysis multicentre Italy	Relapsed 169 patients with myeloma who relapsed after auto-SCT underwent HLA typing and search for a donor. 75 patients found a donor (median age 55 years (34-68)) and 68 underwent allo-SCT. Median follow-up after the beginning of salvage treatment was 19 months (range 1-97) in all patients and 29 months (range 6-88) in surviving patients.	allo-SCT	n/a	Variables considered as possible prognostic factors: - time between diagnosis and allo-SCT (months) - disease status before SCT (responsive or unresponsive) - donor (sibling or unrelated) - HLA typing (HLA-matched related versus HLAmatched unrelated versus HLA-mismatched unrelated) - stem cell source (bone marrow or peripheral blood), - ATG (yes or no) - acute GVHD (grade 0-I or grade II-IV) - chronic GVHD (absent or present), - donor lymphocyte infusion (DLI; yes or no) Prognostic factors that were significantly (P $\leq$ .10) associated with PFS in the univariate proportional hazards model: • interval between diagnosis and allo-SCT (HR, 1.01; 95%CI, 1.00-1.02; P=.08) • progressive disease before transplant (HR, 4.27; 95%CI, 1.01-16.56; P= .04) • development of chronic GVHD (HR, 0.43; 95%CI, 0.18-1.04; P=.06) The final survival model showed no significant prognostic factors for PFS. The variables with a significant association with OS in univariate analysis: • interval between auto-SCT and relapse (HR,1.012; 95%CI, 1.00-1.04; P=.08) • progressive disease before transplant (HR, 3.74; 95%CI, 0.81-17.28; P=.09) • T cell depletion with ATG (HR, 0.52; 95%CI, 0.26-1.05; P= .07) • development of chronic GVHD (HR, 0.32; 95%CI, 0.10-0.95; P=.04). In multivariate analysis, development of chronic GVHD maintained a protective effect on OS (HR,0.11; 95%CI, 0.17-0.68; P= .02), whereas an increased interval between auto-SCT and relapse was associated with poor OS (HR, 1.07; 95% CI, 1.01-1.13; P =.02).	Non-comparative/single intervention study but included as study reports predictive factors.
Qazilbash et al., 2006 Retrospective analysis USA	Relapsed patients relapsing after an autograft In general, younger patients (up to age 65 yrs) with available human	RIC allo N=26 15 male , 11 female median age 51 yrs (32–65)	n/a	Prognostic indicators for survival in the allogeneic transplant group: On univariate analysis, an interval of > 1 year between the first and the salvage transplant (*P* = 0.02) predicted a significantly better OS. Age, cytogenetics, disease status at the time of transplantation, type of donor,	Multivariate analysis was not performed due to a small sample size.

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td>leukocyte antigen-matched donors, financial clearance, better performance status, and less comorbidity were treated with an allogeneic transplant.</td><td>median interval between the first and the second transplant was 17 months

median follow-up of 30 months</td><td></td><td>tumour mass, B2 microglobulin level, serum albumin level, and chronic GVHD also were studied and were found to have no effect on survival.</td><td></td></tr>
<tr><td>Rosinol et al., 2008

Prospective study

Spain</td><td>Newly diagnosed

110 chemosensitive myeloma patients failing to achieve at least near complete remission (nCR) after a first ASCT were scheduled to receive a second ASCT or allo-RIC depending on HLA–identical sibling donor availability.

follow-up median 5.2 years</td><td>allo-RIC
n=25
Mean age 52 + 6</td><td>2nd auto
n=85
Mean age 55 + 8</td><td><table><tr><th></th><th>CR rate</th><th>Median PFS</th><th>Median EFS</th><th>Median OS</th><th>TRM</th></tr><tr><td>allo</td><td>40%</td><td>Not reached</td><td>26 months</td><td>Not reached</td><td>16%</td></tr><tr><td>2nd auto</td><td>11%</td><td>31 months</td><td>19.6 months</td><td>58 months</td><td>5%</td></tr><tr><td></td><td>p=0.001</td><td>p=0.08</td><td>P=0.4</td><td>P=0.9</td><td>p=0.09</td></tr></table></td><td></td></tr>
<tr><td>Sahbe</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Shimoni et al., 2010

retrospective analysis

Israel and Germany</td><td>Relapsed

Retrospective analysis was conducted of allo- SCT outcomes in 50 patients who received RIC for recurrent/refractory myeloma in 2 participating centres.

Female 21, male 29 median age 53 years (32-64)

Median years from diagnosis = 3 (range 6 months – 14 years).

Median follow-up 6.4 years</td><td>RIC allo- SCT</td><td>n/a</td><td>Variables considered as possible prognostic factors:
- time between diagnosis and allo-SCT
- disease status at SCT
- donor type (sibling or unrelated)
- donor gender
- prior auto STC
- time from auto STC
- prior lines of therapy

The independent factors found to be predictive of worse OS were:
- refractory disease (hazard ratio [HR], 2.5; 95% CI, 1.4-4.6% [P=.003])
- SCT from a female donor to a male recipient (HR, 5.5; 95% CI, 2.5-12.5% [P=.001]).

The factors found to be predictive of worse PFS were:
- refractory disease (HR, 3.6; 95% CI, 1.4-4.6% [P=.001])
- SCT from a female donor to a male recipient (HR, 4.1; 95% CI, 1.7-9.6% [P=.001])
- disease duration of >5 years (HR, 2.8; 95% CI, 1.3-6.1% [P=.01])</td><td>Non-comparative/single intervention study but included as study reports predictive factors.</td></tr>
</table>

Study	Population	Intervention	Comparator	Results	Additional comments
	(5-7.9).			The 7-year PFS in 19 patients with none of these adverse prognostic factors was 47% (95% CI, 25-70%). Could not assess the prognostic effect of deletion 13 accurately due to missing data (32% of patients had no genetic data).	

References of included studies

1. Björkstrand B, Iacobelli S, Hegenbart U, Gruber A, Greinix H, Volin L, Narni F, Musto P, Beksac M, Bosi A, Milone G, Corradini P, Goldschmidt H, de Witte T, Morris C, Niederwieser D, Gahrton G. (2011) Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. J Clin Oncol.;29(22):3016-22.
2. Bruno, B., Rotta, M., Patriarca, F., Mordini, N., Allione, B., Carnevale-Schianca, F., Giaccone, L., Sorasio, R., Omede, P., Baldi, I., Bringhen, S., Massaia, M., Aglietta, M., Levis, A., Gallamini, A., Fanin, R., Palumbo, A., Storb, R., Ciccone, G. & Boccadoro, M. (2007) A comparison of allografting with autografting for newly diagnosed myeloma. New England Journal of Medicine, 356: 1110-1120.
3. Efebera, Y. A., Qureshi, S. R., Cole, S. M., Saliba, R., Pelosini, M., Patel, R. M., Koca, E., Mendoza, F. L., Wang, M., Shah, J., Alousi, A., Hosing, C., Popat, U., Kebriaei, P., Anderlini, P., Khouri, I. F., Champlin, R., Giralt, S. & Qazilbash, M. H. (2010) Reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed multiple myeloma. Biology of Blood & Marrow Transplantation, 16: 1122-1129.
4. Freytes, C. O., Vesole, D. H., LeRademacher, J., Zhong, X., Gale, R. P., Kyle, R. A., Reece, D. E., Gibson, J., Schouten, H. C., McCarthy, P. L., Lonial, S., Krishnan, A. Y., Dispenzieri, A. & Hari, P. N. (2014) Second transplants for multiple myeloma relapsing after a previous autotransplant-reduced-intensity allogeneic vs autologous transplantation. Bone Marrow Transplantation, 49: 416-421.
5. Gahrton G, Iacobelli S, Björkstrand B, Hegenbart U, Gruber A, Greinix H, Volin L, Narni F, Carella AM, Beksac M, Bosi A, Milone G, Corradini P, Schönland S, Friberg K, van Biezen A, Goldschmidt H, de Witte T, Morris C, Niederwieser D, Garderet L, Kröger N; EBMT Chronic Malignancies Working Party Plasma Cell Disorders Subcommittee. (2013) Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 20;121(25):5055-63.
6. Garban, F., Attal, M., Michallet, M., Hulin, C., Bourhis, J. H., Yakoub, A., I, Lamy, T., Marit, G., Maloisel, F., Berthou, C., Dib, M., Caillot, D., Deprijck, B., Ketterer, N., Harousseau, J. L., Sotto, J. J. & Moreau, P. (2006) Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood, 107: 3474-3480.
7. Krishnan A, Pasquini B, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN0102): a phase 3 biological assignment trial. Lancet Oncol. 2011;12(13):1195-1203.
8. Lokhorst HM, van der Holt B, Cornelissen JJ, et al. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. Blood. 2012;119(26):6219-6225.
9. Patriarca, F., Einsele, H., Spina, F., Bruno, B., Isola, M., Nozzoli, C., Nozza, A., Sperotto, A., Morabito, F., Stuhler, G., Festuccia, M., Bosi, A., Fanin, R. & Corradini, P. (2012) Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: a multicenter retrospective study based on donor availability. Biology of Blood & Marrow Transplantation, 18: 617-626.
10. Qazilbash, M. H., Saliba, R., De, L. M., Hosing, C., Couriel, D., Aleman, A., Roden, L., Champlin, R. & Giralt, S. A. (2006) Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. *Cancer,* 106: 1084-1089.
11. Rosinol L, Pe´rez-Simo´n JA, Sureda A, de la Rubia J, de Arriba F, Lahuerta JJ et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood 2008; 112: 3591–3593.
12. Shimoni, A., Hardan, I., Ayuk, F., Schilling, G., Atanackovic, D., Zeller, W., Yerushalmi, R., Zander, A. R., Kroger, N. & Nagler, A. (2010) Allogenic hematopoietic stem-cell transplantation with reduced-intensity conditioning in patients with refractory and recurrent multiple myeloma: long-term follow-up. Cancer, 116: 3621-3630.

1 ***Excluded papers (after checking full text)***

Paper	Reasons for exclusion
1. Arora, M., McGlave, P. B., Burns, L. J., Miller, J. S., Barke, J. N., Defor, T. E. & Weisdorf, D. J. (2005) Results of autologous and allogeneic hematopoietic cell transplant therapy for multiple myeloma. Bone Marrow Transplantation, 35: 1133-1140.	Sample size n=17, below cut-off set in review protocol.
2. Bashir, Q., Khan, H., Orlowski, R. Z., Amjad, A. I., Shah, N., Parmar, S., Wei, W., Rondon, G., Weber, D. M., Wang, M., Thomas, S. K., Shah, J. J., Qureshi, S. R., Dinh, Y. T., Popat, U., Anderlini, P., Hosing, C., Giralt, S., Champlin, R. E. & Qazilbash, M. H. (2012) Predictors of prolonged survival after allogeneic hematopoietic stem cell transplantation for multiple myeloma. *American Journal of Hematology,* 87: 272-276.	Mix of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations.
3. Corradini, P., Cavo, M., Lokhorst, H., Martinelli, G., Terragna, C., Majolino, I., Valagussa, P., Boccadoro, M., Samson, D., Bacigalupo, A., Russell, N., Montefusco, V., Voena, C., Gahrton, G. & Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT) (2003) Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood,* 102: 1927-1929.	Study not relevant to question/PICO. Study assessed the molecular evaluation of minimal residual disease.
4. Costa, L. J., Kumar, S., Dispenzieri, A., Hayman, S. E., Buadi, F. K., Dingli, D., Litzow, M. R., Gertz, M. A. & Lacy, M. Q. (2009) Factors associated with favorable outcome after allogeneic hematopoietic stem cell transplantation for multiple myeloma. *Leukemia & Lymphoma,* 50: 781-787.	Mixed population of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations.
5. Crawley, C. (2005) Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: An analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. *Blood,* 105: 4532-4539.	Mixed population of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations.
6. de Lavallade H, El-Cheikh J, Faucher C, Fürst S, Stoppa AM, Coso D, Bouabdallah R, Chabannon C, Gastaut JA, Blaise D, Mohty M. (2008) Reduced-intensity conditioning allogeneic SCT as salvage treatment for relapsed multiple myeloma. Bone Marrow Transplant 41(11):953-60.	Sample size n=18, below cut-off set in review protocol.
7. Devillier, R. (2014). The impact of allogeneic stem cell transplantation as part of first line treatment on outcome of patients with multiple myeloma depends on the method of analysis. Blood, Conference, 21.	Compares induction chemotherapy – comparison not in PICO
8. Donato, M. L., Siegel, D. S., Vesole, D. H., McKiernan, P., Nyirenda, T., Pecora, A. L., Baker, M., Goldberg, S. L., Mato, A., Goy, A. & Rowley, S. D. (2014) The graft-versus-myeloma effect: chronic graft-versus-host disease but not acute graft-versus-host disease prolongs survival in patients with multiple myeloma receiving allogeneic transplantation. Biology of Blood & Marrow Transplantation, 20: 1211-1216.	Mixed population 56 patients: 26 consolidation 30 salvage
9. Einsele, H., Schafer, H. J., Hebart, H., Bader, P., Meisner, C., Plasswilm, L., Liebisch, P., Bamberg, M., Faul, C. & Kanz, L. (2003) Follow-up of patients with progressive multiple myeloma undergoing allografts after reduced-intensity conditioning. British Journal of Haematology, 121: 411-418.	Not comparative study. Not prognostic study.
10. Einsele, H. (2011). Allogeneic stem cell transplantation for high-risk myeloma. Haematologica,	Conference abstract with insufficient study details for inclusion

Conference, S11.	
11. El-Cheikh, J., Crocchiolo, R., Furst, S., Stoppa, A. M., Ladaique, P., Faucher, C., Calmels, B., Lemarie, C., De Colella, J. M., Granata, A., Coso, D., Bouabdallah, R., Chabannon, C. & Blaise, D. (2013) Long-term outcome after allogeneic stem-cell transplantation with reduced-intensity conditioning in patients with multiple myeloma. American Journal of Hematology, 88: 370-374.	Mixed population 53 patients: 22 allo-SCT a first line treatment 31 allo-SCT as salvage therapy Unable to separate the results for the 2 populations.
12. Engelhardt, M., Terpos, E., Kleber, M., Gay, F., Wasch, R., Morgan, G., Cavo, M., van de Donk, N., Beilhack, A., Bruno, B., Johnsen, H. E., Hajek, R., Driessen, C., Ludwig, H., Beksac, M., Boccadoro, M., Straka, C., Brighen, S., Gramatzki, M., Larocca, A., Lokhorst, H., Magarotto, V., Morabito, F., Dimopoulos, M. A., Einsele, H., Sonneveld, P., Palumbo, A. & European, M. N. (2014) European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica,* 99: 232-242.	Recommendations. Relevant papers from the review are reviewed independently.
13. Fabre, C., Koscielny, S., Mohty, M., Fegueux, N., Blaise, D., Maillard, N., Tabrizi, R., Michallet, M., Socie, G., Yakoub-Agha, I., Garban, F., Uzunov, M., Francois, S., Contentin, N., Lapusan, S. & Bourhis, J. H. (2012) Younger donor's age and upfront tandem are two independent prognostic factors for survival in multiple myeloma patients treated by tandem autologous-allogeneic stem cell transplantation: a retrospective study from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC). Haematologica, 97: 482-490.	Mixed population: newly diagnosed +relapsed patients. Unable to separate the results for the 2 populations.
14. Farina, L., Bruno, B., Patriarca, F., Spina, F., Sorasio, R., Morelli, M., Fanin, R., Boccadoro, M. & Corradini, P. (2009) The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia,* 23: 1131-1138.	Mixed population: newly diagnosed +relapsed patients. Unable to separate the results for the 2 populations.
15. Gahrton, G., Iacobelli, S., Apperley, J., Bandini, G., Bjorkstrand, B., Blade, J., Boiron, J. M., Cavo, M., Cornelissen, J., Corradini, P., Kroger, N., Ljungman, P., Michallet, M., Russell, N. H., Samson, D., Schattenberg, A., Sirohi, B., Verdonck, L. F., Volin, L., Zander, A. & Niederwieser, D. (2005) The impact of donor gender on outcome of allogeneic hematopoietic stem cell transplantation for multiple myeloma: reduced relapse risk in female to male transplants. *Bone Marrow Transplantation,* 35: 609-617.	Mixed population of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations. Also: Not comparative study. Not prognostic study.
16. Gahrton, G. & Krishnan, A. (2014) Allogeneic transplantation in multiple myeloma. *Expert Review of Hematology,* 7: 79-90	Expert review
17. Gerull, S., Stern, M., Ben, A. A., Manz, M. G., Schanz, U., Stussi, G., Chalandon, Y., Passweg, J. & Mohty, B. (2013) Allo-SCT for multiple myeloma in the era of novel agents: a retrospective study on behalf of Swiss Blood SCT. *Bone Marrow Transplantation,* 48: 408-413.	Heterogeneous patient population: Newly diagnosed: 47% Relapsed: 51% All analysed together. Unable to separate the results for the 2 populations.
18. Grullich, C. (2008) A fludarabine, thiotepa reduced toxicity conditioning regimen designed specifically for allogeneic second haematopoietic cell transplantation after failure of previous autologous or allogeneic transplantation. *Bone Marrow Transplantation,* 41: 845-850.	Mixed population. N=11 myeloma.

19. Hahn, T. & P.L. (2003) Acute renal failure requiring dialysis after allogeneic blood and marrow transplantation identifies very poor prognosis patients. *Bone Marrow Transplantation,* 32: 405-410.	Mixed population. N=2 myeloma.
20. Imrie, K., Esmail, R., Meyer, R. M. & Members of the Hematology Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. (2002) The role of high-dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative. *Annals of Internal Medicine,* 136: 619-629.	Recommendations/guidelines. Relevant papers from the review are reviewed independently.
21. Kröger N, Sayer HG, Schwerdtfeger R, Kiehl M, Nagler A, Renges H, Zabelina T, Fehse B, Ayuk F, Wittkowsky G, Schmitz N, Zander AR. (2002) Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. Blood 1;100(12):3919-24.	21 patients All patients had received at least one previous cycle of high-dose chemotherapy followed by autologous SCT. Eleven patients experienced relapse after autologous transplantation, whereas 10 patients received an allogeneic transplant as consolidation therapy after an autograft. Consolidation not in PICO. 11 relapsed patients below our cut-off sample size.
22. Kroger, N., Schilling, G., Einsele, H., Liebisch, P., Shimoni, A., Nagler, A., Perez-Simon, J. A., San Miguel, J. F., Kiehl, M., Fauser, A., Schwerdtfeger, R., Wandt, H., Sayer, H. G., Myint, H., Klingemann, H., Zabelina, T., Dierlamm, J., Hinke, A. & Zander, A. R. (2004) Deletion of chromosome band 13q14 as detected by fluorescence in situ hybridization is a prognostic factor in patients with multiple myeloma who are receiving allogeneic dose-reduced stem cell transplantation. *Blood,* 103: 4056-4061.	Mixed population: newly diagnosed +relapsed patients. Unable to separate the results for the 2 populations.
23. Kroger, N., Perez-Simon, J. A., Myint, H., Klingemann, H., Shimoni, A., Nagler, A., Martino, R., Alegre, A., Tomas, J. F., Schwerdtfeger, R., Kiehl, M., Fauser, A., Sayer, H. G., Leon, A., Beyer, J., Zabelina, T., Ayuk, F., San Miguel, J. F., Brand, R. & Zander, A. R. (2004) Relapse to prior autograft and chronic graft-versus-host disease are the strongest prognostic factors for outcome of melphalan/fludarabine-based dose-reduced allogeneic stem cell transplantation in patients with multiple myeloma. Biology of Blood & Marrow Transplantation, 10: 698-708.	Mix of newly diagnosed and relapsed patients. Data pooled for all patients. No separate results/predictive factors for newly diagnosed and relapsed.
24. Kroger, N., Badbaran, A., Zabelina, T., Ayuk, F., Wolschke, C., Alchalby, H., Klyuchnikov, E., Atanackovic, D., Schilling, G., Hansen, T., Schwarz, S., Heinzelmann, M., Zeschke, S., Bacher, U., Stubig, T., Fehse, B. & Zander, A. R. (2013) Impact of high-risk cytogenetics and achievement of molecular remission on long-term freedom from disease after autologous-allogeneic tandem transplantation in patients with multiple myeloma. Biology of Blood & Marrow Transplantation, 19: 398-404.	Not comparative study. Not prognostic study.
25. Kumar, S., Zhang, M. J., Li, P., Dispenzieri, A., Milone, G. A., Lonial, S., Krishnan, A., Maiolino, A., Wirk, B., Weiss, B., Freytes, C. O., Vogl, D. T., Vesole, D. H., Lazarus, H. M., Meehan, K. R., Hamadani, M., Lill, M., Callander, N. S., Majhail, N. S., Wiernik, P. H., Nath, R., Kamble, R. T., Vij, R., Kyle, R. A., Gale, R. P. & Hari, P. N. (2011) Trends in allogeneic stem cell transplantation for multiple myeloma: a CIBMTR analysis. *Blood,* 118: 1979-1988.	Not relevant to PICO: Study looking at changes in practice of allo-SCT 1989-1994; 1905-2000; 2001-2005.
26. Kuruvilla, J., Shepherd, J. D., Sutherland, H. J., Nevill, T. J., Nitta, J., Le, A., Forrest, D. L., Hogge, D. E., Lavoie, J. C., Nantel, S. H., Toze, C. L., Smith, C. A., Barnett, M. J. & Song, K. W. (2007)	Mix of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations.

Long-term outcome of myeloablative allogeneic stem cell transplantation for multiple myeloma. *Biology of Blood & Marrow Transplantation,* 13: 925-931.	
27. Le, B. A., Lestang, E., Guillaume, T., Delaunay, J., Ayari, S., Blin, N., Clavert, A., Tessoulin, B., Dubruille, V., Mahe, B., Roland, V., Gastinne, T., Le, G. S., Moreau, P., Mohty, M., Planche, L. & Chevallier, P. (2013) Prognostic impact of immune status and hematopoietic recovery before and after fludarabine, IV busulfan, and antithymocyte globulins (FB2 regimen) reduced-intensity conditioning regimen (RIC) allogeneic stem cell transplantation (allo-SCT). *European Journal of Haematology,* 90: 177-186.	Mixed population. N=3 myeloma.
28. Le, B. R., Montminy-Metivier, S., Belanger, R., Busque, L., Fish, D., Roy, D. C., Kassis, J., Boileau, J., Lavallee, R., Belanger, D., Letendre, F., Hebert, J., Sauvageau, G., Perreault, C. & Roy, J. (2001) Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. [Review] [38 refs]. *Bone Marrow Transplantation,* 28: 841-848.	Mix of newly diagnosed and relapsed patients. Unable to separate the results for the 2 populations.
29. Lee, C. K., Badros, A., Barlogie, B., Morris, C., Zangari, M., Fassas, A., van, R. F., Cottler-Fox, M., Jacobson, J., Thertulien, R., Muwalla, F., Mazher, S., Anaissie, E. & Tricot, G. (2003) Prognostic factors in allogeneic transplantation for patients with high-risk multiple myeloma after reduced intensity conditioning. *Experimental Hematology,* 31: 73-80.	Mix of newly diagnosed and relapsed patients analysed together. 14 newly diagnosed 31 relapsed Unable to separate the results for the 2 populations.
30. Lee, C. K., Barlogie, B., Zangari, M., Fassas, A., Anaissie, E., Morris, C., van, R. F., Cottler-Fox, M., Thertulien, R., Muwalla, F., Mazher, S., Badros, A. & Tricot, G. (2002) Transplantation as salvage therapy for high-risk patients with myeloma in relapse. *Bone Marrow Transplantation,* 30: 873-878.	Transplantation as salvage therapy – auto and allo analysed together. 50 patients – auto. 26 patients – allo.
31. Lokhorst, H., Einsele, H., Vesole, D., Bruno, B., San, M. J., Perez-Simon, J. A., Kroger, N., Moreau, P., Gahrton, G., Gasparetto, C., Giralt, S., Bensinger, W. & International Myeloma Working Group. (2010) International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *Journal of Clinical Oncology,* 28: 4521-4530.	Consensus statement from IMWG. Relevant included papers are reviewed independently.
32. Moreau P, Garban F, Attal M, et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma. *Blood*. 2008;112(9):3914-3915.	Letter to editor so limited details. Summary of data from Garban et al and comparison to other studies.
33. Majolino, I., Corradini, P., Scime, R., Falda, M., Bosi, A., Tarella, C., Musso, M., Olivieri, A., Boccadoro, M., Marceno, R., Santoro, A. & Pileri, A. (2003) High rate of remission and low rate of disease recurrence in patients with multiple myeloma allografted with PBSC from their HLA-identical sibling donors. *Bone Marrow Transplantation,* 31: 767-773.	Study not relevant for review question. No population subgroups. No prognostic factors.
34. Michallet, M. (2013). Evolving strategies with immunomodulating drugs and tandem autologous/allogeneic hematopoietic stem cell transplantation in first line high risk multiple myeloma patients. Experimental Hematology, 41, 1008-1015.	Compares tandem auto-HSCT followed by auto-RIC-allo-HSCT with and without boretezomib.
35. Nishihori, T., Ochoa-Bayona, J. L., Kim, J., Pidala, J., Shain, K., Baz, R., Sullivan, D., Jim, H. S., Anasetti, C. & Alsina, M. (2013) Allogeneic hematopoietic cell transplantation for consolidation of VGPR or CR for newly diagnosed multiple myeloma. *Bone Marrow Transplantation,* 48:	Study not relevant for review question. No population subgroups. No prognostic factors.

1179-1184.	
36. Osman, K., Elliott, B., Mandeli, J., Scigliano, E., Malone, A., Isola, L. & Grosskreutz, C. (2010) Non-myeloablative conditioning and allogeneic transplantation for multiple myeloma. American Journal of Hematology, 85: 249-254.	Not comparative study. Not prognostic study.
37. Oyan, B., Koc, Y., Ozdemir, E., Kars, A., Turker, A., Tekuzman, G. & Kansu, E. (2009) High complete remission rate and durable remissions achieved with rational use of autologous stem-cell transplantation, thalidomide maintenance, and non-myeloablative allogeneic transplantation in patients with multiple myeloma. *Clinical Transplantation,* 23: 839-847.	Sample size n=10, below cut-off set in review protocol.
38. Radocha, J., Maisnar, V., Zavrelova, A., Cermanova, M., Lanska, M., Kmonicek, M., Jebavy, L., Blaha, M., Maly, J. & Zak, P. (2013) Fifteen years of single center experience with stem cell transplantation for multiple myeloma: a retrospective analysis. *Acta Medica (Hradec Kralove),* 56: 9-13. .	Sample size n=15, below cut-off set in review protocol.
39. Roos-Weil, D., Moreau, P., Avet-Loiseau, H., Golmard, J. L., Kuentz, M., Vigouroux, S., Socie, G., Furst, S., Soulier, J., Le, G. S., Francois, S., Thiebaut, A., Buzyn, A., Maillard, N., Yakoub-Agha, I., Raus, N., Fermand, J. P., Michallet, M., Blaise, D., Dhedin, N. & Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC) (2011) Impact of genetic abnormalities after allogeneic stem cell transplantation in multiple myeloma: a report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *Haematologica,* 96: 1504-1511.	Mix of newly diagnosed and relapsed patients analysed together: 48 newly diagnosed 92 relapsed Unable to separate the results for the 2 populations.
40. Rotta, M., Storer, B. E., Sahebi, F., Shizuru, J. A., Bruno, B., Lange, T., Agura, E. D., McSweeney, P. A., Pulsipher, M. A., Hari, P., Maziarz, R. T., Chauncey, T. R., Appelbaum, F. R., Sorror, M. L., Bensinger, W., Sandmaier, B. M., Storb, R. F. & Maloney, D. G. (2009) Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood,* 113: 3383-3391.	Mix of newly diagnosed and relapsed patients analysed together: 72% newly diagnosed Unable to separate the results for the 2 populations.
41. Russell, N., Bessell, E., Stainer, C., Haynes, A., Das-Gupta, E. & Byrne, J. (2000) Allogeneic haemopoietic stem cell transplantation for multiple myeloma or plasma cell leukaemia using fractionated total body radiation and high-dose melphalan conditioning. *Acta Oncologica,* 39: 837-841.	Mixed population of 25 patients: 21 myeloma 4 plasma cell leukemia 13 Newly diagnosed 12 relapsed Unable to separate the results for the 2 populations.
42. Schilling, G. (2008) Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma. *Leukemia,* 22: 1250-1255.	Mixed population of relapsed and newly-diagnosed patients. 50 patients had experienced relapse to a prior autologous transplantation and 51 were treated within an autologous-allogeneic-tandem approach Unable to separate the results for the 2 populations.
43. Sahebi, F. (2015). Comparison of upfront tandem autologous-allogeneic transplantation versus reduced intensity allogeneic transplantation for multiple myeloma. Bone Marrow	Study shows superiority of tandem auto-allo compared to early RIC but results are not stratified by the factors in the PICO

Transplantation, 50, 802-807.	
44. Servais, S., Porcher, R., Xhaard, A., Robin, M., Masson, E., Larghero, J., Ribaud, P., Dhedin, N., Abbes, S., Sicre, F., Socie, G. & Peffault de, L. R. (2014) Pre-transplant prognostic factors of long-term survival after allogeneic peripheral blood stem cell transplantation with matched related/unrelated donors. *Haematologica,* 99: 519-526.	Mixed population: 13% myeloma.
45. Wirk, B., Byrne, M., Dai, Y. & Moreb, J. S. (2013) Outcomes of salvage autologous versus allogeneic hematopoietic cell transplantation for relapsed multiple myeloma after initial autologous hematopoietic cell transplantation. *Journal of Clinical Medicine Research,* 5: 174-184.	Sample size n=19, below cut-off set in review protocol.

1 ***Checklists to identify risk of bias***

2 comparative studies

Study identification: Björkstrand et al., 2011 and Gahrton et al., 2013					
Myeloma			**Topic J**		
Study Type			Prospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *Of the 108 patients allocated to the auto-allo arm, 91 received an RIC alloSCT according to the protocol. Seventeen patients did not receive their planned allogeneic transplantation for the following reasons: disease progression (seven patients), patient declined transplantation (four), died before allogeneic transplantation (one), renal failure (one), failure to mobilize donor stem cells (one), and donor ill or unavailable for other reason (three; in one of the latter cases in which the donor declined, the patient received a matched unrelated donorRICalloSCT.*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				

	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

Study identification: Bruno et al., 2017					
Myeloma		**Topic J**			
Study Type		Prospective analysis			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A

B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *60 were enrolled in auto-allo group but 2 did not complete treatment due to disease-related renal failure. 59 were enrolled in double auto group but 13 did not complete: disease progression (n=4), adverse events (n=1), poor mobilisation (n=2) renal failure (n=3), withdrew consent (n=3)*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Study identification: Freytes et al., 2014					
Myeloma				**Topic J**	
Study Type				Retrospective analysis	
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *unclear*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			

Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

2

Study identification: Garban et al., 2006					
Myeloma			**Topic J**		
Study Type			Prospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			

Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *Allo-SCT 65 patients recruited. 19 did not complete treatment: progressive disease (n=7), donor refusal (n=2), recipient refusal (n=3), ongoing infection (n=4), unknown causes (n=3).* *Second ASCT: 53 of 219 patients did not proceed because of severe complications or disease progression before second ASCT.*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Study identification: Krishnan et al., 2011					
Myeloma			**Topic J**		
Study Type			Phase 3 multicentre trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *Compliance with second transplant was 83% (156/189) and 84% (366/436) for auto-allo and auto-auto respectively. Reasons for not proceeding are reported. No significant differences in reasons between 2 groups.*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its					

effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

2

Study identification: Lokhorst et al., 2012					
Myeloma			**Topic J**		
Study Type			Prospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					

Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *In the donor group treatment was not completed in 7% (8/122)* *In the no-donor group treatment was not completed in 30% (41/138)*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

2

Study identification: Rosinol et al., 2008					
Myeloma			**Topic J**		
Study Type			Prospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment	Yes	No	Unclear	N/A

	groups is not expected to affect the outcome[s] under study)				
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? *Not reported*				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A

D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

single intervention prognostic studies

Efebera et al., 2010		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Patriarca et al., 2012		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Qazilbash et al., 2006		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes

1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Shimoni et al., 2010		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Primary plasma cell leukaemia

Review Question:

What are the most effective treatments for patients with primary plasma cell leukaemia?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients diagnosed with primary plasma cell leukaemia	• Chemotherapy regimes - Proteosome inhibitor based regimens Bortezomib carfilzomib - Imid based regimens Thalidomide Lenalidomide pomalidomide - Combination regimens VTD-PACE DT-PACE VRD-PACE ESHAP DCEP PACE PAD VRD	• Each other • observation	• Overall survival • Progression free survival • HRQOL • Adverse events (e.g. graft-versus-host disease, sepsis)

	• Maintenance • Consolidation • autologous stem cell transplantation • allogeneic stem cell transplantation		

Evidence statements

See Tables 6.16 to 6.24.

Overall survival and progression-free survival

Very low quality evidence from 7 observational studies reporting on overall survival (OS) and progression-free survival (PFS) in primary plasma cell leukemia (pPCL) following treatment with autologous transplant (Drake et al., 2010; Mahindra et al., 2012), allogeneic transplant (Mahindra et al., 2012; Landsburg et al, 2014), lenalidomide (Musto et al., 2014), bortezomib-based regimens (Katodritou et al., 2014), bortezomib/thalidomide/lenalidomide (Talamo et al., 2012) and total therapy protocol (Usmai et al., 2012) was identified. Median OS ranged from 18 to 28 months across the studies and OS at 3 years ranged from 39 to 65%. Median PFS ranged from 10 to 14.3 months across the studies and PFS at 3 years ranged from 20 to 34%.

Median OS was lowest at 18 months in patients (n=18) treated with bortezomib-based regimens (Katodritou et al., 2014). In a study of bortezomib, thalidomide or lenalidomide-based regimes (Talamo et al., 2012) median OS and PFS was 21 and 10 months respectively with treatment. However the sample size was small (n=12) and it is unclear how many pPCL patients were on each treatment. A study of 27 patients on total therapy protocols reported similar results with a median OS 22 months and median PFS 10 months (Usmani et al., 2012). There was heterogeneity in the treatment protocols but with successive TT protocols there was no advance in OS or PFS. A study exploring lenalidomide reported the greatest median OS of 28 months and PFS of 14 months (Mutso et al., 2014). However this study of 23 patients has not been peer-reviewed (published as a letter to the editor) and the authors have conflicts of interest and so the validity of the data is questioned. OS and PFS in patients that had undergone transplant were investigated in 2 studies. Drake et al. (2010) examined autologous transplant in 272 patients and reported a median OS of 25.7 months and OS at 3 years was 39.5%. Median PFS was 14.3 months. Mahindra et al. (2012) examined both autologous and allogeneic transplant in 97 and 50 patients, respectively. OS at 3 years was 39% for allogeneic transplant and 64% for autologous transplant. PFS at 3 years was 20% for allogeneic transplant and 34% for autologous transplant. To what extent the OS and PFS associated with transplant is related to the treatment itself or to the patient selection for transplant is unclear as the studies are retrospective cohort studies and have a high patient selection bias in that transplanted patients are generally younger and with better performance status than non transplanted patients.

Overall survival was compared in transplanted (n=23: 21 auto, 2 allo) and non-transplanted (n=50) patients in one study (Pagano et al, 2011). Median overall survival was 29 months longer in transplanted patients compared to non-transplanted patients. In another study progression-free survival was compared in transplanted (n=9: 8 auto, 1 allo) and non-transplanted (n=14) patients (Musto et al, 2014). Progression free survival was 25 months longer in transplanted patients compared to non-transplanted patients.

Overall response rate

Very low quality evidence from 5 observational studies reporting on overall response rate (ORR) in pPCL following treatment with allogeneic transplant (Charbonnier et al., 2014; Landsburg et al,

2014), bortezomib (D'Arena et al., 2012; Katodritou et al., 2014; Pagano et al., 2011), thalidomide (Pagano et al., 2011), bortezomib+thalidomide (Pagano et al., 2011) and lenalidomide (Musto et al., 2014) was identified. ORR ranged from 45 to 89%.

ORR ranged from 71% to 88% in two observational studies of 24 patients that had undergone allogeneic transplant (Charbonnier et al., 2014; Landsburg et al, 2014). However this Charbonnier et al. (2014) was published as a conference poster abstract and so full details of the study are outstanding and we await publication of the complete study to assess the study quality and validity. Bortezomib was associated with an ORR of 79% in a study of 29 patients (D'Arena et al., 2012) and 89% in a study of 18 patients (Katodritou et al., 2014). However bortezomib was administered in various combinations to different patients in both these studies. Bortezomib was also used in another study of 4 patients (Pagano et al., 2011) and here the ORR was lower at 50%. Pagano also assessed thalidomide (5 patients) and here the ORR was also low at 45%. But in patients that received both bortezomib and thalidomide (n=10) ORR was much higher at 80%. A study exploring lenalidomide reported an ORR of 74% (Mutso et al., 2014). However this study of 23 patients has not been peer-reviewed and the authors have conflicts of interest and so the validity of this data is questioned.

Adverse events

Very low quality evidence from 4 observational studies reporting on adverse events in plasma cell leukemia following treatment with allogeneic transplant (Charbonnier et al., 2014; Mahindra et al., 2012), bortezomib (D'Arena et al., 2012) and lenalidomide (Musto et al., 2014) was identified.

Graft-versus host disease (GvHD) was reported in patients receiving allogeneic transplant. The incidence of acute GvHD was 28% in a retrospective study of 50 patients (Mahindra et al., 2012), 29% in a retrospective series of 7 patients (Landsburg et al, 2014) and 35% in a prospective study of 17 patients (Charbonnier et al., 2014). The incidence of chronic GvHD was 26% in a retrospective study of 50 patients (Mahindra et al., 2012), 29% in a retrospective series of 7 patients (Landsburg et al, 2014) and 20% in a prospective study of 17 patients (Charbonnier et al., 2014). Treatment related mortality occurred in 2/7 (29%) of patients treated with allogeneic transplant in Landsburg et al (2014).

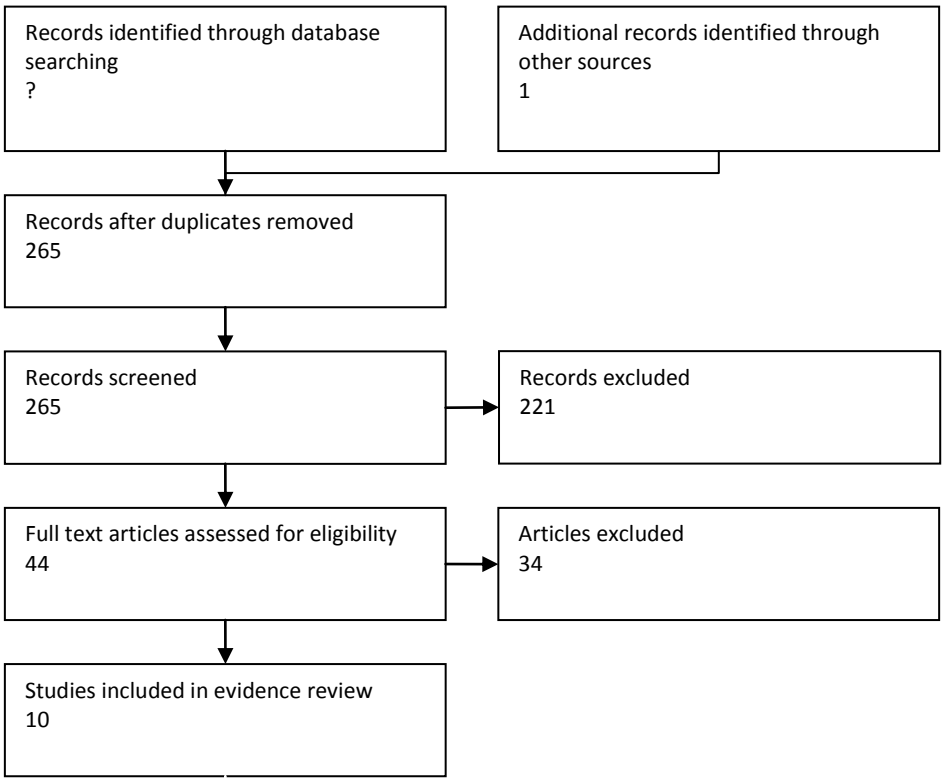
Various toxicities were reported in patients receiving chemotherapy regimes. In a study of 29 patients receiving bortezomib grade 3–4 haematological toxicities were reported in 20% of patients and grade 3–4 non-haematological toxicities were reported in 55% of patients (D'Arena et al., 2012). In a study of 23 patients receiving lenalidomide grade 3–4 haematological toxicities were reported in 48% of patients and grade 3–4 non-haematological toxicities were reported in 52% of patients (Musto et al., 2014).

HRQOL

We did not find evidence for this outcome.

Search Results

Figure 6.12: Screening results


Records identified through database searching
?
Additional records identified through other sources
1
Records after duplicates removed
265
Records screened
265
Records excluded
221
Full text articles assessed for eligibility
44
Articles excluded
34
Studies included in evidence review
10

1

Table 6.16: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (autologous transplant)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	Median OS: 25.7 Months OS at 3 years 40-64%	⊕OOO VERY LOW
progression free survival									
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	369	Median PFS: 14.3 Months PFS at 3 years 34%	⊕OOO VERY LOW
Overall response rate									
0									
Adverse events									
0									
HRQOL									
0									

[1] *retrospective case series*

Table 6.17: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (allogeneic transplant)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	OS at 3 years 39%	⊕OOO VERY LOW
progression free survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	PFS at 3 years 20%	⊕OOO VERY LOW
Overall response rate									
1	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17	ORR: 88%	⊕OOO VERY LOW
Adverse events									
2	observational studies	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	Incidence of acute GvHD: 28-35% Incidence of chronic GvHD: 20-26%	⊕OOO VERY LOW
HRQOL									
0									

[1] *retrospective case series*
[2] *poster conference abstract*

Table 6.18: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (transplant versus no transplant)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	no transplant	transplant	Relative (95% CI)	Absolute	
overall survival											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	23	-	Median overall survival was 29 months longer in transplanted patients	⊕OOO VERY LOW
progression free survival											
1	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14	9	-	Progression-free survival was 25 months longer in transplanted patients	⊕⊕OO LOW

[1] *retrospective case series*
[2] *published as letter: not peer-reviewed. Conflicts of interest.*

***Table 6.19: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (bortezomib)*?**

Quality assessment							Summary of findings		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality
overall survival									
1	observational studies	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	18	Median OS: 18 months	⊕OOO VERY LOW
progression free survival									
0									
Overall response rate									
3	observational studies	Serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	51	ORR: 50-89%	⊕OOO VERY LOW
Adverse events									
1	observational studies	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	29	Grade3-4 hematological toxicities: 20% of patients Grade3-4 non-hematological toxicities: 55% of patients	⊕OOO VERY LOW
HRQOL									
0									

[1] *retrospective case series*
[2] *not consistent treatment combinations*

Table 6.20: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (thalidomide)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
0									
progression free survival									
0									
Overall response rate									
1	observational studies	Serious[1]	serious inconsistency	no serious indirectness	no serious imprecision	none	5	ORR: 45%	⊕OOO VERY LOW
Adverse events									
0									
HRQOL									
0									

[1] *retrospective case series*

Table 6.21: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (bortezomib plus thalidomide)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
0									
progression free survival									
0									
Overall response rate									
1	observational studies	Serious[1]	serious inconsistency	no serious indirectness	no serious imprecision	none	10	ORR: 80%	⊕OOO VERY LOW
Adverse events									
0									
HRQOL									
0									

[1] *retrospective case series*

Table 6.22: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (bortezomib or thalidomide or lenalidomide)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	12	Median OS: 21 months	⊕OOO VERY LOW
progression free survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	12	Median PFS: 10 months	⊕OOO VERY LOW
Overall response rate									
0									
Adverse events									
0									
HRQOL									
0									

[1] *retrospective case series*
[2] *small population and unclear how many patients in each regime*

Table 6.23: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (lenalidomide)?

Quality assessment							Summary of findings		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No of patients**	**Effect**	**Quality**
overall survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision	none	23	Median OS: 28 months	⊕OOO VERY LOW
progression free survival									
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision	none	23	Median PFS: 14 months	⊕OOO VERY LOW
Overall response rate									
1	observational studies	Serious[1]	serious inconsistency	no serious indirectness	no serious imprecision	none	23	ORR: 74%	⊕OOO VERY LOW
Adverse events									
1	observational studies	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	23	Grade3-4 hematological toxicities: 48% of patients Grade3-4 non-hematological toxicities: 52% of patients	⊕OOO VERY LOW
HRQOL									
0									

[1] *published as letter: not peer-reviewed. Conflicts of interest.*

Table 6.24: GRADE profile: What are the most effective treatments for patients with primary plasma cell leukaemia (total therapy protocol)?

Quality assessment							Summary of findings		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients	Effect	Quality
overall survival									
1	observational studies	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	27	Median OS: 22 Months	⊕OOO VERY LOW
progression free survival									
1	observational studies	serious[1]	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	27	Median PFS: 10 Months	⊕OOO VERY LOW
Overall response rate									
0									
Adverse events									
0									
HRQOL									
0									

[1] *retrospective case series*

[2] *not consistent treatment protocols across the population*

1

2 ***Evidence table***

<table>
<tr><th>Study</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Charbonnier et al., 2014

Prospective trial

France</td>
<td>17 pPCL patients

Male: 5
Female:12

Median age: 51
Range: 28-60</td>
<td>Allo-HSCT after an induction with doxorubicin-bortezomib-cyclophosphamide and dexamethasone

1 syngenic, 1 after a reduced intensity conditioning (RIC)-Allo-HSCT and 15 after a tandem Auto/RIC-Allo-HSCT.</td>
<td>Patients were allotransplanted at a median time of 7.4 months (range: 7-18) from diagnosis.
All patients achieved engraftment.

<table>
<tr><td>Overall response rate*[1]</td><td>88%</td></tr>
<tr><td>CR</td><td>7 (44%)</td></tr>
<tr><td>VGPR</td><td>5 (31%)</td></tr>
<tr><td>PR</td><td>2 (12%)</td></tr>
<tr><td>Alive patients*[2]</td><td>12 (71%)</td></tr>
<tr><td>In remission</td><td>6</td></tr>
<tr><td>Relapsed</td><td>6</td></tr>
</table>
*[1] At day 100, 16 patients were evaluable.
*[2]The median follow-up was 22 months [7-41] from diagnosis and 14 months [1-32] from Allo-HSCT.

Six patients developed an acute GvHD which responded to steroid in 5 cases and 1 was steroid-resistant and responded secondary to anti-IL2Rα antibody. Five patients experienced chronic GvHD: mild (n=4) and extensive (n=1).</td>
<td>Poster conference abstract so limited details.

Non-comparative study</td>
</tr>
<tr>
<td>D'Arena et al., 2012

multicenter retrospective survey

Italy</td>
<td>29 pPCL patients

Male: 17
Female:12

Mean age: 62
Range: 42-82</td>
<td>Bortezomib as first line therapy at standard doses and schedules, in various combinations:
9 VTD
7 BD
7 PAD
2 VMP
2 PAD-V
1 VMPT
1 VCD

After bortezomib-containing induction therapies, there were 12 transplants:
7 AuSCT,
4 AuSCT followed by reduced-intensity Allo-SCT,
1 myeloablative Allo-SCT</td>
<td>
<table>
<tr><td>Overall response rate</td><td>79%</td></tr>
<tr><td>CR</td><td>8 (28%)</td></tr>
<tr><td>VGPR</td><td>3 (10%)</td></tr>
<tr><td>PR</td><td>12 (41%)</td></tr>
<tr><td>Alive patients*</td><td>16 (55%)</td></tr>
<tr><td>In remission</td><td>12</td></tr>
<tr><td>Relapsed</td><td>4</td></tr>
<tr><td>Transplanted patients</td><td>12</td></tr>
<tr><td>Alive</td><td>10 (83%)</td></tr>
<tr><td>Non transplanted patients</td><td>17</td></tr>
<tr><td>Alive</td><td>6 (35%)</td></tr>
</table>
*Median follow-up: 24 months

Grade 3–4 haematological, neurological, infectious, and renal toxic effects occurred in five (20%), six (21%), four (16%), and one (4%) patient, respectively. No case of tumour lysis syndrome was observed.</td>
<td>Non-comparative study.

Heterogeneous treatment combinations.</td>
</tr>
</table>

Study	Population	Interventions	Results	Additional comments
Drake et al., 2010 multicenter retrospective analysis Europe	272 pPCL patients Male: 149 Female:123 Median age: 55	autologous transplant	At 100 days the proportion of patients converting from a less than complete remission to complete remission was 25%. The median post-transplant overall survival was 25.7 months (CI:19.5–31.9 months). The median post-transplant PFS was 14.3 months. The proportion of PCL patients alive at 1 year: 69.3% (CI: 63.4–75.7%) 2 years: 54.1% (CI: 47.3–61.8%) 3 years: 39.5% (CI:32.3–48.2%) 5 years: 27.2% (CI: 20.2–36.8%).	Non-comparative study.
Katodritou et al., 2014 multicenter retrospective analysis Greece	25 pPCL patients Male: 19 Female:6 Median age: 66 (47-85)	Bortezomib-based regimens N=18 Conventional treatment N=7 Autologous transplant N=6 5 after induction treatment with BBR, 1 after induction with conventional chemotherapy	pPCL patients treated with bortezomib-based regimens: ORR: 88.9% At least VGPR: 33.3% Median OS from PCL diagnosis: 18 months Median OS after relapse: 8 months At time of data recording , with longest median follow-up reported so far (51 months) 7 patients with pPCL, all belonging to BRR group, were still alive.	No outcome data provided for patients treated with conventional chemotherapy. Heterogeneity in bortezomib-based regimens.

<table>
<tr><th>Study</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Landsburg 2014

Retrospective single centre study

USA</td><td>7 PCL patients</td><td>Allogeneic transplant with dose reduced myeloablative regimen of melphalan 100 mg/m^3 and 9 Gy of total body irradiation (MEL100/TBI9-Allo).</td><td>
<table>
<tr><th></th><th>MEL100/TBI9-Allo</th></tr>
<tr><td>n</td><td>7</td></tr>
<tr><td>Median age (range)</td><td>48
(41-57)</td></tr>
<tr><td>males</td><td>14%</td></tr>
<tr><td>Treatment related mortality</td><td>2/7 (29%)</td></tr>
<tr><td>OS (range)</td><td>0.03 to 4.2 years</td></tr>
<tr><td>PFS (range)</td><td>0.03 to 4.2 years</td></tr>
<tr><td>Overall response rate (at day 100)</td><td>5/7 (71%)</td></tr>
<tr><td>chronic graft v host disease</td><td>2/7 (29%)</td></tr>
</table>
</td><td>Non comparative study</td></tr>
<tr><td>Mahindra et al., 2012

multicenter retrospective analysis

USA</td><td>147 pPCL patients</td><td>Autologous transplant

Allogeneic transplant Myeloablative

Allogeneic transplant NMA/RIC</td><td>
<table>
<tr><th></th><th>Autologous</th><th>Allogeneic</th><th>Allogeneic Myeloablative</th><th>Allogeneic NMA/RIC</th></tr>
<tr><td>n</td><td>97</td><td>50</td><td>34</td><td>16</td></tr>
<tr><td>Median age (range)</td><td>56
(32-74)</td><td>48
(24-62)</td><td>47
(27-60)</td><td>49
(24-62)</td></tr>
<tr><td>males</td><td>64%</td><td>46%</td><td>53%</td><td>31%</td></tr>
<tr><td>PFS at 3 years</td><td>34%
95% CI: 23-46%</td><td>20%</td><td>21%
95% CI: 8-37%</td><td>18%
95% CI: 2-44%</td></tr>
<tr><td>OS at 3 years</td><td>64%
95% CI: 52-75%</td><td>39%</td><td>32%
95% CI: 17-50%</td><td>56%
95% CI: 31-79%</td></tr>
<tr><td>Median follow up</td><td>38 months</td><td>52 months</td><td></td><td></td></tr>
<tr><td>alive</td><td>64 (66%)</td><td>19 (38%)</td><td>11 (32%)</td><td>8 (50%)</td></tr>
</table>

Allogeneic transplant:
Incidence of acute GVHD (Grade II-IV) was 28% (95% CI, 17--41%) while chronic GVHD at 3 years was 26% (95% CI, 14--41%) (18% with extensive, 8% with limited cGVHD).
</td><td>Patient selection bias.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Musto et al., 2014

open label, multicenter, exploratory, single arm prospective study aiming to explore efficacy and safety of lenalidomide and dexamethasone combination (LD)

Italy</td>
<td>23 consecutive newly diagnosed PPCL patients with ECOG performance status of 0–2, with a life expectancy of at least 12 weeks and without severe co-morbidities undue to PPCL were eligible.

Male: 12
Female:11

Median age: 60
Range 44-80</td>
<td>Lenalidomide at a dose of 25 mg/day for 21 days and oral dexamethasone at a dose of 40mg on days 1, 8, 15 and 22 for each 28-day cycle.

After four cycles, responding patients not eligible for SCT continued up to eight cycles of full dose Ld, followed by a 10 mg/day maintenance dose on days 1–21 of each 28-day cycle, administered, if tolerated, until relapse.

Responders after four cycles eligible for SCT proceeded according to the Centre’s transplant policy.

Patients not responding after or progressing during the first four cycles were taken off-study, but were included in the safety population</td>
<td>During Ld administrations, there were 21 episodes of grade 3/4 haematological toxicities (occurring in 11 patients) and 16 episodes of grade 3/4 non-haematological toxicities (occurring in 12 patients), including 4 pulmonary and 1 cytomegalovirus infection, 3 renal failures, and 1 case each of hypercalcemia, hyperglycemia, skin rash, Stevens-Johnson’s syndrome, fatigue, deep vein thrombosis, diarrhoea and fecalith requiring surgery.

<table>
<tr><td>Overall response rate</td><td>74%</td></tr>
<tr><td>CR</td><td>3 (13%)</td></tr>
<tr><td>VGPR</td><td>6 (26%)</td></tr>
<tr><td>PR</td><td>8 (35%)</td></tr>
<tr><td>Alive patients*</td><td>11 (48%)</td></tr>
<tr><td>In remission</td><td>7</td></tr>
<tr><td>Relapsed</td><td>4</td></tr>
<tr><td>Transplanted patients</td><td>9</td></tr>
<tr><td>Alive</td><td>6</td></tr>
</table>
*Median follow-up: 34 months

<table>
<tr><th></th><th>PFS months</th><th>OS months</th></tr>
<tr><td>Total population</td><td>14</td><td>28</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>transplant</td><td>27</td><td>n/a</td></tr>
<tr><td>No transplant</td><td>2</td><td>12</td></tr>
</table>
</td>
<td>Published as letter to editor rather than original article so not peer-reviewed.

Conflicts of interest: Study funded by Celgene. And most authors have received honoraria from Celgene.

Patient selection bias - transplanted patients were younger (median age 58 years, range 46–65) than non-transplanted ones (median age 68 years, range 44–80).

Non-comparative study.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Interventions</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Pagano et al., 2011

multicenter retrospective cohort study

Italy</td>
<td>73 pPCL patients

Male: 43
Female:30</td>
<td>From 73 PPCL patients 19 patients received first line treatment with Bortezomib and/or thalidomide

23 patients (32%) underwent HSCT after first-line therapy. Of these, 21 patients had auto-HSCT and 2 had allo-HSCT.</td>
<td>
<table>
<tr><th></th><th>n</th><th>CR (n)</th><th>PR (n)</th><th>ORR (%)</th><th>Deaths (n)</th></tr>
<tr><td>Bortezomib +thalidomide</td><td>10</td><td>3</td><td>5</td><td>80</td><td>5</td></tr>
<tr><td>thalidomide</td><td>5</td><td>1</td><td>1</td><td>45</td><td>3</td></tr>
<tr><td>Bortezomib</td><td>4</td><td>1</td><td>1</td><td>50</td><td>2</td></tr>
</table>
CR, complete response; PR, partial response; ORR, overall response rate

Median overall survival for Bortezomib and/or thalidomide was 12.6 months. Range 1.4-31.5 months.

<table>
<tr><th></th><th>Median OS in months (range)</th><th>Median DOR in months (range)</th></tr>
<tr><td>Transplant</td><td>38.1
(4.8-75.8)</td><td>26.7
(1.4-72.1)</td></tr>
<tr><td>Non-transplant</td><td>9.1
(0.5-50.2)</td><td>7.3
(1.7-17.7)</td></tr>
</table>
</td>
<td>Patient selection bias – transplant carried out only in responders and in younger patients.</td>
</tr>
<tr>
<td>Talamo et al., 2012

Single centre retrospective cohort study

USA</td>
<td>12 pPCL patients

For whole sample primary + secondary PCL (n=17):
Male: 10
Female:7

Median age: 60
Range: 21-92</td>
<td>For whole population n=17 treatment included
thalidomide-based regimen (9 pts, 53%),
lenalidomide-based regimen (9 pts, 53%),
bortezomib-based regimen (15 pts, 88%),</td>
<td>For pPCL patients on Thalidomide, lenalidomide and bortezomib treatment
Median progression free survival: 10 months (range, 2-63)
Median overall survival: 21 months (range not reported)</td>
<td>Non-comparative study.

Small sample size.</td>
</tr>
</table>

Study	Population	Interventions	Results	Additional comments
Usmani et al., 2012 Single centre retrospective cohort study USA	27 pPCL patients Male: 17 Female:10 7 patients 65 years or younger	7 TT1 12 TT2 8 TT3 TT1: VAD induction, followed by high dose cyclophosphamide-based hematopoietic progenitor cell mobilization and EDAP; after tandem transplant with melphalan 200 mg/m2, interferon maintenance was applied indefinitely. TT2: Randomized between a control arm and a thalidomide arm. After one cycle of VAD, patients received filgrastim-supported DCEP and CAD for hematopoietic progenitor cell collection, and another cycle of DCEP. After tandem melphalan-based transplants, patients received 1 year of consolidation therapy of DCEP alternating with CAD, and later, with D-PACE. This was followed by interferon maintenance with high-dose dexamethasone pulsing, limited to the first year of maintenance. TT3 TT3A phase II trial that added bortezomib to two cycles each of DT	Regardless of the therapeutic protocol, patients with PPCL median OS: 1.8 years PFS: 0.8 years CRD: 1.3 years With the successive TT protocols from TT1 to TT3, no advances in OS, PFS and CRD were observed (data not reported).	

Study	Population	Interventions	Results	Additional comments
		(thalidomide)-PACE for induction before and consolidation after tandem transplants; this was followed by maintenance with thalidomide-dexamethasone for 3 years, to which bortezomib was added (VTD) in the first year only. TT3B Validate the bortezomib pharmacogenomic data generated in TT3A. The two trials were the same, except that TT3B used VRD for all 3 years of maintenance therapy.		

References of included studies

1. Charbonnier, A., Michalet, M., Xhaard, A., Karlin, L., Fermand, J. P., Wetter-Wald, M., Yacoub-Agha, I., Chantepie, S., Chevallier, P., Fuzibet, J. G., Ledoux, M. P., Maillard, N., Roussel, M., Belhadj, K., Brechignac, S., Benboubker, L. & Royer, B. (2014) Allogeneic Hematopoietic Stem Cell Transplantation (Allo-Hsct) for Primary Plasma Cell Leukemia (Ppcl): A Prospective Study of Ifm Group. *Haematologica,* 99: 165.
2. D'Arena, G., Valentini, C. G., Pietrantuono, G., Guariglia, R., Martorelli, M. C., Mansueto, G., Villani, O., Onofrillo, D., Falcone, A., Specchia, G., Semenzato, G., Di, R. N., Mastrullo, L., Venditti, A., Ferrara, F., Palumbo, A., Pagano, L. & Musto, P. (2012) Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party. *Annals of Oncology,* 23: 1499-1502.
3. Drake, M. B., Iacobelli, S., van, B. A., Morris, C., Apperley, J. F., Niederwieser, D., Bjorkstrand, B., Gahrton, G. & European Group for Blood and Marrow Transplantation and the European Leukemia Net. (2010) Primary plasma cell leukemia and autologous stem cell transplantation. *Haematologica,* 95: 804-809.
4. Landsburg, D. J. (2014). Melphalan/total body irradiation-conditioned myeloablative allogeneic hematopoietic cell transplantation for patients with primary plasma cell leukemia. Clinical Lymphoma, Myeloma and Leukemia, 14, e225-e228.
5. Katodritou, E., Terpos, E., Kelaidi, C., Kotsopoulou, M., Delimpasi, S., Kyrtsonis, M. C., Symeonidis, A., Giannakoulas, N., Stefanoudaki, A., Christoulas, D., Chatziaggelidou, C., Gastari, V., Spyridis, N., Verrou, E., Konstantinidou, P., Zervas, K. & Dimopoulos, M. A. (2014) Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group. *American Journal of Hematology,* 89: 145-150.
6. Mahindra, A., Kalaycio, M. E., Vela-Ojeda, J., Vesole, D. H., Zhang, M. J., Li, P., Berenson, J. R., Bird, J. M., Dispenzieri, A., Gajewski, J. L., Gale, R. P., Holmberg, L., Kumar, S., Kyle, R. A., Lazarus, H. M., Lonial, S., Mikhael, J., Milone, G. A., Munker, R., Nath, R., Saccaro, S., To, L. B., Vogl, D. T., Wirk, B. & Hari, P. (2012) Hematopoietic cell transplantation for primary plasma cell leukemia: results from the Center for International Blood and Marrow Transplant Research. *Leukemia,* 26: 1091-1097.
7. Musto P, Simeon V, Martorelli MC, Petrucci MT, Cascavilla N, Di Raimondo F, Caravita T, Morabito F, Offidani M, Olivieri A, Benevolo G, Mina R, Guariglia R, D'Arena G, Mansueto G, Filardi N, Nobile F, Levi A, Falcone A, Cavalli M, Pietrantuono G, Villani O, Bringhen S, Omedè P, Lerose R, Agnelli L, Todoerti K, Neri A, Boccadoro M, Palumbo A. (2014) Lenalidomide and low-dose dexamethasone for newly diagnosed primary plasma cell leukemia. Leukemia. 28(1), 222-225.
8. Pagano, L., Valentini, C. G., De, S., V, Venditti, A., Visani, G., Petrucci, M. T., Candoni, A., Specchia, G., Visco, C., Pogliani, E. M., Ferrara, F., Galieni, P., Gozzetti, A., Fianchi, L., De, M. M., Leone, G., Musto, P., Pulsoni, A. & GIMEMA-ALWP (Gruppo Italiano Malattie EMatologiche dell'Adulto, A. L. W. P. c. S. A. (2011) Primary plasma cell leukemia: a retrospective multicenter study of 73 patients. *Annals of Oncology,* 22: 1628-1635.
9. Talamo, G., Dolloff, N.G., Sharma, K., Zhu, J., Malysz, J. (2012) Clinical features and outcomes of plasma cell leukemia: A single-institution experience in the era of novel agents. *Rare Tumors,* 4: 123-126.
10. Usmani, S. Z., Nair, B., Qu, P., Hansen, E., Zhang, Q., Petty, N., Waheed, S., Shaughnessy, J. D., Jr., Alsayed, Y., Heuck, C. J., van, R. F., Milner, T., Hoering, A., Szymonifka, J., Sexton, R., Sawyer, J., Singh, Z., Crowley, J. & Barlogie, B. (2012) Primary plasma cell leukemia: clinical and laboratory presentation, gene-expression profiling and clinical outcome with Total Therapy protocols. *Leukemia,* 26: 2398-2405.

1

2 ***Excluded papers (after checking full text)***

3

Paper	Reasons for exclusion
1. Bernasconi, C., Castelli, G., Pagnucco, G. & Brusamolino, E. (1989) Plasma cell leukemia: a report on 15 patients. [Review] [35 refs]. *European Journal of Haematology,* Supplementum. 51: 76-83.	Older treatments – not in PICO: Cyclophosphamide Vinvristine Melphalan Prednisone
2. Cernelc, P. & Mlakar, U. (2002) Maintenance treatment of primary plasma cell leukemia with interferon alpha. *Transplantation Proceedings,* 34: 2929-2930.	3 patients. Below our cut off.
3. Colovic, M., Jankovic, G., Suvajdzic, N., Milic, N., Dordevic, V. & Jankovic, S. (2008) Thirty patients with primary plasma cell leukemia: a single centre experience. *Medical Oncology,* 25: 154-160.	Older treatments – not in PICO: Treatment protocols were VBCMP in 14 patients and VAD in 16 patients.
4. Costello, R., Sainty, D., Bouabdallah, R., Fermand, J. P., Delmer, A., Divine, M., Marolleau, J. P., Gastaut, J. A., Olive, D., Rousselot, P. & Chaibi, P. (2001) Primary plasma cell leukaemia: a report of 18 cases. [Review] [14 refs]. *Leukemia Research,* 25: 103-107.	Older treatments – not in PICO: The most common first line therapy was the VAD regimen (eight patients), followed by C2H2OP (three patients), VMCP (two patients), DEX (two patients)
5. Demirkan, F. (2001) Plasma cell leukemia: A report of 5 cases and review of the literature. *Turkish Journal of Haematology,* 18: 275-279.	5 patients. 4 primary PCL. Below our cut-off.
6. Dimopoulos, M. A., Palumbo, A., Delasalle, K. B. & Alexanian, R. (1994) Primary plasma cell leukaemia. *British Journal of Haematology,* 88: 754-759.	Older treatments – not in PICO: melphalan-prednisone in 10 patients VAD or CE in 17 patients
7. Fernandez de, L. C., Kyle, R. A., Durie, B. G., Ludwig, H., Usmani, S., Vesole, D. H., Hajek, R., San Miguel, J. F., Sezer, O., Sonneveld, P., Kumar, S. K., Mahindra, A., Comenzo, R., Palumbo, A., Mazumber, A., Anderson, K. C., Richardson, P. G., Badros, A. Z., Caers, J., Cavo, M., LeLeu, X., Dimopoulos, M. A., Chim, C. S., Schots, R., Noeul, A., Fantl, D., Mellqvist, U. H., Landgren, O., Chanan-Khan, A., Moreau, P., Fonseca, R., Merlini, G., Lahuerta, J. J., Blade, J., Orlowski, R. Z., Shah, J. J. & International Myeloma Working Group. (2013) Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. [Review]. *Leukemia,* 27: 780-791.	Expert review: consensus statement by the International Myeloma Working Group.
8. Gonsalves, W. I., Rajkumar, S. V., Go, R. S., Dispenzieri, A., Gupta, V., Singh, P. P., Buadi, F. K., Lacy, M. Q., Kapoor, P., Dingli, D., Lust, J. A., Zeldenrust, S. R., Hayman, S. R., Kyle, R. A., Gertz, M. A. & Kumar, S. K. (2014) Trends in survival of patients with primary plasma cell leukemia: a population-based analysis. *Blood,* 124: 907-912.	Study does not examine treatment
9. Grosbois, B. (1992) Primary plasma cell leukemia. A	Older treatments - not in PICO

retrospective study of 20 cases. *European Journal of Internal Medicine,* 3: 27-34.	
10. Iriuchishima, H., Murakami, H., Ozaki, S., Handa, H., Saitoh, T., Nagura, E. et al. (2014). Primary Plasma Cell Leukemia in the Era of Novel Agent: Report of Multicenter Study from Japanese Society of Myeloma. Blood, 124.	Abstract only. N=38 patients, 21 treated with novel agents but insufficient information to include in the evidence review.
11. Isobe, T. (1977) Plasma cell leukemia. A clinical study of 13 cases, with a demonstration of small-sized plasma cells. *Acta Haematologica Japonica,* 40: 529-540.	Older treatments – not in PICO: Melphalan Steroids Cyclophosphamide
12. Jimenez-Zepeda, V. H. & Dominguez, V. J. (2006) Plasma cell leukemia: a rare condition. *Annals of Hematology,* 85: 263-267.	Older treatments – not in PICO: 7 VAD 1 MFL/PDN
13. Kar, R., Priyadarshini, S. G., Niraimathi, M., Basu, D. & Badhe, B. A. (2012) Clinico-pathological spectrum of primary plasma cell leukemia diagnosed at a tertiary care centre in South India over 5 year period. *Indian Journal of Hematology & Blood Transfusion,* 28: 170-174.	Study does not examine treatment
14. Kraj, M. (2011) Plasma cell leukemia: Clinical and immunophenotypic characteristics, treatment and survival. *Nowotwory,* 61: 230-243.	Too few patients received treatments listed in PICO:
15. Kyle, R. A., Maldonado, J. E. & Bayrd, E. D. (1974) Plasma cell leukemia. Report on 17 cases. *Archives of Internal Medicine,* 133: 813-818.	Older treatments - Not in PICO. Urethane, 32phosphorus, alkylating agents. And no data provided for outcomes such as OS and PFS with different treatments
16. Lebovic, D., Zhang, L., Alsina, M., Nishihori, T., Shain, K. H., Sullivan, D., Ochoa-Bayona, J. L., Kharfan-Dabaja, M. A. & Baz, R. (2011) Clinical outcomes of patients with plasma cell leukemia in the era of novel therapies and hematopoietic stem cell transplantation strategies: a single-institution experience. *Clinical lymphoma, myeloma & leukemia,* 11: 507-511.	13 primary PCL and 12 secondary PCL. Results for response to treatment cannot be separated for primary and secondary PCL.
17. Majumdar, N., Kumar, R., Anand, M., Kalita, D., Ghara, N., Chopra, A., Medhi, K., Sharma, A., Kumar, L. & Raina, V. (2009) Plasma cell leukemia--a study of 28 cases from India. *Hematology,* 14: 198-203.	Follow up-incomplete. Therefore limited data on 5 cases.
18. Moscetti, A. (2011). Outcome improvement in plasma cell leukaemia patients treated with autograft and or novel agents: A single centre experience. Haematologica, Conference, S177.	N=6 no comparison of treatments
19. Musto, P., Rossini, F., Gay, F., Pitini, V., Guglielmelli, T., D'Arena, G., Ferrara, F., Filardi, N., Guariglia, R., Palumbo, A., GISMM Cooperative Group, GISL Cooperative Group & GIMEMA Cooperative Group. (2007) Efficacy and safety of bortezomib in patients with plasma cell leukemia. *Cancer,* 109: 2285-2290.	8 primary PCL and 4 secondary PCL. Results for response to treatment cannot be separated for primary and secondary PCL.
20. Musto, P. (2013). Conclusive analysis of clinical and molecular results. From RV-PCL-PI-350 trial, the first prospective study of a novel agent (lenalidomide) in primary plasma cell leukemia. Haematologica, Conference, 10-11.	See Musto (2014) for full publication

21. Noel, P. & Kyle, R. A. (1987) Plasma cell leukemia: an evaluation of response to therapy. *American Journal of Medicine,* 83: 1062-1068.	Older treatments. Not in PICO. Urethane, Melphalan, 32phosphorus.
22. Pasqualetti, P., Festuccia, V., Collacciani, A., Acitelli, P. & Casale, R. (1996) Plasma cell leukemia. A report on 11 patients and review of the literature. [Review] [30 refs]. *Panminerva Medica,* 38: 179-184.	Study does not examine treatment
23. Peijing, Q. (2009) A retrospective analysis of thirty-one cases of plasma cell leukemia from a single center in China. *Acta Haematologica,* 121: 47-51.	Older treatments. Not in PICO. VAD VBMCP MP
24. Pruzanski, W., Platts, M. E. & Ogryzlo, M. A. (1969) Leukemic form of immunocytic dyscrasia (plasma cell leukemia). A study of ten cases and a review of the literature. *American Journal of Medicine,* 47: 60-74.	Cases between 1946 and 1968. Older treatments. Not in PICO. Urethane alone or with 6-MP, ACTH or amethopterin.
25. Ramasamy, K., Mahmood, S., Lim, Z., Corderoy, S., Devereux, S., Mufti, G. J., Pagliuca, A. & Schey, S. (2011) Alemtuzumab-based reduced-intensity conditioning allogeneic transplantation for myeloma and plasma cell leukemia - a single-institution experience. *Clinical lymphoma, myeloma & leukemia,* 11: 242-245.	4 patients. Below our cut off.
26. Ramsingh, G., Mehan, P., Luo, J., Vij, R. & Morgensztern, D. (2009) Primary plasma cell leukemia: a Surveillance, Epidemiology, and End Results database analysis between 1973 and 2004. *Cancer,* 115: 5734-5739.	Study evaluates demographics and survival but does not examine treatments.
27. Russell, N., Bessell, E., Stainer, C., Haynes, A., Das-Gupta, E. & Byrne, J. (2000) Allogeneic haemopoietic stem cell transplantation for multiple myeloma or plasma cell leukaemia using fractionated total body radiation and high-dose melphalan conditioning. *Acta Oncologica,* 39: 837-841.	4 patients. Below our cut off.
28. Saccaro S., F. (2005) Primary plasma cell leukemia: Report of 17 new cases treated with autologous or allogeneic stem-cell transplantation and review of the literature. *American Journal of Hematology,* 78: 288-294.	Cases of PPCL who underwent stem-cell transplantation - 2 cases observed by the authors and 15 cases from the International Bone Marrow Transplant Registry. No relevant data on effect of treatment.
29. Vela-Ojeda, J. (2000) Primary plasma cell leukemia. Clinical results using different chemotherapy regimens. *Cancer Research Therapy and Control,* 10: 45-49.	Same cases plus updated in later paper. See Vela-Ojeda et al., 2002.
30. Vela-Ojeda, J., Garcia-Ruiz Esparza, M. A., Rosas-Cabral, A., Padilla-Gonzalez, Y., Garcia-Chavez, J., Tripp-Villanueva, F., Sanchez-Cortes, E., Ayala-Sanchez, M., Garcia-Leon, L. D., Montiel-Cervantes, L. & Rubio-Borja, M. E. (2002) Intermediate doses of melphalan and dexamethasone are better than vincristine, adriamycin, and dexamethasone (VAD) and polychemotherapy for the treatment of primary plasma cell leukemia. *Annals of Hematology,* 81: 362-367.	Older treatments – not in PICO: VMCPA VAD M-80 chemotherapy
31. Verelst S., K.-K. (2012). Are we making progress? Survival in plasma cell malignancies in the era of novel treatments a population based study of 17.790	Does not compare treatments for PCL

patients in the netherlands. Haematologica, Conference, 242.	
32. Wang, J. (2010) Clinical features and treatment of 22 cases of primary plasma cell leukemia. *Chinese Journal of Clinical Oncology,* 37: 1293-1295.	Paper not in english
33. Woodruff, R. K. (1978) Plasma cell leukemia (PCL): A report of 15 patients. *Blood,* 52: 839-845.	Cases between 1957 and 1977. Older treatments: cyclophosphamide or melphalan given in standard continuous or intermittent dosage with or without corticosteroids.
34. Zawadzki, Z. A. (1978) Leukemic myelomatosis (plasma cell leukemia). *American Journal of Clinical Pathology,* 70: 605-611.	Of 6 cases only 3 are primary PCL. Study does not examine treatment

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Chapter 7: Managing acute renal disease caused by myeloma

Review question:
What is the optimal management of acute renal disease in patients with myeloma?

PICO Table

Population	Intervention	Comparison	Outcomes
Patients with myeloma who have myeloma-induced acute renal disease Subgroups: • castnephropathy • amyloid • other causes	• plasmapheresis • hemodialysis (including wide pore membrane dialysis), haemofiltration, CAPD, renal replacement therapy • systemic therapies/chemotherapy regimens: - lenalidomide based regimens - thalidomide based regimens - proteasome based regimens - dexamethasone - bendamustine - VAD	• each other • hydration and supportive management	• improvement in renal function • recovery from dialysis • rate of dialysis • overall survival • progression-free survival • health related quality of life • adverse events
Additional Comments on PICO			
Additional study inclusion criteria: - English language only - Published studies only (no abstracts) - Published from 1995 onwards - N > 10 in each comparison group - During evidence synthesis 'melphalan and prednisone' were added as interventions			

Subgroup: Matther Streetly (Lead), Monica Morris, Hamdi Sati, and Matthew Jenner

Table 7.1: GRADE profile: What is the optimal management of myeloma-induced acute renal disease (Bortezomib-containing regimens + G-CSF, melphalan and auto-SCT' versus 'VAD, VAD-like or TCED chemotherapy + G-CSF, melphalan and auto-SCT)?

Settings: Germany

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib chemotherapy	VAD, VAD-like, or TCED chemotherapy		
Survival (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	The groups did not differ significantly	⊕ o oo Very low
Overall response rate prior to auto-SCT (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	Significantly better in bortezomib group	⊕ o oo Very low
Overall response rate day +100 post auto-SCT (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	Significantly better in bortezomib group	⊕ o oo Very low
Event-free survival (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	Significantly better in bortezomib group	⊕ o oo Very low
Relapse/progression day +100 post auto-SCT (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	The groups did not differ significantly	⊕ o oo Very low
Post transplant toxicity and supportive treatment (follow-up: Bortezomib 53 months; VAD, VAD-like or TCED 84 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	13	14	The groups did not differ significantly	⊕ o oo Very low

[1] Breitkreutz (2014)

[2] Unsure if the patients had acute renal disease.

[3] Low number of events.

Table 7.2: GRADE profile: What is the optimal management of myeloma-induced acute renal disease (chemotherapy with bortezomib-based regimens' versis 'chemotherapy with lenalidomide-based regimens')?

Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib-based chemotherapy	Lenalidomide-based chemotherapy		
Complete renal response (CR; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	Significantly better in bortezomib group	⊕ o oo Very low
Major renal response (CR + PR; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	Significantly better in bortezomib group	⊕ o oo Very low
Any renal response (at least minor response; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	The groups did not differ significantly	⊕ o oo Very low
Time to major renal response (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	Significantly better in bortezomib group	⊕ o oo Very low
Best eGRF (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	The groups did not differ significantly	⊕ o oo Very low
Survival (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	The groups did not differ significantly	⊕ o oo Very low
Early deaths (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	The groups did not differ significantly	⊕ o oo Very low
Myeloma response (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	28	The groups did not differ significantly	⊕ o oo Very low

[1] Dimopoulos (2013)

[2] Unclear of the patients had "myeloma-induced acute renal disease".

[3] Low number of events.

Table 7.3: GRADE profile: What is the optimal management of myeloma-induced acute renal disease (chemotherapy with bortezomib-based regimens' versus 'chemotherapy with thalidomide-based regimens')?

Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib-based chemotherapy	Thalidomide-based chemotherapy		
Major renal response (CR + PR; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low
Any renal response (at least minor response; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low
Best eGRF (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low
Survival (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low
Early deaths (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low
Myeloma response (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	43	62	The groups did not differ significantly	⊕ o oo Very low

[1] Dimopoulos (2013)

[2] Unclear of the patients had "myeloma-induced acute renal disease".

[3] Low number of events.

Table 7.4: GRADE profile: What is the optimal management of myeloma-induced acute renal disease (chemotherapy with thalidomide-based regimens' versus 'chemotherapy with lenalidomide-based regimens')?

Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Thalidomide-based chemotherapy	Lenalidomide-based chemotherapy		
Major renal response (CR + PR; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Any renal response (at least minor response; median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Time to major renal response (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Best eGRF (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Survival (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Early deaths (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low
Myeloma response (median follow-up = 17.5 months)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	62	28	The groups did not differ significantly	⊕ o oo Very low

[1] Dimopoulos (2013)

[2] Unclear of the patients had "myeloma-induced acute renal disease".

[3] Low number of events.

Table 7.5: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with dexamethasone and thalidomide and/or bortezomib' versus 'chemotherapy with VAD, VAD-like, melphalan plus dexamethasone or dexamethasone alone')?

Settings: Greece

Quality assessment							Summary of findings			
							No of patients			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone + thalidomide and/or bortezomib	VAD, VAD-like, melphalan plus dexamethasone or dexamethasone alone	Effect	Quality
Reversal of renal failure (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	15	26	The groups did not differ significantly	⊕ o oo Very low
Time to reversal of renal failure (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	15	26	Dexamethasone + thalidopnide and/or bortezomib significantly faster	⊕ o oo Very low
Myeloma response (CR+PR; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	15	26	The groups did not differ significantly	⊕ o oo Very low

[1] Kastritis (2007)
[2] Unclear of the patients had "myeloma-induced acute renal disease".
[3] Low number of events.

Table 7.6: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with melphalan, prednisone, bortezomib and thalidomide + maintenance with bortezomib and thalidomide (VMPT-VT)' versus 'chemotherapy with bortezomib, melphalan and prednisone without maintenance (VMP)')?

Settings: Italy

Quality assessment							Summary of findings			
							No of patients			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	VMPT-VT	VMP	Effect	Quality
Patients with eGFR ≤ 30: Myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low

Patients with eGFR ≤ 30: Complete myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Time to first myeloma response (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Duration of myeloma response (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Reversal of renal impairment (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Progression-free survival (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: 2-year overall survival (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Adverse events (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	11	19	The groups did not differ significantly in any adverse event rates, including discontinuation due to adverse events, apart from neutropenia which was experienced significantly more in the VMPT-VT group.	⊕ o oo Very low
Patients with eGFR 31-50: Myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	VMPT-VT significantly better	⊕ o oo Very low
Patients with eGFR 31-50: Complete myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR 31-50: Time to first myeloma response (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR 31-50: Duration of myeloma response (median follow-up = 21.6 months)										

1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR 31-50: Progression-free survival (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	VMPT-VT significantly better	⊕ o oo Very low
Patients with eGFR 31-50: Adverse events (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	52	58	The groups did not differ significantly in any adverse event rates, but significantly more VMPT-VT patients discontinued treatment due to adverse events.	⊕ o oo Very low
Patients with eGFR ≤ 50: Myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	VMPT-VT significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Complete myeloma response rate (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	VMPT-VT significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Time to first myeloma response (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 50: Duration of myeloma response (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 50: Reversal of renal impairment (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 50: Progression-free survival (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	VMPT-VT significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Adverse events (median follow-up = 21.6 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	63	77	The groups did not differ significantly in any adverse event rates, including discontinuation due to adverse events.	⊕ o oo Very low

[1] Morabito (2011)
[2] Unclear risk of patient selection, no blinding details reported.
[3] Unclear of the patients had "myeloma-induced acute renal disease".

[4] Low number of events.

Table 7.7: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('bortezomib and dexamethasone-containing regimens' versus 'chemotherapy with thalidomide or lenalidomide-based regimens with high-dose dexamethasone and/or cyclophosphamide or melphalan (IMiDs-based chemotherapy)')?
Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib-based chemotherapy	IMiDs-based chemotherapy		
Major renal response (PR + CR; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	47	Bortezomib-based significantly better	⊕ o oo Very low
Complete renal response										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	47	The groups did not differ significantly	⊕ o oo Very low
Time to major renal response (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	47	Bortezomib-based significantly faster	⊕ o oo Very low

[1] Roussou (2010)
[2] Unclear of the patients had "myeloma-induced acute renal disease".
[3] Low number of events.

Table 7.8: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('bortezomib and dexamethasone-containing regimens' versus 'chemotherapy with VAD or VAD-like regimens, melphalan plus dexamethasone (conventional chemotherapy)')?
Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bortezomib-based chemotherapy	Conventional chemotherapy		
Any renal response (at least minor response; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	32	Bortezomib-based significantly better	⊕ o oo Very low
Major renal response (PR + CR; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	32	Bortezomib-based significantly better	⊕ o oo Very low
Complete renal response										

1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	32	The groups did not differ significantly	⊕ o oo Very low
Time to major renal response (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	17	32	Bortezomib-based significantly faster	⊕ o oo Very low

[1] Roussou (2010)
[2] Unclear of the patients had "myeloma-induced acute renal disease".
[3] Low number of events.

Table 7.9: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with VAD or VAD-like regimens, melphalan plus dexamethasone (conventional chemotherapy)' versus 'chemotherapy with thalidomide or lenalidomide-based regimens with high-dose dexamethasone and/or cyclophosphamide or melphalan (IMiDs-based chemotherapy)')?

Settings: Greece

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Conventionel chemotherapy**	**IMiDs-based chemotherapy**		
Any renal response (at least minor response; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	32	47	IMiDs-based significantly better	⊕ o oo Very low
Major renal response (PR + CR; follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	32	47	The groups did not differ significantly	⊕ o oo Very low
Complete renal response										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	32	47	The groups did not differ significantly	⊕ o oo Very low
Time to major renal response (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness[2]	very serious imprecision[3]	none	32	47	The groups did not differ significantly	⊕ o oo Very low

[1] Roussou (2010)
[2] Unclear of the patients had "myeloma-induced acute renal disease".
[3] Low number of events.

Table 7.10: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with bortezomib, doxorubicin and dexamethasone; melphalan/ASCT + maintenance bortezomib (PAD)' versus 'chemotherapy with vincristine, doxorubicin and dexamethasone; melphalan/ASCT + maintenance thalidomide (VAD)')?

Settings: Belgium, the Netherlands and Germany

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PAD	VAD		
Renal function after induction (creatinine level and clearance; follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	The groups did not differ significantly	⊕ o oo Very low
Renal response after 3 cycles of induction therapy (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	The groups did not differ significantly	⊕ o oo Very low
Myeloma response after 1-3 cycles of induction therapy (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	PAD significantly better	⊕ o oo Very low
Best myeloma response achieved any time during trial treatment (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	PAD significantly better	⊕ o oo Very low
3-year progression-free survival (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	PAD significantly better	⊕ o oo Very low
3-year overall survival (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	PAD significantly better	⊕ o oo Very low
Adverse events (follow-up not reported)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	36	45	The groups did not differ significantly in frequency or type of adverse events.	⊕ o oo Very low

[1] Scheid (2014)
[2] Unclear risk of patient selection, no blinding details reported.
[3] Unclear of the patients had "myeloma-induced acute renal disease".
[4] Low number of events.

Table 7.11: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with melphalan, prednisone, and bortezomib (VMP)' versus 'chemotherapy with melphalan and prednisone (MP)')?

Settings: Europe

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	VMP	MP		
Patients with eGFR ≤ 30: Myeloma response rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	19	15	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Complete myeloma response rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	19	15	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Time to progression (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	19	15	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 30: Overall survival (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	19	15	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR 31-50: Myeloma response rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	92	99	VMP significantly better	⊕ o oo Very low
Patients with eGFR 31-50: Complete myeloma response rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	92	99	VMP significantly better	⊕ o oo Very low
Patients with eGFR 31-50: Time to progression (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	92	99	VMP significantly better	⊕ o oo Very low
Patients with eGFR 31-50: Overall survival (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	92	99	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 50: Myeloma response rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	VMP significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Complete myeloma response rate (median follow-up = 25.9 months)										

1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	VMP significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Reversal of renal impairment rate (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	The groups did not differ significantly	⊕ o oo Very low
Patients with eGFR ≤ 50: Time to reversal of renal impairment (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	VMP significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Time to progression (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	VMP significantly better	⊕ o oo Very low
Patients with eGFR ≤ 50: Overall survival (median follow-up = 25.9 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	111	114	The groups did not differ significantly	⊕ o oo Very low

[1] Dimopoulos (2009)
[2] Unclear risk of patient selection, no blinding details reported.
[3] Unclear of the patients had "myeloma-induced acute renal disease".
[4] Low number of events.

Table 7.12: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with bortezomib' versus 'chemotherapy with dexamethasone')?

Settings: International

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bortezomib**	**Dexamethasone**		
Time to progression (median follow-up ≤ 22 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	58	62	Bortezomib significantly better	⊕ o oo Very low
Overall survival (median follow-up ≤ 22 months)										
1	Randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	58	62	The groups did not differ significantly	⊕ o oo Very low

[1] San-Miguel (2008)
[2] Unclear risk of patient selection, no blinding details reported.
[3] Unclear of the patients had "myeloma-induced acute renal disease".
[4] Low number of events.

Table 7.13: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('chemotherapy with melphalan, prednisone, and thalidomide (MPT)' versus 'chemotherapy with cyclophosphamide, dexamethasone and thalidomide (TCD)')?

Settings: South Korea

Quality assessment							Summary of findings			
							No of patients			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	MPT: Divided into MPT-GFR < 40 and MPT-GFR ≥ 40	TCD: Divided into TCD-GFR < 40 and TCD-GFR ≥ 40	Effect	Quality
Myeloma complete response rate (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	The groups did not differ significantly	⊕ o oo Very low
At least very good partial myeloma complete response rate (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	MPT-GRF < 40 significantly worse than the other 3 groups	⊕ o oo Very low
At least very good partial myeloma complete response rate (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	MPT-GRF < 40 significantly worse than the other 3 groups	⊕ o oo Very low
Event-free survival (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	MPT-GRF < 40 significantly worse than the other 3 groups	⊕ o oo Very low
Overall survival (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	MPT-GRF < 40 significantly worse than the other 3 groups	⊕ o oo Very low
Serum creatinine (median follow-up = 36 months)										

1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	GFR ≥ 40: MPT = TCD after 2, 4, 6 and 8 cycles; GRF < 40: Significantly higher in MPT after 2, 4, 6 and 8 cycles	⊕ o oo Very low
Haematological adverse effects (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	Neutropenia: MPT-GRF < 40 significantly worse than the other 3 groups; Anaemia and thrombocytopenia: The groups did not differ significantly	⊕ o oo Very low
Non-haematological adverse effects (median follow-up = 36 months)										
1	Randomised trial[1] or observational study	serious limitations[2]	no serious inconsistency	no serious indirectness[3]	very serious imprecision[4]	none	30/44	38/45	Infection with febrile neutropenia and mortality due to this: MPT-GRF < 40 significantly worse than the other 3 groups; Embolism, peripheral neuropathy, infection without neutropenia and gastrointestinal: The groups did not differ significantly	⊕ o oo Very low

[1] Song (2012)
[2] Unclear risk of patient selection, no blinding details reported.
[3] Unclear of the patients had "myeloma-induced acute renal disease".
[4] Low number of events.

Table 7.14: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('plasmapheresis plus chemotherapy with melphalan and prednisone' versus 'chemotherapy with melphalan and prednisone')?

Settings: Saudi Arabia

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasmapheresis + chemotherapy**	**Chemotherapy**	**Relative (95% CI)**	
Survival (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	15	14	Significantly longer in plasmapheresis group	⊕ o oo Very low
Renal function (follow-up not reported)										
1	observational study[1]	no serious limitations	no serious inconsistency	no serious indirectness	very serious imprecision[2]	none	15	14	Similar or significantly bettter in plasmapheresis group	⊕ o oo Very low

[1] Abdulrahman (2003)
[2] Low number of events.

Table 7.15: GRADE profile: What is the optimal management of myeloma-induced acute renal disease ('plasmapheresis plus chemotherapy with melphalan and prednisone or with VAD' versus 'chemotherapy with melphalan and prednisone or VAD')?
Settings: Canada

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Plasmapheresis + chemotherapy	Chemotherapy	Relative (95% CI)	
Composite outcome (death, dialysis dependence and an estimated GFR < 0.29 mL • s-2 • m-2) and its constituent parts (6 month follow-up)										
1	randomised trial[1]	serious limitations[2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	58	39	No difference between the groups	⊕ o oo Very low

[1] Clark (2005)
[2] No blinding.
[3] Low number of events.

Summary Table

Table 7.16. Summary of findings (inferential statistical analyses)

Treatment options and comparisons			Studies	N	Outcome
Bortezomib-containing regimens + G-CSF, melphalan and auto-SCT (a)	Vs.	VAD, VAD-like or TCED chemotherapy + G-CSF, melphalan and auto-SCT (b)	1	27	Significantly higher overall response rate prior to auto-SCT and on day +100 after auto-SCT, and longer event-free survival in (a) than (b); - No difference between (a) and (b) in relapse/progression on day +100 post auto-SCT, post-transplant toxicity and supportive treatment or overall survival.
Thalidomide-based regimens (c)	Vs.	Lenalidomide-based regimens (d) Bortezomib-based regimens (e)	1	133	- No difference between (c) and (e) in major renal response rate (CR+PR) or in time to major renal response. - Significantly shorter time to major renal response (CR+PR), shorter time to at least renal PR, higher major renal response rate (CR + PR) and higher CR response rate in (e) than (d) - No difference in major renal response rate (CR+PR) between (c) and (e). - Significantly higher myeloma response rate in (d) and (e) than (c) - No difference between (c), (d) and (e) in overall survival, early deaths, renal

					response rate (at least minor response), median best eGFR
VAD, VAD-like, melphalan + dexamethasone or dexamethasone-alone chemotherapy (f)	Vs.	Dexamethasone with thalidomide and/or bortezomib (g)	1	41	No difference in reversal of renal failure or myeloma response between (f) and (g). Significantly shorter time to reversal of renal failure in (g) than (f).
Induction with melphalan, prednisone, bortezomib, thalidomide plus maintenance with bortezomib + thalidomide (h)	Vs.	Induction with bortezomib, melphalan, prednisone (i)	1	149	Patients with eGFR ≤ 30: - No difference between (h) and (i) in myeloma response rate, CR response rate, median time to first myeloma response, median duration of myeloma response, reversal of renal impairment, median progression-free survival, 2-year overall survival, discontinuation due to adverse events, and all reported adverse events apart from neutropenia, which was significantly higher in (h) than (i). Patients with eGFR 31-50: - No difference between (h) and (i) in median time to first myeloma response, median duration of myeloma response, and all reported adverse events. - Significantly higher myeloma response rate, CR response rate, median progression-free survival, and discontinuation due to adverse events rate in (h) than (i). Patients with eGFR ≤ 50: - No difference between (h) and (i) in median time to first myeloma response, median duration of myeloma response, reversal of renal impairment rate, time to reversal of renal impairment, discontinuation due to adverse events rate, and all reported adverse events. - Significantly higher myeloma response rate, CR response rate, and median progression-free survival in (h) than (i).
VAD or VAD-like regimens, melphalan plus dexamethasone chemotherapy (j)	Vs.	Thalidomide or lenalidomide-based regimens with dexamethasone and/or cyclophosphamide or melphalan chemotherapy (k) Bortezomib and	1	96	- Significantly higher renal response rate (at least minor response) in (k) and (l) than (j) - Significantly higher major renal response rate (CR+PR) and shorter time to major renal response in (l) than in (j) and (k) - No difference between (j), (k) and (l) in renal CR response rate - No difference between (j) and (k) in time to major renal response.

		dexamethasone-containing chemotherapy (l)			
Induction with bortezomib, doxorubicin and dexamethasone, plus melphalan/ASCT plus maintenance with bortezomib (m)	Vs.	Induction with vincristine, doxorubicin and dexamethasone plus melphalan/ASCT plus maintenance with thalidomide (n)	1	81	- No difference between (m) and (n) in adverse events, renal function before melphalan therapy (creatinine level and clearance), and overall renal response rate after 3 cycles of induction treatment. - Significantly higher myeloma response rate after 1-3 cycles of induction treatment and best myeloma response achieved anytime during the trial-rate, and significantly longer 3-year progression-free survival and 3-year overall survival in (m) than (n).
Melphalan, prednisone and bortezomib (o)	Vs.	Melphalan and prednisone (p)	1	227	Patients with eGFR ≤ 30: - No difference between (o) and (p) in myeloma response rate, myeloma complete response rate, time-to-progression, median overall survival; Patients with eGFR 31-50: - No difference between (o) and (p) in median overall survival; - Significantly higher myeloma response rate and myeloma complete response rate, significantly longer time-to-progression in (o) than in (p) Patients with eGFR ≤ 50: - No difference between (o) and (p) in median overall survival or reversal of renal impairment rate; - Significantly higher myeloma response rate and myeloma complete response rate, significantly longer time-to-progression and significantly shorter time to reversal of renal impairment in (o) than in (p)
Bortezomib (q)	Vs	Dexamethasone (r)	1	130	- No difference between (q) and (r) in median overall survival; - Significantly longer time-to-progression in (q) than in (r)
Melphalan, prednisone and thalidomide (MPT)	Vs	Cyclophosphamide, dexamethasone, thalidomide (TCD)	1	157	Patients divided into 4 subgroups depending on treatment and GFR (≥ 40, < 40): - No difference between groups in complete myeloma response rate, anaemia, thrombocytopenia, embolism, peripheral neuropathy, infection without neutropenia, and gastrointestinal adverse effects; - 'MPT-GFR < 40' significantly inferior compared to the other 3 groups in 'at least very good partial response rate', 'at least partial response rate', event-free survival, overall survival, neutropenia, and infection with febrile neutropenia, including

					mortality due to such infections; - Serum creatinine at baseline and after 2, 4, 6, and 8 cycles did not differ between MPT-GFR ≥ 40 and TCD-GFR ≥ 40; - Serum creatinine at baseline did not differ significantly between MPT-GFR < 40 and TCD-GFR < 40; - Serum creatinine after 2, 4, 6, and 8 cycles was significantly higher in MPT-GFR < 40 than TCD-GFR < 40;
Plasmapheresis + chemotherapy with melphalan and prednisone (s)	Vs.	Chemotherapy with melphalan and prednisone (t)	1	29	Significantly longer survival and significantly improved renal function (creatinine, oliguric/polyuric) in (s) than (t); no difference between (s) and (t) in hypercalcaemia or hyperuricaemia.
Plasmapheresis + chemotherapy with melphalan and prednisone or VAD (u)	Vs.	Chemotherapy with melphalan and prednisone or VAD (v)	1	97	No difference between (u) and (v) in composite outcome (death, dialysis dependence and an estimated GFR < 0.29 mL • s^{-2} • m^{-2}), in death at 6 months, in death or dialysis at 6 months, in dialysis at 6 months, in receiving dialysis or GFR < 0.29 mL • s^{-2} • m^{-2}, at 6 months, nor in mean increase in GFR at 6 months

Evidence statements

Bortezomib-containing regimens + G-CSF, melphalan and auto-SCT versus VAD, VAD-like or TCED chemotherapy + G-CSF, melphalan and auto-SCT

The overall response rate prior to auto-SCT, overall response rate day +100 post auto-SCT and event-free survival were significantly better in the bortezomib group, whereas survival, relapse/progression day +100 post auto-SCT and post transplant toxicity and supportive treatment did not differ between the treatment groups (1 study [Breitkreutz 2014], N = 27; very low quality).

Bortezomib-based regimens versus lenalidomide-based regimens

The complete renal response rate, major renal response rate, and time to major renal response were significantly better in the bortezomib group, whereas survival, early deaths, myeloma response, best eGFR and any renal response rate did not differ between the treatment groups (1 study [Dimopoulos 2013], N = 71; very low quality).

Bortezomib-based regimens versus thalidomide-based regimens

The major renal response rate, any renal response rate, survival, early deaths, myeloma response, and best eGFR did not differ between the treatment groups (1 study [Dimopoulos 2013], N = 105; very low quality).

Chemotherapy with thalidomide-based regimens versus chemotherapy with lenalidomide-based regimens

The major renal response rate, any renal response rate, time to major renal response, survival, early deaths, myeloma response, and best eGFR did not differ between the treatment groups (1 study [Dimopoulos 2013, N = 90; very low quality).

Dexamethasone, thalidomide and/or bortezomib versus VAD, VAD-like, melphalan plus dexamethasone or dexamethasome alone

Time to reversal of renal failure was significantly better in the dexamethasone, thalidomide and/or bortezomib group, whereas the reversal of renal failure rate and myeloma response rate did not differ between the treatment groups (1 study [Kastritis 2007], N = 41; very low quality).

Melphalan, prednisone, bortezomib and thalidomide + maintenance with bortezomib and thalidomide (VMPT-VT) versus bortezomib, melphalan and prednisone without maintenance (VMP)

In patients with eGFR ≤ 30, the complete myeloma response rate, myeloma response rate, time to first myeloma response, duration of myeloma response, reversal of renal impairment rate, progression-free survival, 2-year overall survival, discontinuation due to adverse events and adverse events rates did not differ between the treatment groups, apart from neutropenia, which was experienced significantly more in the VMPT-VT group (1 study [Morabito 2011], N = 30; very low quality).

In patients with eGFR 31-50, myeloma response rate, and progression-free survival were significantly better in the VMPT-VT group, wheres discontinuation due to adverse events was significantly higher in the VMPT-VT group also, with the complete myeloma response rate, time to first myeloma response, duration of myeloma response, and adverse events rates not differing between the treatment groups (1 study [Morabito 2011], N = 110; very low quality).

In patients with eGFR ≤ 50, the myeloma response rate, complete myeloma response rate, and progression-free survival were significantly better in the VMPT-VT group, whereas the time to first myeloma response, duration of myeloma response, reversal of renal impairment rate, discontinuation due to adverse events and adverse events rates did not differ between the treatment groups (1 study [Morabito 2011], N = 140; very low quality).

Bortezomib and dexamethasone-containing regimens versus thalidomide or lenalidomide-based regimens with dexamethasone and/or cyclophosphamide or melphalan (IMiDs-based chemotherapy)

The major renal response rate and time to major renal response were significantly better in the bortezomib-based group whereas the complete renal response rate did not differ between the treatments groups (1 study [Roussou 2010], N = 64; very low quality).

Bortezomib and dexamethasone-containing regimens versus VAD or VAD-like regimens, melphalan plus dexamethasone (conventional chemotherapy)

The major renal response rate, any renal response rate and time to major renal response were significantly better in the bortezomib-based group whereas the complete renal response rate did not differ between the treatment groups (1 study [Roussou 2010], N = 49; very low quality).

VAD or VAD-like regimens, melphalan plus dexamethasone (conventional chemotherapy) versus thalidomide or lenalidomide-based regimens with high-dose dexamethasone and/or cyclophosphamide or melphalan (IMiDs-based chemotherapy)

The any renal response rate was significantly better in the IMiDs-based group whereas the major renal response rate, complete renal response rate and time to major renal response did not differ between the treatment groups (1 study [Roussou 2010], N = 79; very low quality).

Chemotherapy with bortezomib, doxorubicin and dexamethasone; melphalan/ASCT + maintenance bortezomib (PAD) versus vincristine, doxorubicin and dexamethasone; melphalan/ASCT + maintenance thalidomide (VAD)

The myeloma response after 1-3 cycles of induction therapy, best myeloma response achived any time during the trial treatment, 3-year progression-free survival, and 3-year overall survival were significantly better in the PAD group whereas renal function (creatinine level and clearance), renal response after 3 cycles of induction therapy, and adverse events (type and frequency) did not differ between the treatment groups (1 study [Scheid 2014], N = 81; very low quality).

Chemotherapy with melphalan, prednisone and bortezomib (VMP) versus melphalan and prednisone (MP)

In patients with eGFR ≤ 30, the complete myeloma response rate, myeloma response rate, time to progression, and overall survival did not differ between the treatment groups (1 study [Dimopoulos 2009], N = 34; very low quality).

In patients with eGFR 31-50, the complete myeloma response rate, myeloma response rate, and time to progression were significantly better in the VMP group, with overall survival differing between the treatment groups (1 study [Dimopoulos 2009], N = 191; very low quality).

In patients with eGFR ≤ 50, the myeloma response rate, complete myeloma response rate, time to progression and time to reversal of renal impairment were significantly better in the VMP group, whereas the reversal of renal impairment rate and overall survival did not differ between the treatment groups (1 study [Dimopoulos 2009], N = 225; very low quality).

Chemotherapy with bortezomib versus dexamethasone

The time to progression was significantly longer in the bortezomib group, whereas overall survival did not differ significantly between the treatment groups (1 study [San-Miguel 2008], N = 120; very low quality).

Chemotherapy with melphalan, prednisone and thalidomide versus cyclophosphamide, dexamethasone and thalidomide

The 'at least a very good partial myeloma response rate', 'at least partial myeloma response rate', event-free survival, overall survival, neutropenia and infection with febrile neutropenia (including mortality thereof) were significantly worse in MPT-GRF < 40 group, compared to MPT-GRF ≥ 40, TCD-GRF < 40 group, and TCD-GRF ≥ 40 groups whereas the myeloma complete response rate, anaemia, thrombocytopenia, embolism, peripheral neuropathy, infection without neutropenia and gastrointestinal adverse effects did not differ significantly between the 4 treatment groups. Moreover, in patients with GFR ≥ 40, serum creatinine did not differ after 2, 4, 6, and 8 cycles between the treatments, whereas in patients with GFR < 40, serum creatinine was significantly higher in the MPT group after 2, 4, 6, and 8 cycles compared to the TCD group (1 study [Song 2012], N = 157; very low quality).

Plasmapheresis + chemotherapy with melphalan and prednisone versus chemotherapy with melphalan and prednisone

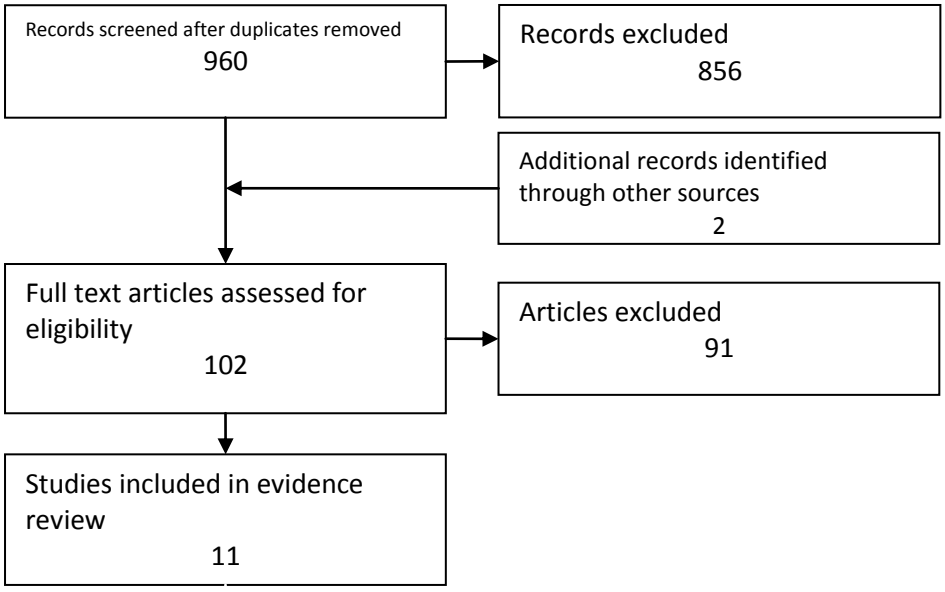
Survival was longer and renal function was either similar (hypercalcaemia, hyperuricaemia) or better (creatinine, oliguric at presentation and polyuric after treatment) after treatment with plasmapheresis and chemotherapy compared to chemotherapy alone (1 study [Abdulrahman 2003], N = 29; very low quality).

Plasmapheresis + chemotherapy with melphalan and prednisone or VAD versus chemotherapy with melphalan and prednisone or VAD

The compositive oputcome (death, dialysis dependence and an estimated GFR < 0.29 mL • s^{-2} • m^{-2}) and its constituent parts did not differ after treatment with either plasmapheresis and chemotherapy or chemotherapy alone (1 study [Clark 2005], N = 97; very low quality).

No evidence was found for the following outcome: *Health-related quality of life.*

Figure 6.13. Study flow diagram



Ordered References (n=97)

Included studies (N =11)

Abdulrahman, I. S. (2003) A prospective study of renal failure in multiple myeloma: A promising role for plasmapheresis. *HAEMA,* 6: 358-365.

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Clark, W. F., Stewart, A. K., Rock, G. A., Sternbach, M., Sutton, D. M., Barrett, B. J., Heidenheim, A. P., Garg, A. X., Churchill, D. N. & Canadian Apheresis Group. (2005) Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial.[Erratum appears in Ann Intern Med. 2007 Mar 20;146(6):471; PMID: 17402169], [Summary for patients in Ann Intern Med. 2005 Dec 6;143(11):I20; PMID: 16330784]. *Annals of Internal Medicine,* 143: 777-784.

Dimopoulos, M. A., Richardson, P. G., Schlag, R., Khuageva, N. K., Shpilberg, O., Kastritis, E., Kropff, M., Petrucci, M. T., Delforge, M., Alexeeva, J., Schots, R., Masszi, T., Mateos, M. V., Deraedt, W., Liu, K., Cakana, A., Velde, H. & San-Miguel, J. F. (2009) VMP (Bortezomib, Melphalan, and Prednisone) is active and well tolerated in newly

diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *Journal of clinical.oncology,* 27: 6086-6093.

Dimopoulos, M. A. (2013) The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. *Leukemia,* 27: 423-429.

Kastritis E., A. (2007) Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. *Haematologica,* 92: 546-549.

Morabito, F., Gentile, M., Mazzone, C., Rossi, D., Raimondo, F., Bringhen, S., Ria, R., Offidani, M., Patriarca, F., Nozzoli, C., Petrucci, M. T., Benevolo, G., Vincelli, I., Guglielmelli, T., Grasso, M., Marasca, R., Baldini, L., Montefusco, V., Musto, P., Cascavilla, N., Majolino, I., Musolino, C., Cavo, M., Boccadoro, M. & Palumbo, A. (2011) Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment. *Blood,* 118: 5759-5766.

Roussou, M. (2010) Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. *Leukemia Research,* 34: 1395-1397.

San-Miguel, J. F., Richardson, P. G., Sonneveld, P., Schuster, M. W., Irwin, D., Stadtmauer, E. A., Facon, T., Harousseau, J. L., Ben, Y. D., Lonial, S., Goldschmidt, H., Reece, D., Bladé, J., Boccadoro, M., Cavenagh, J. D., Neuwirth, R., Boral, A. L., Esseltine, D. L. & Anderson, K. C. (2008) Efficacy and safety of bortezomib in patients with renal impairment: results from the APEX phase 3 study. *Leukemia,* 22: 842-849.

Scheid, C., Sonneveld, P., Schmidt, W., I, Holt, B., El, J. L., Bertsch, U., Salwender, H., Zweegman, S., Blau, I. W., Vellenga, E., Weisel, K., Pfreundschuh, M., Jie, K. S., Neben, K., Velde, H., Duehrsen, U., Schaafsma, M. R., Lindemann, W., Kersten, M. J., Peter, N., Hanel, M., Croockewit, S., Martin, H., Wittebol, S., Bos, G. M., Marwijk, K. M., Wijermans, P., Goldschmidt, H. & Lokhorst, H. M. (2014) Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: A subgroup analysis from the HOVON-65/GMMG-HD4 trial. *Haematologica,* 99: 148-154.

Song, M.-K. (2012) Cyclophosphamide-containing regimen (TCD) is superior to melphalan-containing regimen (MPT) in elderly multiple myeloma patients with renal impairment. *Annals of Hematology,* 91: 889-896.

Excluded studies (N =86)

Al-Mueilo, S. H. (2008) Renal failure in patients with multiple myeloma: A single center experience. *Saudi Medical Journal,* 29: 466-468.
Exclude: Comparisons/analyses not in PICO

Bayraktar, U. D., Warsch, S. & Pereira, D. (2011) High-dose glucocorticoids improve renal failure reversibility in patients with newly diagnosed multiple myeloma. *American Journal of Hematology,* 86: 224-227.
Exclude: N < or = 10 in one of the comparison groups; compares high v low dose glucocorticoids; patients received a variety of glucocorticoids within each group

Beksac, M., Haznedar, R., Firatli, T. T., Ozdogu, H., Aydogdu, I., Konuk, N., Sucak, G., Kaygusuz, I., Karakus, S., Kaya, E., Ali, R., Gulbas, Z., Ozet, G., Goker, H. & Undar, L. (2011) Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. *European.journal of haematology.,* 86: 16-22.
Population not in PICO

Blade, J. (1998) Renal failure in multiple myeloma: Presenting features and predictors of outcome in 94 patients from a single institution. *Archives of Internal Medicine,* 158: 1889-1893.
Comparison not in PICO: Melphalan + prednisone versus N = 42 patients getting either (1) VCMP, (2) alternating VCMP and vincristine, carmustine, adriamycin and prednisone, or (3) VAD

Bringhen S., M. (2013) Age and organ damage correlate with poor survival in myeloma patients: Meta-analysis of 1435 individual patient data from 4 randomized trials. *Haematologica,* 98: 980-987.
Exclude: Analyses not in PICO

Chanan-Khan, A. A. (2007) Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: A multicenter retrospective study. *Blood,* 109: 2604-2606.
Exclude: Non-comparative study

Chanan-Khan, A. A., San Miguel, J. F., Jagannath, S., Ludwig, H. & Dimopoulos, M. A. (2012) Novel therapeutic agents for the management of patients with multiple myeloma and renal impairment. [Review]. *Clinical Cancer Research,* 18: 2145-2163.
Exclude: Narrative review

Cicci, J. D. (2014) Denosumab for the management of hypercalcemia of malignancy in patients with multiple myeloma and renal dysfunction. *Clinical lymphoma, myeloma & leukemia,* 14: e207-e211.
N = 4

Clark, W. F. (2012) Plasma exchange for renal disease: evidence and use 2011. [Review]. *Journal of Clinical Apheresis,* 27: 112-116.
Exclude: Narrative review

Cockwell, P. & Cook, M. (2012) The rationale and evidence base for the direct removal of serum-free light chains in the management of myeloma kidney. [Review]. *Advances in Chronic Kidney Disease,* 19: 324-332.
Exclude: Narrative review

de la Rubia, J. (2010) Activity and safety of lenalidomide and dexamethasone in patients with multiple myeloma requiring dialysis: a Spanish multicenter retrospective study. *European Journal of Haematology,* 85: 363-365.
N = 15 whio received a variety of treatment schedules

Dimopoulos, M. A. (2009) Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. *Clinical lymphoma & myeloma,* 9: 302-306.
Exclude: Comparison not in PICO (bortezomib + dexamethasone (N = 17) versus bortezomib + dexamethasone + a variety of other agents (N = 29); retrospective study)

Dimopoulos, M. A., Terpos, E., Chanan-Khan, A., Leung, N., Ludwig, H., Jagannath, S., Niesvizky, R., Giralt, S., Fermand, J. P., Blade, J., Comenzo, R. L., Sezer, O., Palumbo, A., Harousseau, J. L., Richardson, P. G., Barlogie, B., Anderson, K. C., Sonneveld, P., Tosi, P., Cavo, M., Rajkumar, S. V., Durie, B. G. & San, M. J. (2010) Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. [Review]. *Journal of Clinical Oncology,* 28: 4976-4984.
Exclude: Narrative review/consensus-based guideline

Dimopoulos, M. A. (2010) Renal impairment is not an independent adverse prognostic factor in multiple myeloma patients who are treated upfront with novel agent-based regimens. *Blood,* 116: 1250-1251.
Conference abstract

Dimopoulos, M. A. (2010) Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: Dosing of lenalidomide according to renal function and effect on renal impairment. *European Journal of Haematology,* 85: 1-5.
Non-comparative study: Lenalidomide and dexamethasone (N = 12); for comparative purposes: exclude: N < or = 10 per group

Dimopoulos, M. A. (2014) Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. *Annals of Oncology,* 25: 195-200.
Exclude: Comparison not in PICO (bortezomib + a variety of other agents, including thalidomide, versus thalidomide or lenalidomide in combination with a variety of other agents; retrospective study)

Eleutherakis-Papaiakovou, V. (2007) Renal failure in multiple myeloma: Incidence, correlations, and prognostic significance. *Leukemia and Lymphoma,* 48: 337-341.
Retrospective study; patients received a variety of chemotherapy regimens ("All patients received primary treatment with chemotherapeutic agents combined with corticosteroids").

Gao, D. (2012) Therapeutic effects of high-dose dexamethasone combined with thalidomide and bortezomib on renal function in patients newly diagnosed multiple myeloma. *Journal of Leukemia and Lymphoma,* 21: 604-606.
Exclude: Published in Chinese

Gertz, M. A., Lacy, M. Q., Dispenzieri, A., Hayman, S. R., Kumar, S., Leung, N. & Gastineau, D. A. (2007) Impact of age and serum creatinine value on outcome after autologous blood stem cell transplantation for patients with multiple myeloma. *Bone Marrow Transplantation,* 39: 605-611.
Non-comparative study: Melphalan + SCT (N = 44)

Glavey, S. V., Gertz, M. A., Dispenzieri, A., Kumar, S., Buadi, F., Lacy, M., Hayman, S. R., Kapoor, P., Dingli, D., McCurdy, A., Hogan, W. J., Gastineau, D. A. & Leung, N. (2013) Long-term outcome of patients with multiple [corrected] myeloma-related advanced renal failure following auto-SCT.[Erratum appears in Bone Marrow

Transplant. 2014 Jul;49(7):996 Note: Kapoor, P [added]]. *Bone Marrow Transplantation,* 48: 1543-1547.
Exclude: Non-comparative study; intervention not in PICO (Auto SCT)

Gonsalves, W. I. (2015) Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. *Blood Cancer Journal,* 5: e296.
Patients received a variety of treatment regimens

Goranov, S. (2001) Chronic renal failure in multiple myeloma. Clinical characteristics, therapeutic management, prognostic significance. *Nephrology, Hemodialysis and Transplantation,* 7: 50-53.
Foreign language paper

Gupta, D., Bachegowda, L., Phadke, G., Boren, S., Johnson, D. & Misra, M. (2010) Role of plasmapheresis in the management of myeloma kidney: a systematic review. [Review]. *Hemodialysis International,* 14: 355-363.
Exclude: Systematic review without meta-analysis. Checked for included studies and included relevant ones separately.

Haynes, R. J. (2010) Presentation and survival of patients with severe acute kidney injury and multiple myeloma: A 20-year experience from a single centre. *Nephrology Dialysis Transplantation,* 25: 419-426.
Exclude: Retrospective study with "many different chemotherapy regimens were used during the 20 years"

Heyne, N. (2012) Extracorporeal light chain elimination: High cut-off (HCO) hemodialysis parallel to chemotherapy allows for a high proportion of renal recovery in multiple myeloma patients with dialysis-dependent acute kidney injury. *Annals of Hematology,* 91: 729-735.
Exclude: N < or = 10 per group; patients received a variety of treatments

Hillengass, J. (2015) The application of Gadopentate-Dimeneglumin has no impact on progression free and overall survival as well as renal function in patients with monoclonal plasma cell disorders if general precautions are taken. *European Radiology,* 25: 745-750.
Comparison/intervention not in PICO (CE MRI v noCE MRI)

Huang, T. C., Chen, J. H., Wu, Y. Y., Chang, P. Y., Dai, M. S., Chao, T. Y., Kao, W. Y., Chen, Y. C. & Ho, C. L. (2015) The treatment outcome of multiple myeloma patients ineligible for hematopoietic transplantation-a single institutional experience in Taiwan. *Annals of Hematology,* 94: 107-115.
Mixed population, RI and no RI; analyses only presented for all patients

Hutchison, C. A. (2009) Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off hemodialysis. *Clinical Journal of the American Society of Nephrology,* 4: 745-754.
Non-comparative study, possibly: Haemodialysis (N = 19); for comparison purposes exclude: N < or = 10 per group

Hutchison, C. A. (2012) Immunoglobulin free light chain levels and recovery from myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis. *Nephrology Dialysis Transplantation,* 27: 3823-3828.
Exclude: Non-comparative study: Patients received a variety of chemotherapy regimens.

Irish, A. B. (1997) Presentation and survival of patients with severe renal failure and myeloma. *QJM - Monthly Journal of the Association of Physicians,* 90: 773-780.
Exclude: Unclear which interventions the patients have received: Results only reported for the following three groups: (1) patients never dialysed [7 patients] or dialysed but recovered renal function [7 patients] (N = 14) vs (2) patients who never recovered renal function and were established on chronic haemodialysis [NOS] (N = 23) vs (3) patients who never recovered renal function and were established on chronic CAPD [NOS] (N = 17), but the paper also reports that “the first modality was haemodialysis or haemofiltration in all patients, without specifying further who received what in terms of the groups analysed.

Kastritis, E., Zervas, K., Symeonidis, A., Terpos, E., Delimbassi, S., Anagnostopoulos, N., Michali, E., Zomas, A., Katodritou, E., Gika, D., Pouli, A., Christoulas, D., Roussou, M., Kartasis, Z., Economopoulos, T. & Dimopoulos, M. A. (2009) Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). *Leukemia,* 23: 1152-1157.
Mixed population, RI and no RI. Analyses only presented for all patients.

Katagiri, D. (2011) Factors associated with recovery of renal function in patients with multiple myeloma who were treated with hemodialysis. *Nephron - Clinical Practice,* 117: c28-c32.
Exclude: Non-comparative study: Haemodialysis (N = 32)

Kleber, M. (2012) Prognostic risk factor evaluation in patients with relapsed or refractory multiple myeloma receiving lenalidomide treatment: Analysis of renal function by eGFR and of additional comorbidities by comorbidity

appraisal. *Clinical Lymphoma, Myeloma and Leukemia,* 12: 38-48.
Exclude: Non-comparative study: Lenalidomide-based therapy (N = 45)

Klein, U. (2011) Lenalidomide in combination with dexamethasone: effective regimen in patients with relapsed or refractory multiple myeloma complicated by renal impairment. *Annals of Hematology,* 90: 429-439.
Non-comparative study: Lenalidomide + dexamethasone (N = 33) (Comparative analyses not split by renal function)

Knudsen, L. M. (2000) Renal failure in multiple myeloma: Reversibility and impact on the prognosis. *European Journal of Haematology,* 65: 175-181.
Exclude: Non-comparative study: Patients received a variety of treatments

Kourelis, T. V., Manola, A., Moustakakis, M. N. & Bilgrami, S. F. (2013) Role of plasma exchange in the treatment of myeloma nephropathy: experience of one institution and systematic review. [Review]. *Connecticut Medicine,* 77: 147-151.
Exclude: Non-comparative study: Patients received a variety of treatments

Landau, H. (2012) Bortezomib, liposomal doxorubicin and dexamethasone followed by thalidomide and dexamethasone is an effective treatment for patients with newly diagnosed multiple myeloma with Internatinal Staging System stage II or III, or extramedullary disease. *Leukemia and Lymphoma,* 53: 275-281.
Exclude: Population not in PICO

Landoni, G., Bove, T., Szekely, A., Comis, M., Rodseth, R. N., Pasero, D., Ponschab, M., Mucchetti, M., Bove, T., Azzolini, M. L., Caramelli, F., Paternoster, G., Pala, G., Cabrini, L., Amitrano, D., Borghi, G., Capasso, A., Cariello, C., Carpanese, A., Feltracco, P., Gottin, L., Lobreglio, R., Mattioli, L., Monaco, F., Morgese, F., Musu, M., Pasin, L., Pisano, A., Roasio, A., Russo, G., Slaviero, G., Villari, N., Vittorio, A., Zucchetti, M., Guarracino, F., Morelli, A., De, S., V, Del Sarto, P. A., Corcione, A., Ranieri, M., Finco, G., Zangrillo, A. & Bellomo, R. (2013) Reducing mortality in acute kidney injury patients: systematic review and international web-based survey. [Review]. *Journal of Cardiothoracic & Vascular Anesthesia,* 27: 1384-1398.
Not specific to myeloma; consensus statement

Lee, C.-K. (2004) Dialysis-dependent renal failure in patients with myeloma can be reversed by high-dose myeloablative therapy and autotransplant. *Bone Marrow Transplantation,* 33: 823-828.
Exclude: Non-comparative study: Melphalan + autologous transplant (N = 59)

Leung, N., Gertz, M. A., Zeldenrust, S. R., Rajkumar, S. V., Dispenzieri, A., Fervenza, F. C., Kumar, S., Lacy, M. Q., Lust, J. A., Greipp, P. R., Witzig, T. E., Hayman, S. R., Russell, S. J., Kyle, R. A. & Winters, J. L. (2008) Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains. *Kidney International,* 73: 1282-1288.
Exclude: Non-comparative study

Li, J., Zhou, D. B., Jiao, L., Duan, M. H., Zhang, W., Zhao, Y. Q. & Shen, T. (2009) Bortezomib and dexamethasone therapy for newly diagnosed patients with multiple myeloma complicated by renal impairment. *Clinical lymphoma & myeloma,* 9: 394-398.
Exclude: Non-comparative study: Bortezomib + dexamethasone (N = 18); for comparative purposes: exclude: N < or = 10 per group

Li, Z. (2010) Clinical application of therapeutic plasma exchange in the Three Gorges Area. *Transfusion and Apheresis Science,* 43: 305-308.
Exclude: Only 2 patients with MM

Ludwig, H. (2010) Light chain-induced acute renal failure can be reversed by bortezomib-doxorubicin-dexamethasone in multiple myeloma: Results of a phase II study. *Journal of Clinical Oncology,* 28: 4635-4641.
Exclude: Non-comparative study

Ludwig; H.; Rauch,E.; Kuehr,T.; Adam,Z.; Weissmann,A.; Kasparu,H.; Autzinger,E.-M.; Heintel,D.; Greil,R.; Poenisch,W.; Muldur,E.; Zojer,N. (2015). Lenalidomide and dexamethasone for acute light chain-induced renal failure: A phase II study. *Haematologica*, 100: 385-391.
Exclude: Non-comparative study

Magee, C. (1998) Multiple myeloma and renal failure: One center's experience. *Renal Failure,* 20: 597-606.
Exclude: Non-comparative study possibly: Haemodialysis (N = 24 or 26); for comparative purposes exclude: N < or = 10 per group

Matsue, K. (2010) Reversal of dialysis-dependent renal failure in patients with advanced multiple myeloma: Single institutional experiences over 8 years. *Annals of Hematology,* 89: 291-297.
Exclude: Non-comparative study/analyses not in PICO/total N = 12 who received a variety of treatments

Moist, L. (1999) Plasma exchange in rapidly progressive renal failure due to multiple myeloma. *American Journal of Nephrology,* 19: 45-50.
Exclude: Non-comparative study

Montseny, J. J., Kleinknecht, D., Meyrier, A., Vanhille, P., Simon, P., Pruna, A. & Eladari, D. (1998) Long-term outcome according to renal histological lesions in 118 patients with monoclonal gammopathies. *Nephrology Dialysis Transplantation,* 13: 1438-1445.
Exclude: Comparisons/analyses not in PICO (interventions grouped together in the analyses:"Chemotherapy was given to 91 of 118 patients. Twenty-eight received mephalan and prednisone, according to Alexanian's protool [16], 20 cyclophosphamide and prednisone, 2 steroids alone, 2 alpha-interferon alone, and 39 multidrup chemotherapy including steroids, an alkylating agent, and various types of cytostatic drugs (mainly VAD or VMCP.")

Morabito, F. (2010) Safety and efficacy of bortezomib-based regimens for multiple myeloma patients with renal impairment: A retrospective study of Italian Myeloma Network GIMEMA. *European Journal of Haematology,* 84: 223-228.
Exclude: Comparison not in PICO (bortezomib + dexamethasone (N = 54) versus bortezomib + dexamethasone + a variety of other agents (N = 63); retrospective study)

Movshev, B. E. (2001) Osmotic activity of plasma in plasmapheresis in patients with multiple myeloma. *Terapevticheskii Arkhiv,* 73: 57-60.
Foreign language paper

Nayak, L. & Lazarus, H. M. (2013) Renal allografts in plasma cell myeloma hematopoietic cell graft recipients: on the verge of an explosion?. [Review]. *Bone Marrow Transplantation,* 48: 338-345.
Exclude: Narrative review

Nedeva, A. (2011) Reversal of the renal failure after therapy with bortezomib in patients with multiple myeloma. *Clinical and Transfusion Haematology,* 47: 43-47.
Exclude: Comparison/analyses not in PICO/foreign langauge publication

Niesvizky, R. (2002) Impact of early response to sequential high-dose chemotherapy on outcome of patients with advanced myeloma and poor prognostic features. *Leukemia and Lymphoma,* 43: 607-612.
Exclude: Non-comparative study/analyses not in PICO

Oehrlein, K. (2012) Successful treatment of patients with multiple myeloma and impaired renal function with lenalidomide: Results of 4 German centers. *Clinical Lymphoma, Myeloma and Leukemia,* 12: 191-196.
Exclude: Non-comparative study/analyses not in PICO

Onitilo, A. A., Engel, J., Olatosi, B. & Fagbemi, S. (2007) Community experience with bortezomib in patients with multiple myeloma. *Am J Hematol,* 82: 637-639.
Non-comparative study: Bortezomib (N = 47; from Piro)

Parikh, G. C., Amjad, A. I., Saliba, R. M., Kazmi, S. M., Khan, Z. U., Lahoti, A., Hosing, C., Mendoza, F., Qureshi, S. R., Weber, D. M., Wang, M., Popat, U., Alousi, A. M., Champlin, R. E., Giralt, S. A. & Qazilbash, M. H. (2009) Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma. *Biology of Blood & Marrow Transplantation,* 15: 812-816.
Exclude: Non-comparative study/analyses not in PICO

Park S., H. (2014) Renal insufficiency in newly-diagnosed multiple myeloma: Analysis according to international myeloma working group consensus statement. *Anticancer Research,* 34: 4299-4306.
Unclear exactly which treatments the patients received

Piro, E. & Molica, S. (2011) A systematic review on the use of bortezomib in multiple myeloma patients with renal impairment: what is the published evidence?. [Review]. *Acta Haematologica,* 126: 163-168.
Systematic review including comparative and non-comparative studies; checked for relevant studies

Ponisch, W. (2012) Successful treatment of patients with newly diagnosed/untreated multiple myeloma and advanced renal failure using bortezomib in combination with bendamustine and prednisone. *Journal of Cancer Research and Clinical Oncology,* 138: 1405-1412.

Non-comparative study: Bortezomib, bendamustine (and prednisone) (N = 18); for comparative purposes: exclude: N < or = 10 per group

Ponisch, W. (2013) Bendamustine and prednisone in combination with bortezomib (BPV) in the treatment of patients with relapsed or refractory multiple myeloma and light chain-induced renal failure. *Journal of Cancer Research and Clinical Oncology,* 139: 1937-1946.
Exclude: Non-comparative study: Bendamustine, bortezomib, and prednisone (N = 36)

Pozzi, C. (1995) Renal disease and patient survival in light chain deposition disease. *Clinical Nephrology,* 43: 281-287.
Exclude: N < or = 10 per group; patients received a variety of treatments

Prakash, J. (2009) Renal disease is a prodrome of multiple myeloma: An analysis of 50 patients from Eastern India. *Renal Failure,* 31: 267-271.
Non-comparative study: Melphalan and prednisone (N = 40); for comparative purposes: exclude: N < or = 10 per group

Prakash, J., Niwas, S. S., Parekh, A., Vohra, R., Wani, I. A., Sharma, N. & Usha. (2009) Multiple myeloma--presenting as acute kidney injury. *Journal of the Association of Physicians of India,* 57: 23-26.
Exclude: Non-comparative study: Patients received different chemotherapy treatments

Rekhtina, I. G. (2007) Treatment and survival of multiple myeloma patients on programmed hemodialysis. *Terapevticheskii Arkhiv,* 79: 9-13.
Foreign language paper

Rodrigues, L. (2014) Severe acute kidney injury and multiple myeloma: Evaluation of kidney and patient prognostic factors. *European Journal of Internal Medicine,* 25: 652-656.
Intervention not in PICO: "Various chemotherapy regimens were used."

Roig, M. (2009) Activity and safety of lenalidomide and dexamethasone in multiple myeloma patients with advanced renal failure: A Spanish multicenter retrospective study. *Blood,* 114: 749.
Exclude: Conference abstract

Roussou, M., Kastritis, E., Migkou, M., Psimenou, E., Grapsa, I., Matsouka, C., Barmparousi, D., Terpos, E. & Dimopoulos, M. A. (2008) Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens. [Review] [24 refs]. *Leukemia & lymphoma,* 49: 890-895.
Non-comparative study: Bortezomib-based (N = 20); for comparative purposes: exclude: N < or = 10 per group

Sakhuja, V. (2000) Renal involvement in multiple myeloma: A 10-year study. *Renal Failure,* 22: 465-477.
Exclude: Non-comparative study with patients receiving a variety of treaments

Saunders, I. M. (2014) A lower dose of melphalan (140 mg/ m2) as preparative regimen for multiple myeloma in patients >65 or with renal dysfunction. *Biology of Blood and Marrow Transplantation,* 20: S293-S294.
Conference abstract

Scheid, C., Sonneveld, P., Schmidt, W., I, Holt, B., Hielscher, T., Jarari, L., Bertsch, U., Salwender, H., Zweegman, S., Hanel, M., Vellenga, E., Schubert, J., Blau, I. W., Jie, A., Elde, H., Peter, N., Schaafsma, M., Lindemann, W., Kersten, M. J., Duehrsen, U., Delforge, M., Weisel, K., Croockewit, S., Martin, H., Wittebol, S., Schouten, H., Marwijk, K. M., Wijermans, P., Lokhorst, H. M. & Goldschmidt, H. (2010) Influence of renal function on outcome of vad or bortezomib, doxorubicin, dexamethasone (PAD) induction treatment followed by high-dose melphalan (HDM): A subgroup analysis from the hovon-65/GMMG-HD4 randomized phase III trial for newly diagnosed multiple myeloma. *Blood,* 116.
Exclude: Conference abstact

Schooneman, F., Claise, C. & Stoltz, J. F. (1997) Hemorheology and therapeutic hemapheresis. *Transfusion Science,* 18: 531-540.
Outcome not in PICO

Sekiguchi, N. (2014) The comparison of bortezomib-containg regimen and thalidomide-containing regimen; superiority of bortezomib, doxorubicin, and dexamethasone theraypy in newly diagnosed myeloma with renal impairment. *Haematologica,* 99: 638-639.
Exclude: Conference abstract

Sharland, A. (1997) Hemodialysis: An appropriate therapy in myeloma-induced renal failure. *American Journal of Kidney Diseases,* 30: 786-792.
Exclude: Non-comparative study: Patients received a variety of treatments

Shi, H. (2014) Application of RIFLE criteria in patients with multiple myeloma with acute kidney injury: A 15-year retrospective, single center, cohort study. *Leukemia and Lymphoma,* 55: 1076-1082.
Patients received a variety of different treatments

Sonneveld, P., Scheid, C., Holt, B., Jarari, L., Bertsch, U., Salwender, H., Zweegman, S., Vellenga, E., Broyl, A., Blau, I. W., Weisel, K., Wittebol, S., Bos, G. M. J., Stevens, M., Schmidt, W., I, Pfreundschuh, M., Hose, D., Jauch, A., Velde, H., Raymakers, R., Schaafsma, M. R., Kersten, M. J., Marwijk, K. M., Duehrsen, U., Lindemann, H. W., Wijermans, P. W., Lokhorst, H. & Goldschmidt, H. (2013) Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma:Extended follow-up of the HOVON-65/GMMG-HD4 trial. *Blood,* 122.
Exclude: Conference abstract

Spencer, A., Roberts, A., Kennedy, N., Ravera, C., Cremers, S., Bilic, S., Neeman, T., Copeman, M., Schran, H. & Lynch, K. (2008) Renal safety of zoledronic acid with thalidomide in patients with myeloma: a pharmacokinetic and safety sub-study. *BMC.clinical.pharmacology,* 8: 2.
Population not in PICO

Sugihara, H. (2014) Percentage of urinary albumin excretion and serum-free light-chain reduction are important determinants of renal response in myeloma patients with moderate to severe renal impairment. *Blood Cancer Journal,* 4.
Unclear exactly what treatments the patients received; comparison/analyses (responder v non-responder) not in PICO

Taparia, B. N. (1996) Renal involvement in multiple myeloma. *The Journal of the Association of Physicians of India,* 44: 240-242.
Exclude: N < or = 10 per group; patients received a variety of treatments

Terpos E., K. (2009) Cystatin-C is an independent prognostic factor for survival in multiple myeloma and is reduced by bortezomib administration. *Haematologica,* 94: 372-379.
Various treatments given; population not in PICO

Torra, R. (1995) Patients with multiple myeloma requiring long-term dialysis: Presenting features, response to therapy, and outcome in a series of 20 cases. *British Journal of Haematology,* 91: 854-859.
Exclude: Non-comparative study: Patients received a variety of treatments

Tosi, P. (2004) Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. *European Journal of Haematology,* 73: 98-103.
Exclude: Non-comparative study/N < or = 10 in one of the groups

Tosi, P. (2010) Thalidomide-Dexamethasone as Induction Therapy before Autologous Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma and Renal Insufficiency. *Biology of Blood and Marrow Transplantation,* 16: 1115-1121.
Non-comparative study: Thalidomide, dexamethasone + cyclophosphamide + AHSCT (N = 31); for comparative purposes: exclude: N < or = 10 per group

Tricot, G. (1996) Safety of autotransplants with high-dose melphalan in renal failure: A pharmacokinetic and toxicity study. *Clinical Cancer Research,* 2: 947-952.
N = 6 with RI and MM

Tsakiris, D. J. (2010) Incidence and outcome of patients starting renal replacement therapy for end-stage renal disease due to multiple myeloma or light-chain deposit disease: An ERA-EDTA Registry study. *Nephrology Dialysis Transplantation,* 25: 1200-1206.
Exclude: Comparison (MM v non-MM; years) not in PICO

Uchida, M. (1995) Renal dysfunction in multiple myeloma. *Internal medicine (Tokyo, Japan),* 34: 364-370.
Exclude: Comparisons/analyses not in PICO

Uttervall, K. (2014) The use of novel drugs can effectively improve response, delay relapse and enhance overall survival in multiple myeloma patients with renal impairment. *PLoS ONE,* 9.
Non-comparative study (possibly): Bortezomib (N = 72); otherwise mixed treatment regimens

Viertel, A. (2000) Management of renal complications in patients with advanced multiple myeloma. *Leukemia and Lymphoma,* 38: 513-519.
Exclude: N < or = 10 per group; patients received a variety of treatments.

Yang, G. Z., Wang, J., Fu, L. N., Shen, M., Jiang, L., Zhang, Y., Huang, Z. X., Gao, W., Zhang, L., Wu, Y., Li, L. H. & Chen, W. M. (2012) Effects of bortezomib on the prognosis of the newly-diagnosed multiple myeloma patients with renal impairment. *African Journal of Pharmacy and Pharmacology,* 6: 793-797.
Exclude: Comparison not in PICO (bortezomib + other agents (N = 25) versus VAD or TAD or TD+/-CTX (N = 38); retrospective study)

Yang, G. Z., Chen, W. M. & Wu, Y. (2013) Bortezomib, dexamethasone plus thalidomide for treatment of newly diagnosed multiple myeloma patients with or without renal impairment. *Chinese Journal of Cancer Research,* 25: 155-160.
Exclude: Non-comparative study: Bortezomib, dexamethasone, thalidomide (N = 30); comparison/analyses not in PICO (different levels of renal impairment)

Yang, J. (2011) Effects of DVD and VAD in the treatment of newly diagnosed mutiple myeloma with renal failure. *Journal of Leukemia and Lymphoma,* 20: 656-658.
Exclude: Published in Chinese

Yu, X. (2015) Chemotherapy with or without plasmapheresis in acute renal failure due to multiple myeloma: a meta-analysis. *International Journal of Clinical Pharmacology & Therapeutics,* 53: 391-397.
Meta-analysis, checked for eligible studies (no new relevant studies; includes studies published before 1995)

1 Evidence tables

Abdulrahman (2003).

Pub year: 2003		Patient Characteristics	Intervention	Comparison	Outcome
Country	Saudi Arabia	Inclusion: – All diagnosed cases of multiple myeloma from January 1994-2000 with renal failure (defined as serum creatinine > 175 µmol/l – "Chemotherapy regimens consisted of cycles of melphalan and prednisolone." – "The ultrasound of the kidneys were within acceptable range for their age and height indicating that the renal failure was most likely acute in nature." "Plasmapheresis was carried out to all patients diagnosed after May, 1996 (since it was not available in our hospital before that).": - <u>Plasmapheresis (N=15):</u> Age: Not reported; 14 males/2 females *Does not add up to 15*; immunoglobobulins IgGk: N = 11, IgAk: N = 3, IgA: N = 1; renal failure at initial diagnosis: N = 6; oliguric at presentation: N = 4; mean initial serum creatinine = 370 ±82 µmol/l; hypercalcaemia: N = 8 with mean initial serum calcium = 2.99 ±0.5 mmol/l; hyperuricaemia: N = 9 with mean initial serum uric acid = 710 ±120 µmol/l; required maintenance haemodyialysis: N = 1. - <u>No plasmapheresis (N=14):</u> Age: Not reported; 10 males/3 females *Does not add up to 14*; immunoglobobulins IgGk: N = 8, IgAk: N = 5, IgA: N = 1; renal failure at initial diagnosis: N = 4; oliguric at presentation: N = 6; mean initial serum creatinine = 410 ±130 µmol/l; hypercalcaemia: N = 10 with mean initial serum calcium = 3.4 ±0.72 mmol/l; hyperuricaemia: N = 6 with mean initial serum uric acid = 680 ±100 µmol/l; required maintenance haemodyialysis: N = 5.	Plasmapheresis "performed in 2-4 hours sessions on daily basis or every other day for 1 to 4 weeks (mean number of plasmapheresis [±SD], 8.1 ±3.4, range 4 to 12), the average volume exchanged was 3521 ml of plasma that was substituted simultaneously in a ratio of 1:1 by fresh frozen plasma or a solution of pasteurized plasma proteins. If the patient's renal functions deteriorated, intermittent haemodialysis was carried out." *Not clear of the last sentence covers all or just plasmapheresis patients* AND "supportive care with hydration and transfusion [NOS] when needed"	"supportive care with hydration and transfusion [NOS] when needed"	Survival Renal function
Design, period	Retrospective 1994-2000				
N	29				
Follow-up	Not reported				
Funding source	Not reported				
Results	**Renal function:** - Mean (SD) peak serum creatinine, µmol/l: Plasmapheresis (520 ±93) < No plasmapheresis (860 ±201 or 210 [*both reported*]), p < 0.005 - Mean (SD) change, serum creatinine, µmol/l: Plasmapheresis (373 ±104) > No plasmapheresis (115 ±64), p < 0.001 - Improved serum creatinine after treatment: Plasmapheresis (N = 12) > No plasmapheresis (N = 3) , p < 0.001 - Oliguric at presentation, polyuric after treatment: Plasmapheresis (N = 4/4) > No plasmapheresis (N = 2/6) , p < 0.005 - Mean (SD) hypercalcaemia value after treatment, mmol/l: Plasmapheresis (2.45 ±0.17) = No plasmapheresis (2.8 ±0.35), p non-significant				

Abdulrahman (2003).	
	- Mean (SD) hyperuricaemia value after treatment, µmol/l: Plasmapheresis (350 ±110) = No plasmapheresis (360 ±115), p non-significant **Survival:** - 32-month mortality: Plasmapharesis (N = 6) < No plasmapheresis (N = 13), p < 0.001 (Four patients were alive with stable kidney functions while 6 patients had end stage renal disease requiring maintenance dialysis. - Median survival, months: Plasmapheresis (38) > No plasmapheresis (16) , p < 0.001
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? High risk – Retrospective study, group assignment depended on treatment received, which was time dependednt - Performance bias (blinding of patients, personnel)? High risk – Retrospective study - Detection bias (blinding of outcome assessor)? High risk – Retrospective study - Attrition bias (missing data)? Data from all included patients available - Reporting bias? Unclear risk - Other bias? Unclear risk

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Breitkreutz (2014).					
Pub year: 2014		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Germany	Inclusion: "newly-diagnosed MM, dialysis dependency due to MM-related renal failure and induction treatment with either PAD (bortezomib, doxorubicin, dexamethesone) or VAD/VAD-like regimens". - Bortezomib (N=13): Median age at diagnosis, years: 51 (31-61); Gender: Not reported; Durie-Salmon stage I/II/III: 0/2/11; Monoclonal protein: G/A/BJ/D/hypo-asecretory: 3/2/7/0/1, β_2 MG (diagnosis, mg/L): 14.8 (7.7-28), β_2 MG (auto-SCT, mg/L): 7.6 (2.6-21.8), albumin (diagnosis, g/l): 44.8 (41.7-51.6), albumin (auto-SCT, g/l): 46.5 (43-49.5), creatinine clearance (diagnosis, ml/min): 15.2 (5.5-49), creatinine clearance (auto-SCT, ml/min): 28.3 (4-123); median duration of dialysis (months): 6.1 (0.2-68.2) - Control (N=14): Median age at diagnosis, years: 56 (39-66); Gender: Not reported; Durie-Salmon stage I/II/III: 1/2/11; Monoclonal protein: G/A/BJ/D/hypo-asecretory: 7/1/5/1/0, β_2 MG (diagnosis, mg/L): 22.2 (4.8-36), β_2 MG (auto-SCT, mg/L): 35.1 (2-97), albumin (diagnosis, g/l): 41.5 (32-49), albumin (auto-SCT, g/l): 40.9 (32-52.8), creatinine clearance (diagnosis, ml/min): 7.8 (2-26), creatinine clearance (auto-SCT, ml/min): 10.6 (3.9-114); median duration of dialysis (months): 17.1 (0.7-94.3)	Induction treatment with PAD (bortezomib, doxorubicin, dexamethesone, N = 12) or VCD (bortezomib, cyclophosphamide and dexamethasone, n = 1) followed by G-CSF for stem cell mobilisation, high-dose chemotherapy (melphalan: "Patients who came off dialysis before auto-SCT received full dose melphalan (100 mg/m^2 day -3 and -2), whereas patients still dependent on dialysis were conditioned with one dose of melphalan (100 mg/m^2, day -2) after dialysis on that day, followed by dialysis the day after high-dose therapy (day -1)) and auto-SCT One patient had received VAD in the first cycle of induction, but was then switched to a	Induction treatment with VAD (N = 11) or VAD-like (thalidomide, adrimycin and dexamethasone, TAD, N = 1) or TCED (thalidomide, cyclophosphamide, etoposide and dexamethasone, N = 1) regimens followed by G-CSF for stem cell mobilisation, high-dose chemotherapy (melphalan: "Patients who came off dialysis before auto-SCT received full dopse melphalan (100 mg/m^2 day -3 and -2), whereas patients still dependent on dialysis were conditioned with one dose of melphalan (100 mg/m^2, day -2) after dialysis on that day, followed by dialysis the day after high-dose therapy (day -1)) and auto-SCT *Control group*	Dialysis Response Survival Adverse events
Design, period	Retrospective 1997-2011				
N	27				
Follow-up	Bortezomib: 53 months; Control: 84 months				
Funding source	Dietmar-Hopp Foundation, German Cancer Aid, and University of Heidelberg				

Breitkreutz (2014).					
		The authors state that "Overall patient characteristics were comparable between the two groups", but only present a p-value for duration of dialysis which was 0.38. "A total of 17 patients went on to receive maintenance therapy post auto-SCT. For those patients whio did not receive bortezomib before auto-SCT, maintenance treatment consisted of alpha-IFN in three patients. Thalidomide was given to two patients of the bortezomib group and to eight patients of the VAD/VAD-like group. A total of four patients who received a bortezomib-containing induction regimen was also given bortezomib as maintenance."	bortezomib-containing regimen		
Results	**Dialysis:** - After induction: 38.5% bortezomib patients and 35.7% control group patients came off dialysis. *No inferential statistics presented for this comparison.* - After first auto-SCT: 15.4% bortezomib patients and 28.6% control group patients came off dialysis. *No inferential statistics presented for this comparison.* - Dialysis-dependence until death: 23.1% bortezomib patients and 35.7% control group patients. *No inferential statistics presented for this comparison.* **Myeloma response:** - Overall response rate (PR or better) prior to auto-SCT: 83.3% bortezomib patients and 35.7% control group, p = 0.021. - Overall response rate (PR or better) day +100 post auto-SCT: 100% bortezomib patients and 58.3% control group, p = 0.014. - Relapse/progression prior to auto-SCT: 0% bortezomib patients and 7.1% control group, p = 0.021. *No inferential statistics presented for this comparison.* - Relapse/progression day +100 post auto-SCT: 0% bortezomib patients and 8.3% control group, p = NS. - Median event-free survival (months): Bortezomib patients not yet reached, control group = 27.6, p = 0.04; HR = 0.39 (95% CI 0.14-0.98), p = 0.04. **Survival:** - Median overall survival (months): Bortezomib patients not yet reached, control group = 34.8, p = NS; HR = 0.51 (95% CI 0.18-1.46), p = 0.21. **Adverse events:** - Post-transplant toxicity and supportive treatment: The groups did not differ significantly in hospitalisation (days), leucocytes > 1/nl (days), granulocytes > 0.5/nl (days), thrombocytes > 20/nl (days), thrombocytes > 50/nl (days), fever (days), antibiotic therapy (days), thrombocyte transfusion (number), and erythrocyte transfusion (number).			
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? High risk – Retrospective study, group assignment depended on treatment received, which was time dependent - Performance bias (blinding of patients, personnel)? High risk – Retrospective study - Detection bias (blinding of outcome assessor)? High risk – Retrospective study - Attrition bias (missing data)? Data from all included patients available - Reporting bias? Unclear risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.				

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Clark et al. (2005)				
Pub year: 2005	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**

Clark et al. (2005)					
Country	Canada	Inclusion: "patients with newly diagnosed multiple myeloma and progressive acute kidney failure. All had a bone marrow aspirate with more than 10% plasma cells and a monoclonal light chain in their urine, plasma, or renal tissue. We defined progressive acute kidney failure as a serum creatinine level greater than 200 µmol/L (>2.3 mg/dL) with an increase greater than 50 µmol/L (>0.6 mg/dL) in the preceding 2 weeks despite correction of hypercalcaemia, hypovolemia, and metabolic acidosis in patients with normal-sized kidneys on renal ultrasonography." Exclusion: "age less than 18 years or greater than 81 years, obstruction on renal ultrasonography (required examination), use of intravenous contrast or nonsteroidal anti-inflammatory drugs during the previous 2 weeks, previous treatment for myeloma, pregnancy, or inability to provide informed consent." Randomisation and masking: – Patients were stratified by 4 strata according to whether they were receiving VAD, and whether they were receiving short-term haemodialysis. – Patients were treated in an unblinded manner - <u>Plasma exchange (N=58):</u> Mean (SD) age = 65.2 (11.5) years; 37 males/21 females; mean (SD) serum calcium level: 2.22 (0.35) mmol/l, 8.9 (1.4) mg/dl; mean (SD) serum albumin level: 29.8 (7.1) g/l; mean (SD) urine protein level: 4.7 (7.05) g/l; mean (SD) serum creatinine level (only from people not receiving dialysis): 422.5 (213.6) µmol/l, 4.78 (2.42) mg/dl; mean (SD) glomerular filtration rate (calculated with the Modified Diet in Renal Disease formula 2; includes only patients not receiving dialysis): 0.14 (0.07) mL • s^{-2} • m^{-2}, 14.84 (7.53) mL/min per 1.73 m^2; Durie-Salmon myeloma stage IIIB: N = 24; monoclonal Bence-Jones protein: N = 58, κ type: N = 22, λ type: N = 22. - <u>No plasma exchange (N=39)</u>: Mean (SD) age = 61.3 (11) years; 28 males/11 females; mean (SD) serum calcium level: 2.26 (0.29) mmol/l, 9.06 (1.16) mg/dl; mean (SD) serum albumin level: 32.2 (8.2) g/l; mean (SD) urine protein level: 7.25 (13.08) g/l; mean (SD) serum creatinine level (only from people not	Plasma exchange: 5-7 procedures within the first 10 days of study entry (concurrent with initiation of chemotherapy); 50 mL/kg with acid citrate dextrose through a Spectra cell separator, using 5% human serum albumin and normal saline AND chemotherapy of either melphalan and prednisone daily for 4 days every 28 days up to 12 cycles or 4 days of slow IV VAD on days 1-4, 9-12, and 17-20 for 28-day cycles up to 6 cycles. VAD treatment stopped 1.5 hours before plasma exchange; afterwards a bolus volume of VAD that would have been infused during the plasma exchange time period was given.	Chemotherapy of either melphalan and prednisone daily for 4 days every 28 days up to 12 cycles or 4 days of slow IV VAD on days 1-4, 9-12, and 17-20 for 28-day cycles up to 6 cycles.	Compositve outcome, assessed at 6 months, including death, dialysis dependence and an estimated GFR < 0.29 mL • s^{-2} • m^{-2} (<30mL/min per 1.73 m^2) calculated from the 6-month serum creatinine level Survival
Design, period	RCT (multi-centre) 1998-2003				
N	97				
Follow-up	6 months				
Funding source	Canadian Institute of Health Research; The Kidney Foundation of Canada; Gambro BCT (the purveyor of the Ganbro Spectra, the cell separator used in the trial). "The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the papper for publication."				

Clark et al. (2005)					
		receiving dialysis): 460.4 (187.6) µmol/l, 5.21 (2.12) mg/dl; mean (SD) glomerular filtration rate (calculated with the Modified Diet in Renal Disease formula 2; includes only patients not receiving dialysis): 0.13 (0.06) mL • s^{-2} • m^{-2}, 13.32 (6.16) mL/min per 1.73 m^2; Durie-Salmon myeloma stage IIIB: N = 17; monoclonal Bence-Jones protein: N = 39, κ type: N = 21, λ type: N = 14.			
Results	**Composite outcome:** - No plasma exchange (27 events in 39 patients) = plasma exchange (33 events in 57 patients [data missing from 1 patients]), difference between groups = 11.3% (95% CI -8.3% to 29.1%); unadjusted odds ratio (OR) = 1.71 (95% CI 0.72 – 4.01); adjusted (for baseline VAD, Durie-Salmon stage IIIB, dialysis, age serum albimun level and 24-hour urine protein level) OR = 1.2 (95% CI 0.42 – 3.44), p = 0.31. **Survival**: - Death by 6 months: No plasma exchange (13 deaths in 39 patients) = plasma exchange (19 deaths in 58 patients); unadjusted OR = 1.03 (95% CI 0.43 – 2.43); adjusted (for baseline VAD, Durie-Salmon stage IIIB, dialysis, age serum albimun level and 24-hour urine protein level) OR = 0.89 (95% CI 0.32 – 2.49) - Death by 6 months or receiving dialysis at 6 months: unadjusted OR = 1.49 (95% CI 0.66 – 3.38); adjusted (for baseline VAD, Durie-Salmon stage IIIB, dialysis, age serum albimun level and 24-hour urine protein level) OR = 1.13 (95% CI 0.41 – 3.1) **Renal function:** - Dialysis dependence at 6 months: No plasma exchange (7 of 26 patients very dialysis-dependent) = plasma exchange (5 of 39 patients wre dialysis-dependent), difference between groups = 14.1% (95% CI -5.1% to 34.6%), p = 0.2; unadjusted odds ratio (OR) = 1.71 (95% CI 0.72 – 4.01); adjusted (for baseline VAD, Durie-Salmon stage IIIB, dialysis, age serum albimun level and 24-hour urine protein level) OR = 1.2 (95% CI 0.42 – 3.44). - Excluding deaths, 7/19 patients in the no plasma exchange group and 10/24 plasma exchange patients discontinued dialysis; - 5/25 patients in the no plasma exchange group and 9/43 plasma exchange patients started dialysis in the postinitiation period. - Receiving dialysis or GFR < 0.29 mL • s^{-2} • m^{-2} (<30mL/min per 1.73 m^2) at 6 months: unadjusted OR = 2.08 (95% CI 0.76 – 5.73); adjusted (for baseline VAD, Durie-Salmon stage IIIB, dialysis, age serum albimun level and 24-hour urine protein level) OR = 0.89 (95% CI 0.22 – 3.58) - Mean increases in GFR at 6 months: Mean (SD) increases (from baseline) were statistically significant within each group, but not significantly different between the groups: No plasma exchange: 0.29 (0.25) mL • s^{-2} • m^{-2}, 30.2 (25.65) mL/min per 1.73 m^2, and plasma exchange: 0.3 (0.24) mL • s^{-2} • m^{-2}, 31.36 (25.26) mL/min per 1.73 m^2.			
Comments	- ITT analyses for the 97/104 initially enrolled patients - Patient selection bias (randomisation sequence, allocation concealment)? Low risk - Central randomisation using a computer random-number generator, recruiting physicians unaware of treatment allocation before study entry. - Performance bias (blinding of patients, personnel)? High risk – Open trial - Detection bias (blinding of outcome assessor)? High risk – Open trial - Attrition bias (missing data)? Low risk - Data from all patients appear to have been included - Reporting bias? Unclear risk - Other bias? Unclear risk				

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Dimopoulos et al. (2009)					
Pub year: 2009		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Europe	Inclusion: "Patients with previously untreated MM ineligible for high-dose therapy". Exclusion: sCR > 2 mg/dl, grade≥ 2 peripheral sensory neuropathy/neuropathic pain. The trial also reports on patients with	VMP: 9 6-week cycles of melphalan 9mg/m^2 on days 1-4; prednisone 60mg/m^2 on	MP: Melphalan and prednisone. *No further information reported. Unclear if*	Response Progression-free survival Reversal of renal impairment
Design, period	RCT Study years not reported				
N	227				

Dimopoulos et al. (2009)					
Follow-up	Median: 25.9 months	normal renal function (defined as GFR > 50ml/min), however these patients are not relevant to the current question, so are not reported here. - <u>VMP (N=111, divided into eGFR ≤ 30 and eGFR 31-50):</u> - eGFR ≤ 30: N = 19; Median age, years: 76; % male: 26%; KPS ≤ 70: 63%; ISS stage III: 84%; median β_2 microglobulin (mg/L): 8.2; β_2 microglobulin > 5.5 mg/L: 84%; median albumin (g/dl): 3.3; albumin ≥ 3.5 g/dl: 42%. - eGFR 31-50: N = 92; Median age, years: 75; % male: 48%; KPS ≤ 70: 40%; ISS stage III: 58%; median β_2 microglobulin (mg/L): 6.15; β_2 microglobulin > 5.5 mg/L: 54%; median albumin (g/dl): 3.2; albumin ≥ 3.5 g/dl: 43%. - <u>MP (N=116, divided into eGFR ≤ 30 and eGFR 31-50):</u> - eGFR ≤ 30: N = 15; Median age, years: 76; % male: 27%; KPS ≤ 70: 33%; ISS stage III: 80%; median β_2 microglobulin (mg/L): 9; β_2 microglobulin > 5.5 mg/L: 73%; median albumin (g/dl): 3.2; albumin ≥ 3.5 g/dl: 40%. - eGFR 31-50: N = 101; Median age, years: 75; % male: 39%; KPS ≤ 70: 41%; ISS stage III: 52%; median β_2 microglobulin (mg/L): 5.7; β_2 microglobulin > 5.5 mg/L: 51%; median albumin (g/dl): 3.2; albumin ≥ 3.5 g/dl: 35%. "Patients discontinued treatment due to progressive disease or unacceptable toxicity, or by patient/investigator decision. Dose reductions were required for excessive toxicity"	days 1-4; bortezomib 1.3mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1-4 and in days 1, 8, 22 and 29 during cycles 5-9.	*the VMP doses referred to are the same as those in the VMPT-VT group or not?*	defined as improvement in GFR from < 50 ml/min at baseline to > 60 ml/min on treatment Overall survival Adverse events
Funding source	Johnson & Johnson Pharmaceutical Research & Development LLC and Millennium Pharmaceuticals				
Results	**<u>eGFR ≤ 30</u>:** **Myeloma response:** **-** Response-evaluable: VMP: N = 19; MP: N = 15 - Response rate: VMP (74%), MP (47%); OR 3.57, p = 0.12. - CR rate: VMP (37%), VMP (13%); OR 3.23, p = 0.23. - Median time to first response: VMP (1 month), MP (3.5 months) - Median duration of response: VMP (18.5 months), MP (10.8 months) **Reversal of renal impairment:** **-** VMP (37%), MP (7%). **Time-to-progression:** - Median: VMP (19.8 months), MP (14.5 months); HR 0.21, p = 0.14. **Overall survival:** - Median: VMP (28.7 months), MP (24.7 months); HR 0.63, p = 0.47. - 1-year: VMP (78.9%), MP (71.8%). - 2-year: VMP (65.5%), MP (64.6%). - 3-year: VMP (NE), MP (NE). **Adverse events:** VMP received a median of 9 cycles; MP received a median of 4 cycles. Any AE (VMP: 19/19; MP: 15/15); maximum severity of any AE grade 3/4/5 (VMP: 8/8/2 of 19 patients; MP: 3/7/3 of 15 patients); Grade ≥ 3 adverse events: neutropenia (VMP: 9/19; MP: 10/15), thrombocytopenia (VMP: 13/19; MP: 8/15), anaemia (VMP: 8/19; MP: 5/15), peripheral sensory neuropathy (VMP: 3/19; MP: 0/15), neuralgia (VMP: 0/19; MP: 0/15), pneumonia (VMP: 1/19; MP: 0/15); any SAE (VMP: 12/19; MP: 6/15);			

Dimopoulos et al. (2009)	
	discontinuation due to AE (VMP: 2/19; MP: 4/15); bortezomib dose reduction due to AE (VMP: 7/19; MP: NA); second bortezomib dose reduction due to AE (VMP: 3/19; MP: NA); melphalan dose reduction due to AE (VMP: 5/19; MP: 4/15). **eGFR 31-50:** **Myeloma response:** **-** Response-evaluable: VMP: N = 92; MP: N = 99 - Response rate: VMP (67%), MP (45%); OR 2.34, p = 0.005. - CR rate: VMP (29%), VMP (4%); OR 8.65, p < 0.0001. - Median time to first response: VMP (1.1 month), MP (3.3 months) - Median duration of response: VMP (16.3 months), MP (13.1 months) **Reversal of renal impairment:** **-** VMP (46%), MP (39%). **Time-to-progression:** - Median: VMP (24 months), MP (16.1 months); HR 0.55, p = 0.02. **Overall survival:** - Median: VMP (NE), MP (NE); HR 0.61, p = 0.06. - 1-year: VMP (85.2%), MP (77.4%). - 2-year: VMP (70.9%), MP (59.8%). - 3-year: VMP (68.2%), MP (42.2%). **Adverse events:** VMP received a median of 7 cycles; MP received a median of 8 cycles. Any AE (VMP: 91/92; MP: 98/101); maximum severity of any AE grade 3/4/5 (VMP: 38/33/11 of 92 patients; MP: 43/31/11 of 101 patients); Grade ≥ 3 adverse events: neutropenia (VMP: 36/92; MP: 38/101), thrombocytopenia (VMP: 40/92; MP: 36/101), anaemia (VMP: 18/92; MP: 37/101), peripheral sensory neuropathy (VMP: 8/92; MP: 0/101), neuralgia (VMP: 6/92; MP: 0/101), pneumonia (VMP: 7/92; MP: 9/101); any SAE (VMP: 46/92; MP: 41/101); discontinuation due to AE (VMP: 16/92; MP: 17/101); bortezomib dose reduction due to AE (VMP: 48/92; MP: NA); second bortezomib dose reduction due to AE (VMP: 15/92; MP: NA); melphalan dose reduction due to AE (VMP: 21/92; MP: 16/101). **And grouped together as eGFR ≤ 50:** **Myeloma response:** **-** Response-evaluable: VMP: N = 111; MP: N = 114 - Response rate: VMP (68%), MP (46%); OR 2.46, p = 0.001. - CR rate: VMP (31%), VMP (5%); OR 7.06, p < 0.00001. - Median time to first response: VMP (1 month), MP (3.4 months) - Median duration of response: VMP (16.9 months), MP (12.9 months) **Reversal of renal impairment rate:** **-** VMP (44%), MP (34%); multivariate analysis (adjusting for age, GFR, response by EMBT and best M-protein response) found that the effect of treatment arm was non-significant: OR 1.5 (95% CI 0.88-2.57), p = 0.07. **Time to reversal of renal impairment:** **-** VMP (median, range: 2.1 months, 0.2-11.8 months; 50% quartile: 9 months; 1-month rate: 13.2%), MP (median, range: 2.4 months, 0.2-13.6 months; 50% quartile: 13.9 months; 1-month rate: 9.6%); HR 1.59, p = 0.03. **Renal response:** - Complete response rate: VMP (44%), MP (34%). **Time-to-progression:** - Median: VMP (19.9%), MP (16.1 months); HR 0.52, p = 0.006. **Overall survival:** - Median: VMP (NE), MP (31.9 months); HR 0.7, p = 0.12. - 1-year: VMP (84.1%), MP (76.7%). - 2-year: VMP (70.1%), MP (60.1%). - 3-year: VMP (60.7%), MP (41.5%). **Adverse events:** Any AE (VMP: 110/111; MP: 113/116); maximum severity of any AE grade 3/4/5 (VMP: 46/41/13 of 111 patients; MP: 46/38/14 of 116 patients); Grade ≥ 3 adverse events: neutropenia (VMP: 45/111; MP: 48/116), thrombocytopenia (VMP: 53/111; MP: 44/116), anaemia (VMP: 26/111; MP: 42/116), peripheral sensory neuropathy (VMP: 11/111; MP: 0/116), neuralgia (VMP: 6/111; MP: 0/116), pneumonia (VMP: 8/111; MP: 9/116); any SAE (VMP: 58/111; MP: 47/116); discontinuation due to AE (VMP: 18/111; MP: 21/116); bortezomib dose reduction due to AE (VMP: 55/111; MP: NA); second bortezomib dose reduction due to AE (VMP: 18/111; MP: NA); melphalan dose reduction due to AE (VMP: 26/111; MP: 20/116).
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – RCT but no details provided - Performance bias (blinding of patients, personnel)? Unclear risk – no details reported - Detection bias (blinding of outcome assessor)? Unclear risk – no details reported

Dimopoulos et al. (2009)	
	- Attrition bias (missing data)? Data from all included patients available - Reporting bias? Low risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Dimopoulos et al. (2013)					
Pub year: 2013		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Greece	Inclusion: Patients with newly diagnosed multiple myeloma and renal impairment (defined as an estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73m^2 using the simplified Modification of Diet in Renal Disease formula) were treated upfront with a novel agent-containing regimen. - Thalidomide-based (N=62): Median (range) age = 75 (55-89) years; 27 males/35 females; Performance status ≥ 2: N = 38; ISS stage I: N = 4, II: N = 20, III: N = 38; median (range) eGFR (ml/min/1.73m^2): 38 (6-59); eGRF < 30 ml/min: N = 29; dialysis: N = 4; haemoglobin < 10 g/dl: N = 43; platelet counts < 130 x 10^9/l: N = 11; 24-h urine (Bence-Jones protein) ≥ 2g: N = 15; LDH ≥ 300 IU/l: N = 7; light chain only myeloma: N = 10; total dose (range) of dexamethasone during first month (mg): 160 (0-480); dexamethasone ≥ 160 mg during first month: N = 45; dexamethasone ≥ 320 mg during first month: N = 24; dexamethasone ≥ 160 mg per cycle after first month (includes patients who survived and continued therapy after the first month, N = 56): N = 42; median (range) involved free light chains (iFLC; mg/l; N = 41): 1060 (6.3-30 000); iFLC ≥ 500 mg/l: N = 24; myeloma response ≥ PR: N = 38. - Bortezomib-based (N=43): Median (range) age = 65 (31-84) years; 22 males/21 females; Performance status ≥ 2: N = 28; ISS stage I: N = 3, II: N = 5, III: N = 35; median (range) eGFR (ml/min/1.73m^2): 21 (4-59); eGRF < 30 ml/min: N = 28; dialysis: N = 6; haemoglobin < 10 g/dl: N = 34; platelet counts < 130 x 10^9/l: N = 10; 24-h urine (Bence-Jones protein) ≥ 2g: N = 16; LDH ≥ 300 IU/l: N = 11; light chain only	1) Thalidomide-based regimen such as thalidomide with dexamethasone (TD); TD + cyclophosphamide, (CTD); thalidomide with vincristine, doxorubicin and dexamethasone (T-VAD); or melphalan, prednisone and thalidomide (MPT). 2) Bortezomib-based regimen such as bortezomib + dexamethasone (VD); bortezomib, thalidomide and dexamethasone (VTD; N = 9); or bortezomib, cyclophosphamide and dexamethasone (VCD)	3) Lenalidomide-based regimen such as lenalidomide with low-dose dexamethasone (Rd); or melphalan, prednisone and lenalidomide (MPR). Lenalidomide was given at doses adjusted for renal function.	Renal response - CR defined as increase of baseline eGFR to > 60 ml/min for at least 2 months, - PR defined as increase of eGFR from < 15 to 30-59 ml/min, - MR (minor response) defined as increase of baseline eGFR < 15 ml/min to 15-29 ml/min, or if baseline eGFR = 15-29 ml/min, improvement to 30-59 ml/min for at least 2 months, Myeloma response Survival
Follow-up	Median = 17.5 months				
Funding source	Unclear, not reported				

Dimopoulos et al. (2013)					
		myeloma: N = 14; total dose (range) of dexamethasone during first month (mg): 320 (0-480); dexamethasone ≥ 160 mg during first month: N = 38; dexamethasone ≥ 320 mg during first month: N = 28; dexamethasone ≥ 160 mg per cycle after first month (includes patients who survived and continued therapy after the first month, N = 56): N = 34; median (range) involved free light chains (iFLC; mg/l; N = 36): 2505 (18-24 400); iFLC ≥ 500 mg/l: N = 26; myeloma response ≥ PR: N = 33. - <u>Lenalidomide-based (N=28):</u> Median (range) age = 76 (63-86) years; 12 males/16 females; Performance status ≥ 2: N = 16; ISS stage I: N = 1, II: N = 6, III: N = 21; median (range) eGFR (ml/min/1.73m^2): 37 (6-58); eGRF < 30 ml/min: N = 11; dialysis: N = 0; haemoglobin < 10 g/dl: N = 14; platelet counts < 130 x 10^9/l: N = 3; 24-h urine (Bence-Jones protein) ≥ 2g: N = 7; LDH ≥ 300 IU/l: N = 1; light chain only myeloma: N = 4; total dose (range) of dexamethasone during first month (mg): 160 (80-320); dexamethasone ≥ 160 mg during first month: N = 16; dexamethasone ≥ 320 mg during first month: N = 1; dexamethasone ≥ 160 mg per cycle after first month (includes patients who survived and continued therapy after the first month, N = 27): N = 16; median (range) involved free light chains (iFLC; mg/l; N = 25): 1920 (3.2-28 800); iFLC ≥ 500 mg/l: N = 14; myeloma response ≥ PR: N = 23. Baseline differences between the groups: - Patients were significantly younger in the bortezomib group compared to the other two groups; - Anaemia was significantly more frequent and the doses of dexamethasone were significantly lower in the lenalidomide group compared to the the other two groups (moreover, the total dose of dexamethasone during the first month was significantly higher in the bortezomib group relative to			

Dimopoulos et al. (2013)					
		the other two groups). - The groups also differed significantly on median eGFR (ml/min/1.73m^2) (bortezomib significantly lower), dialysis (lenalidomide-based significantly lower), and LDH ≥ 300 IU/l (lenalidomide-based significantly lower, but unclear if it's relative to both of the other groups or just lower than bortezomib-based). In addition to the interventions, "in all patients additional measures were taken that included intravenous hydration, alkalization of urine, correction of hypercalcemia, discontinuation of all nephrotoxic agents and administration of antibiotic prophylaxis. Renal dialysis was offered when indicated."			
Results	**Renal function:** - Improvement of renal function (at least renalMR [minor response]): Thalidomide (74%), bortezomib (81%), lenalidomide (61%), p = 0.153. - Improvement of renal function (renalCR + renalPR): Thalidomide (55%), bortezomib (77%), lenalidomide (43%), p = 0.011. - Univariate odds ratio (OR) for thalidomide relative to lenalidomide = 1.62 (95% CI 0.66-3.98), p = 0.29 - Multivariate OR for thalidomide relative to lenalidomide (adjusting for age, eGFR, 24-hour urine, light chain only myeloma, myeloma response, and dexamethasone dose) = 2.36 (95% CI 0.87-6.41), p = 0.09 - Univariate odds ratio (OR) for bortezomib relative to lenalidomide = 4.4 (95% CI 1.57-12.32), p = 0.005 - Multivariate OR for bortezomib relative to lenalidomide (adjusting for age, eGFR, 24-hour urine, light chain only myeloma, myeloma response, and dexamethasone dose) = 4.25 (95% CI 1.3-13.94), p = 0.017 - Multivariate OR for bortezomib relative to thalidomide (adjusting for age, eGFR, and dexamethasone dose) = 2.3 (95% CI 0.91-6), p = 0.08 - Multivariate analyses performed on the patients with available involved free light chains (N = 102) adjusting for (at least) eGFR, objective myeloma-response, and dexamethasone dose: OR for bortezomib-based relative to lenalidomide (?) = 6.68 (95% CI 1.5-29.7), p = 0.013; thalidomide-based was not significant (p = 0.1) - Time to major renal response (renal CR + renal PR): "When we adjusted for differences between groups in multivariate analysis then bortezomib-based therapy was associated with shorter time to major renal response (OR: 1.71, 95% CI 1.01-3.5, P = 0.048) compared with lenalidomide-based therapy, whereas there was no significant difference between thalidomide and lenalidomide-based therapies (P = 0.141)." *No further details on which covariates the analysis actually adjusted for.* The authors also report that similar results were observed when the analyses was restricted to the the 102 patients with available involved free light chains. - Median time to achieve at least renalPR: Thalidomide: 2.7 months, bortezomib: 1.34 months, lenalidomide: In excess of 6 months; p = 0.028 (not reported which pairwise comparisons are significant) - Improvement of renal function (renalCR): Thalidomide (53%), bortezomib (67%), lenalidomide (36%), p = 0.032 - Median (range) baseline eGRF (ml/min/1.73 m^2) for patients who achieved renalCR: Thalidomide: 44 (6-58); lenalidomide: 49 (15-58), - Median (range) best eGRF (ml/min/1.73 m^2) for patients who achieved renalCR: Thalidomide: 86 (64-139); lenalidomide: 85 (65-106), *no inferential statistical analyses performed for these comparisons alone.* - Median (range) best eGRF (ml/min/1.73 m^2): Thalidomide: 69 (16-140); bortezomib: 77 (5-175), lenalidomide: 45 (15-106), p = 0.2. - Dialysis: Two of the thalidomide patients who required dialysis became dialysis-independent, and 3 of the bortezomib patients. **Myeloma response:** - Thalidomide (63%), bortezomib (81%), lenalidomide (82%), p = 0.05.				

Dimopoulos et al. (2013)	
	- Median time to myeloma response: Thalidomide: 61 days, bortezomib: 34 days, lenalidomide: 38 days - "some patients who did not achieve a myeloma PR improved their renal function to at least renalPR (7/22 (22%) in group T [thalidomide-based], 4/8 (50%) in group B [bortezomib-based] and 1/5 (20%) in group L [lenalidomide-based]). **Survival:** - Median: Thalidomide (36 months), bortezomib (53 months), lenalidomide (63 months), p = 0.57. - Early deaths (within the first 2 months from initiation of therapy): Thalidomide (10%), bortezomib (7%), lenalidomide (4%), p = 0.59.
Comments	There is complete overlap between these patients and those in Roussou et al. (2010) and substantial overlap between these patients and those in Kastritis et al. (2007). 9 patients in the bortezomib-based group also received thalidomide. - Observational, retrospective study - Patient selection bias (randomisation sequence, allocation concealment)? High risk – no randimisation - Performance bias (blinding of patients, personnel)? High risk – not within a trial - Detection bias (blinding of outcome assessor)? High risk – not within a trial - Attrition bias (missing data)? Unclear risk. - Reporting bias? High risk, adverse events/toxicity not reported - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Kastritis et al. (2007)					
Pub year: 2007		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Greece	Inclusion: Consecutive patients with newly diagnosed multiple myeloma and renal failure (defined as serum creatinine ≥ 2 mg/dl at the time of diagnosis), treated with high dose dexamethasone-based regimens. Patient characteristics only presented for the whole group, not split by treatment regimen: - <u>(N=41):</u> Median (range) age: 65 (42-91) years; 22 males/19 females; ISS stage I/II/III: N = 0/8/33; median (range) creatinine (mg/dl): 3.4 (2-12.8), ≥ 4: N = 18, < 4: N = 23; Myeloma type: IgG: N = 18, IgA: N = 8, light chain only: N = 15; Calcium (mg/dl): ≥ 11.5: N = 10, < 11.5: N = 31; LDH (IU/l): > 300: N = 7, ≤ 300: N = 34; BJ protein (g/day): ≥ 2: N = 14, < 2: N = 27; Anaemia (Hb < 10 g/dl): Yes: N = 32, No: N = 9; BM PCs %: > 40: N = 32, ≤ 40: N = 9. "Besides antimyeloma treatment, all patients received intensive supportive care including intravenous hydration, alkalinisation of urine, correction of hypercalcemia, and discontinuation of all potential peohrotoxic agents. Renal dialysis was offered to all patients with an appropriate indication." - 10 patients required renal replacement with dialysis - No patients received plasmapheresis	Group A: VAD, VAD-like regimens, melphalan plus high-dose dexamethasone or high-dose dexamethasone alone (N = 26)	Group B: High-dose dexamethasone (40 mg daily on days 1-4 and 9-12 with thalidomide 100 mg PO daily every 4 weeks (N = 13), or high-dose dexamethasone (40 mg daily on days 1-4 and 9-12 with bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, 11 every 3 weeks (N = 1) or high-dose dexamethasone (40 mg daily on days 1-4 and 9-12 with bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, 11 every 3 weeks with added thalidomide 100 mg PO (N = 1).	Reversability of renal failure defined as a sustained decrease of serum creatinine to < 1.5 mg/dl. Myeloma response
N	41				
Follow-up	Unclear, not reported				
Funding source	Unclear, not reported				

Kastritis et al. (2007)	
Results	**Renal function:** - Reversal of renal failure: Group A (N = 18) = group B (N = 12), p = 0.45. - Median time to reversal of renal failure: Group A (2 months) > group B (0.8 months), p = 0.005. **Myeloma response (≥ partial response):** - Group A (46%) = Group B (64%), p = 0.27.
Comments	There is substantial overlap between these patients and those in Dimopoulos et al. (2013) and in Roussou et al. (2010). - Observational, retrospective study - Patient selection bias (randomisation sequence, allocation concealment)? High risk – no randomisation - Performance bias (blinding of patients, personnel)? High risk – not within a trial - Detection bias (blinding of outcome assessor)? High risk – not within a trial - Attrition bias (missing data)? Unclear risk. - Reporting bias? High risk, adverse events/toxicity not reported - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Morabito (2011).					
Pub year: 2014		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Italy	Inclusion: "Patients with newly diagnosed MM who were ineligible for autologous stem cell transplantation participated in the trial". Exclusion: sCR ≥ 2.5 mg/dl. The trial also reports on patients with normal renal function (defined as eGFR > 50ml/min), however these patients are not relevant to the current question, so are not reported here. - <u>VMPT-VT (N=70, divided into eGFR ≤ 30 and eGFR 31-50):</u> - eGFR ≤ 30: N = 14; Median age, years: 74.5; % male: 42.9%; KPS ≤ 70: 35.7%; ISS stage III: 90%; median β_2 microglobulin (mg/L): 10.3; median albumin (g/dl): 3.5; bortezomib schedule once weekly: 85.7%, twice weekly: 14.3%. 0 patients had eGFR ≤ 20 ml/min. - eGFR 31-50: N = 56; Median age, years: 73.5; % male: 39.3%; KPS ≤ 70: 33.9%; ISS stage III: 34.7%; median β_2 microglobulin (mg/L): 4.6; median albumin (g/dl): 3.6; bortezomib schedule once weekly: 71.4%, twice weekly: 28.6%. - <u>VMP (N=79, divided into eGFR ≤ 30 and eGFR 31-50):</u> - eGFR ≤ 30: N = 19; Median age, years: 72; % male: 31.6%; KPS ≤ 70: 31.6%; ISS stage III: 73.3%; median β_2 microglobulin (mg/L): 7.2; median albumin (g/dl): 4; bortezomib schedule once weekly: 89.5%, twice weekly: 10.5%. 2 patients had eGFR ≤ 20 ml/min. - eGFR 31-50: N = 60; Median age, years: 74; % male: 46.7%; KPS ≤ 70: 31.7%; ISS stage III: 48.9%; median β_2 microglobulin (mg/L): 5.4; median albumin (g/dl): 3.7; bortezomib schedule once weekly: 71.7%, twice weekly: 28.3%. "After the inclusion of the first 139 patients, the protocol was amended to reduce the incidencve of peripheral neuropathy. Both	VMPT-VT: Induction treatment with 9 cycles, each lasting 6 weeks, of melphalan 9mg/m^2 on days 1-4; prednisone 60mg/m^2 on days 1-4; bortezomib 1.3mg/m^2 on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1-4 and in days 1, 8, 22 and 29 during cycles 5-9; and thalidomide 50mg/d continuously. Patients received maintenance therapy with bortezomib 1.3mg/m^2 every 14 days and thalidomide 50mg/d for 2 years or until progression or relapse.	VMP: "Standard VMP [bortezomib, melphalan-prednisone] therapy consisted of induction therapy with 9 cycles of VMP (6 weeks each), at the doses described previously, without maintenance" *Unclear if the VMP doses referred to are the same as those in the VMPT-VT group or not?*	Response Progression-free survival Overall survival Adverse events
Design, period	RCT Study years not reported				
N	149				
Follow-up	Median: 21.6 months				
Funding source	Fondazione "Amelia Scorza" Onlus, Cosenza, Italy				

Morabito (2011).					
		induction schedules were changed to 9 cycles (5 weeks each) and the bortezomib dose was modified to 1.3mg/m^2 on days 1, 8, 15, and 22 during cycles 1-9."			
Results	**<u>eGFR ≤ 30</u>:** **Myeloma response:** **-** Response-evaluable: VMPT-VT: N = 11; VMP: N = 19 - Response rate: VMPT-VT (81.8%) = VMP (68.4%), p = 0.3. - CR rate: VMPT-VT (36.4%) = VMP (15.8%), p = 0.2. - Median time to first response: VMPT-VT (1.2 months) = VMP (1.4 months), p = 0.62. - Median duration of response: VMPT-VT (19.8 months) = VMP (20 months), p = 0.18. **Reversal of renal impairment:** **-** VMPT-VT (0 patients), VMP (2/19), p = 0.25. **Progression-free survival:** - Median: VMPT-VT (20.9 months), VMP (22.5 months). HR 0.9, 95% CI 0.2-3.6, p = 0.9. - 1-year: VMPT-VT (80%), VMP (83%). - 2-year: VMPT-VT (40%),VMP (46%). **Overall survival:** - Median: VMPT-VT (not reached), VMP (not reached). - 1-year: VMPT-VT (75.2%), VMP (88.9%). - 2-year: VMPT-VT (60.2%), VMP (83.3%, p = 0.25). **Adverse events:** "All renal cohorts received a median of 9 treatment cycles, whereas those treated with VMPT having eGFR ≤ 30 ml/min received a median of 7.5 cycles. Grade 3/4 adverse events during induction treatment: neutropenia (VMTP-VT: 8/14; VMP: 4/19; p = 0.033), thrombocytopenia (VMTP-VT: 6/14; VMP: 6/19), anaemia (VMTP-VT: 4/14; VMP: 6/19), cardiologic events (VMTP-VT: 3/14; VMP: 1/19), infections (VMTP-VT: 1/14; VMP: 4/19), gastrointestinal events (VMTP-VT: 2/14; VMP: 2/19), vascular events (VMTP-VT: 2/14; VMP: 0/19), systemic events (VMTP-VT: 2/14; VMP: 2/19), dermatologic events (VMTP-VT: 1/14; VMP: 0/19), sensory neuropathy and/or neuralgia (VMTP-VT: 3/14; VMP: 2/19), discontinuation attributable to adverse events (VMTP-VT: 4/14; VMP: 4/19). **<u>eGFR 30-51:</u>** **Myeloma response:** **-** Response-evaluable: VMPT-VT: N = 52; VMP: N = 58 - Response rate: VMPT-VT (96.2%) > VMP (81%), p = 0.026. - CR rate: VMPT-VT (42.3%) = VMP (25.9%), p = 0.07. - Median time to first response: VMPT-VT (1.4 months) = VMP (1.4 months), p = 0.61. - Median duration of response: VMPT-VT (not reached) = VMP (22 months), p = 0.47. **Progression-free survival:** - Median: VMPT-VT (not reached), VMP (24.2 months). HR 2.1, 95% CI 1.1-4.3, p = 0.033, favouring VMPT-VT. - 1-year: VMPT-VT (96%), VMP (89%). - 2-year: VMPT-VT (73%),VMP (57%). **Overall survival:** - Median: VMPT-VT (not reached), VMP (not reached). - 1-year: VMPT-VT (94.2%), VMP (93.1%). - 2-year: VMPT-VT (89.6%), VMP (88.7%). **Adverse events:** "All renal cohorts received a median of 9 treatment cycles, whereas those treated with VMPT having eGFR ≤ 30 ml/min received a median of 7.5 cycles. Grade 3/4 adverse events during induction treatment: neutropenia (VMTP-VT: 25/56; VMP: 21/60), thrombocytopenia (VMTP-VT: 17/56; VMP: 19/60), anaemia (VMTP-VT: 12/56; VMP: 8/60), cardiologic events (VMTP-VT: 9/56; VMP: 4/60), infections (VMTP-VT: 10/56; VMP: 6/60), gastrointestinal events (VMTP-VT: 5/56; VMP: 3/60), vascular events (VMTP-VT: 5/56; VMP: 1/60), systemic events (VMTP-VT: 6/56; VMP: 3/60), dermatologic events (VMTP-VT: 4/56; VMP: 1/60), sensory neuropathy and/or neuralgia (VMTP-VT: 7/56; VMP: 4/60), discontinuation attributable to adverse events (VMTP-VT: 14/56; VMP: 6/60, p = 0.033). **<u>And grouped together as eGFR ≤ 50</u>:** **Myeloma response:** **-** Response-evaluable: VMPT-VT: N = 63; VMP: N = 77 - Response rate: VMPT-VT (93.7%) > VMP (77.9%), p = 0.015. - CR rate: VMPT-VT (41.3%) > VMP (23.4%), p = 0.025.				

Morabito (2011).	
	- Median time to first response: VMPT-VT (1.4 months) = VMP (1.4 months), p = 0.51. - Median duration of response: VMPT-VT (not reached) = VMP (21.8 months), p = 0.83. - Renal response according to the criteria of Ludwig et al.: VMPT-VT (25.4%), VMP (40.3%); none of the patients had a partial renal response, but 7 and 8, VMPT-VT and VMP patients, respectively, had a minimal renal response. **Reversal of renal impairment:** - Reversal rate: VMPT-VT (16/63 patients), VMP (31/77 patients), p = 0.092. Multivariate analysis adjusting for age, sex, KPS, eGFR, β_2 microglobulin, albumin, LDH serum levels, cytogenetic risk, response, and bortezomib schedule (once or twice daily): OR = 1.87, 95% CI 0.9-3.9, p = 0.9. (Univeriate p = 0.06). - Time to reversal of renal impairment: VMTP-VT (median = 2.3 months, range 0.5-12 months) = VMP (median = 2.2 months, range 0.4-10 months); HR = 0.61, 95% CI 0.33-1.11, p = 0.11. **Progression-free survival:** - Median: VMPT-VT (not reached), VMP (24.2 months). HR 1.9, 95% CI 1.1-3.5, p = 0.043, favouring VMPT-VT. - 1-year: VMPT-VT (96%), VMP (87%). - 2-year: VMPT-VT (69%),VMP (54%). **Overall survival:** - Median: VMPT-VT (not reached), VMP (not reached). Unclear if overall survival differs significantly between the treatment groups as text says no, but figure (2A) suggests yes. - 1-year: VMPT-VT (90.7%), VMP (92.1%). - 2-year: VMPT-VT (84.2%), VMP (87.3%). **Adverse events:** "All renal cohorts received a median of 9 treatment cycles, whereas those treated with VMPT having eGFR ≤ 30 ml/min received a median of 7.5 cycles. Grade 3/4 adverse events during induction treatment: neutropenia (VMTP-VT: 33/70; VMP: 25/79), thrombocytopenia (VMTP-VT: 23/70; VMP: 25/79), anaemia (VMTP-VT: 16/70; VMP: 14/79), cardiologic events (VMTP-VT: 12/70; VMP: 5/79), infections (VMTP-VT: 11/70; VMP: 10/79), gastrointestinal events (VMTP-VT: 7/70; VMP: 5/79), vascular events (VMTP-VT: 7/70; VMP: 1/79), systemic events (VMTP-VT: 8/70; VMP: 5/79), dermatologic events (VMTP-VT: 5/70; VMP: 1/79), sensory neuropathy and/or neuralgia (VMTP-VT: 10/70; VMP: 6/79), discontinuation attributable to adverse events (VMTP-VT: 18/70; VMP: 10/79).
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – RCT but no details provided - Performance bias (blinding of patients, personnel)? Unclear risk – no details reported - Detection bias (blinding of outcome assessor)? Unclear risk – no details reported - Attrition bias (missing data)? Data from all included patients available - Reporting bias? Low risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Roussou et al. (2010)					
Pub year: 2010		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Greece	Inclusion: Consecutive patients with newly diagnosed multiple myeloma and renal impairment ("defined as a sustained estimated creatinine clearance (CrCl) < 50 ml/min calculated by the Cockroft-Gault formula, despite volume replacement and reversal of hypercalcaemia"). - <u>Conventional chemotherapy (N=32):</u> Age: ≥ 75 years: N = 10, < 75 years: N = 22; 21 males/11 females; ISS stage I: N = 1, II: N = 7, III: N = 23; Creatinine clearance (ml/min): median (range) = 29.2 (4.7-48.3), ≥ 30: N = 15, < 30: N = 17; Myeloma type: IgG: N = 14, IgA: N = 9, light chain only: N = 8; Calcium (mg/dl): ≥ 11.5: N = 9, < 11.5: N =	1) Conventional chemotherapy (CC) plus dexamethasone (VAD, VAD-like regimens, melphalan plus dexamethasone). 2) Bortezomib and dexamethasone-containing regimens	3) IMiDs-based regimens (thalidomide or lenalidomide with high-dose dexamethasone and/or cyclophosphamide or melphalan).	Renal response - CR defined as improvement of CrCl from < 50 ml/min at baseline to ≥ 60 ml/min for at least 2 months, - PR defined as improvement of CrCl from < 15 ml/min at baseline to 30-59 ml/min for at least 2 months, - MR (minor
Design, period	Retrospective, Ca 2000-2009/10				
N	96				
Follow-up	Unclear, not reported				
Funding source	Unclear, not reported				

Roussou et al. (2010)					
		23; LDH (IU/l): > 300: N = 5, ≤ 300: N = 27; BJ protein (g/day): ≥ 2: N = 8, < 2: N = 23; Anaemia (Hb < 10 g/dl): Yes: N = 21, No: N = 11; BM PC%: > 40: N = 23, ≤ 40: N = 9. - Bortezomib-based (N=17): Age: ≥ 75 years: N = 3, < 75 years: N = 14; 7 males/10 females; ISS stage I: N = 0, II: N = 1, III: N = 16; Creatinine clearance (ml/min): median (range) = 20.6 (3.9-48.5), ≥ 30: N = 4, < 30: N = 13; Myeloma type: IgG: N = 7, IgA: N = 2, light chain only: N = 7; Calcium (mg/dl): ≥ 11.5: N = 6, < 11.5: N = 11; LDH (IU/l): > 300: N = 2, ≤ 300: N = 15; BJ protein (g/day): ≥ 2: N = 7, < 2: N = 9; Anaemia (Hb < 10 g/dl): Yes: N = 16, No: N = 1; BM PC%: > 40: N = 16, ≤ 40: N = 1. - IMiDs-based (N=47): Age: ≥ 75 years: N = 28, < 75 years: N = 19; 24 males/23 females; ISS stage I: N = 1, II: N = 15, III: N = 31; Creatinine clearance (ml/min): median (range) = 29.9 (8.3-49.3), ≥ 30: N = 22, < 30: N = 25; Myeloma type: IgG: N = 20, IgA: N = 22, light chain only: N = 4; Calcium (mg/dl): ≥ 11.5: N = 10, < 11.5: N = 37; LDH (IU/l): > 300: N = 3, ≤ 300: N = 44; BJ protein (g/day): ≥ 2: N = 10, < 2: N = 34; Anaemia (Hb < 10 g/dl): Yes: N = 31, No: N = 16; BM PC%: > 40: N = 36, ≤ 40: N = 11. Baseline differences between the groups: Patients in the IMiDs-bassed group were significantly older than those in the other two groups, more patients in the bortezomib-based group had light chain only multiple myeloma. In addition to the interventions, all patients received additional measures that included intravenous hydration, alkalization of urine, correction of hypercalcemia, and discontinuation of all nephrotoxic agents. Renal dialysis was offered when indicated.			response) defined as improvement of CrCl from < 15 at baseline to 15-29 ml/min, or if baseline CrCl = 15-29 ml/min, improvement to 30-59 ml/min for at least 2 months. Myeloma response

Roussou et al. (2010)	
Results	**Renal function:** - Improvement of renal function (at least renalMR [minor response]): Conventional chemotherapy (59%), bortezomib-based (94%), IMiDs-based (79%), p = 0.02 (worse in conventional chemotherapy group relative to the other two groups, unclear if these differ from each other). - Improvement of renal function (renalCR + renalPR): Conventional chemotherapy (47%), bortezomib (82%), IMiDs-based (51%), p = 0.043. Pairwise analyses suggest that bortezomib was superior to the other two groups, which did not differ from each other. Multivariate analyses (not reported which variables are included in the analyses apart from creatinine clearance and not myeloma response) give the following OR for bortezomib-based treatment: OR = 7, 95% CI 1.5-25, p = 0.024. - Improvement of renal function (renalCR): Conventional chemotherapy (41%), bortezomib (71%), IMiDs-based (45%), p = 0.11. - Median (range) time to major renal response (renal CR + renal PR): Conventional chemotherapy (1.8 months, 0.03-8 months) = IMiDs-based (1.6 months, 0.1-6 months), p = 0.65*;* but it was significantly shorter for the bortezomib-based group: 0.69 months (0.07-3 months), p = 0.007. Multivariate analyses (not reported which variables are included in the analyses apart from creatinine clearance) give the following OR for bortezomib-based treatment: OR = 2.5, 95% CI 1.6-6.7, p = 0.009. - "Among nine patients who required renal dialysis two patients who were treated with bortezomib-based regimens became independent of this procedure". **Myeloma response (≥ partial response):** - Conventional chemotherapy (57%), bortezomib (82%), IMiDs-based (69%), *unclear if these rates differ significantly*. - *Improvement of renal response without myeloma response:* Conventional chemotherapy (N = 3), bortezomib (N = 4), IMiDs-based (N = 9), *no inferential statistical analyses performed for this comparison.*
Comments	There is complete overlap between these patients and those in Dimopoulos et al. (2013), and substantial overlap between these patients and those in Kastritis et al. (2007). - Observational, retrospective study - Patient selection bias (randomisation sequence, allocation concealment)? High risk – no randimisation - Performance bias (blinding of patients, personnel)? High risk – not within a trial - Detection bias (blinding of outcome assessor)? High risk – not within a trial - Attrition bias (missing data)? Unclear risk. - Reporting bias? High risk, adverse events/toxicity not reported - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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San-Miguel et al. (2008)					
Pub year: 2008		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	International	Inclusion: This is the APEX phase 3 study. "Patients were required to have calculated CrCl [creatinine clearance] ≥ 20 ml/min^{-1}". The patients were divided into four groups depending on their CrCl: < 30, 30-50, 51-80, and > 80. Data on the former two groups are reported here. - <u>Bortezomib (N = 62, divided into CrCL < 30 and 31-50):</u> - CrCl < 30: N = 17; Median age, years: 69; % male: 35%; KPS ≥ 80%: 53%; ISS stage I/II/III: 0%/0%/100%; median β_2 microglobulin (mg l^{-1}): 11.7; β_2 microglobulin ≥ 5.5 mg/L: 100%; creatinine ≥ 1.5 mg per 100 ml: 100%; median haemoglobin (g l^{-1}): 99; median serum calcium (mmol l^{-1}): 2.3. - CrCl 30-50: N = 45; Median age, years: 71; % male: 47%; KPS ≥ 80%: 84%; ISS stage I/II/III: 16%/29%/56%; median β_2 microglobulin (mg l^{-1}): 5.9;	Bortezomib: 1.3mg m^{-2} on days 1, 4, 8, and 11, for eight 3-week cycles and then on days 1, 8, 15 and 22 for three 5-week cycles.	Dexamethasone: 40 mg on days 1-4, 9-12 and 17-20 for four 5-week cycles and trhen on days 1-4 for five 4-week cycles.	Response Progression-free survival Overall survival Adverse events
Design, period	RCT Study years not reported				
N	130				
Follow-up	Median: ≤22 months				
Funding source	Johnson & Johnson Pharmaceutical Research & Development LLC and Millennium Pharmaceuticals				

San-Miguel et al. (2008)					
		β_2 microglobulin ≥ 5.5 mg/L: 53%; creatinine ≥ 1.5 mg per 100 ml: 51%; median haemoglobin (g l^{-1}): 103.5; median serum calcium (mmol l^{-1}): 2.3. - <u>Dexamethasone (N = 68, divided into CrCL < 30 and 31-50):</u> - CrCl < 30: N = 17; Median age, years: 61; % male: 45%; KPS ≥ 80%: 82%; ISS stage I/II/III: 0%/0%/100%; median β_2 microglobulin (mg l^{-1}): 11.6; β_2 microglobulin ≥ 5.5 mg/L: 100%; creatinine ≥ 1.5 mg per 100 ml: 100%; median haemoglobin (g l^{-1}): 99; median serum calcium (mmol l^{-1}): 2.3. - CrCl 30-50: N = 57; Median age, years: 67; % male: 53%; KPS ≥ 80%: 75%; ISS stage I/II/III: 16%/18%/65%; median β_2 microglobulin (mg l^{-1}): 6.7; β_2 microglobulin ≥ 5.5 mg/L: 64%; creatinine ≥ 1.5 mg per 100 ml: 58%; median haemoglobin (g l^{-1}): 103; median serum calcium (mmol l^{-1}): 2.4.			
Results	**<u>CrCl < 30</u>:** **Myeloma response:** **-** Response-evaluable: Bortezomib: N = 15; Dexamethasone: N = 10 - Response rate (CR + PR): Bortezomib (47%), Dexamethasone (10%). - CR response rate: Bortezomib (0%), Dexamethasone (0%). - PR response rate: Bortezomib (47%), Dexamethasone (10%). - Median time to first response: Bortezomib (1.6 month), Dexamethasone (1.4 month) **Time-to-progression:** - Median [95% CI]: Bortezomib (4.2 months [1.4-7.7]), Dexamethasone (2.1 months [1.9-6.7]). **Overall survival:** - Median [95% CI]: Bortezomib (22 months [18.2-NE]), Dexamethasone (17.4 months [5.5-NE]). **Adverse events:** - At least one AE of any grade(bortezomib: 17/17; dexamethasone: 11/11); diarrhoea NOS (bortezomib: 12/17; dexamethasone: 1/11); nausea (bortezomib: 11/17); constipation (bortezomib: 8/17; dexamethasone: 5/11); fatigue (bortezomib: 9/17; dexamethasone: 3/11); vomiting NOS (bortezomib: 8/17); thrombocytopenia (bortezomib: 4/17); pyrexia (bortezomib: 9/17; dexamethasone: 1/11); anaemia NOS (bortezomib: 5/17; dexamethasone: 4/11); peripheral neuropathy (bortezomib: 1/17); headache NOS (bortezomib: 7/17); anorexia (bortezomib: 5/17); cough (bortezomib: 7/17); paraesthesia (bortezomib: 1/17); insomnia (dexamethasone: 3/11); dyspnea NOS (dexamethasone: 2/11); hyperglycemia NOS (dexamethasone: 0/11); muscle cramps (dexamethasone: 3/11); bone pain (dexamethasone: 0/11); - At least one grade ≥ 3 AE (bortezomib: 14/17; dexamethasone: 9/11); Thrombocytopenia (bortezomib: 4/17; dexamethasone: 0/11); neutropenia (bortezomib: 0/17); anaemia NOS (bortezomib: 2/17; dexamethasone: 4/11); peripheral neuropathy (high level term; bortezomib: 0/17); diarrhoea NOS (bortezomib: 1/17); dyspnea NOS (bortezomib: 1/17); fatigue (bortezomib: 2/17); hyperglycemia (dexamethasone: 0/11); pneumonia NOS (dexamethasone: 2/11); - At least one SAE (bortezomib: 12/17; dexamethasone: 7/11); patients discontinuing treatment due to AE (bortezomib: 7/17; dexamethasone: 4/11); patients with dose reductions/interruptions due to AEs (bortezomib: 12/17; dexamethasone: 2/11). **<u>CrCl 30-50</u>:** **Myeloma response:** **-** Response-evaluable: Bortezomib: N = 43; Dexamethasone: N = 52 - Response rate (CR + PR): Bortezomib (37%), Dexamethasone (17%). - CR response rate: Bortezomib (9%), Dexamethasone (2%). - PR response rate: Bortezomib (28%), Dexamethasone (15%). - Median time to first response: Bortezomib (0.7 month), Dexamethasone (0.8 month) **Time-to-progression:** - Median [95% CI]: Bortezomib (5.6 months [4.2-9.4]), Dexamethasone (2.9 months [2.4-4.3]). **Overall survival:**				

San-Miguel et al. (2008)	
	- Median [95% CI]: Bortezomib (22.8 months [14-NE]), Dexamethasone (12.6 months [8.3-27]). **Adverse events:** - At least one AE of any grade(bortezomib: 44/44; dexamethasone: 56/56); diarrhoea NOS (bortezomib: 24/44; dexamethasone: 12/56); nausea (bortezomib: 24/44); constipation (bortezomib: 23/44; dexamethasone: 7/56); fatigue (bortezomib: 18/44; dexamethasone: 20/56); vomiting NOS (bortezomib: 17/44); thrombocytopenia (bortezomib: 17/44); pyrexia (bortezomib: 15/44; dexamethasone: 11/56); anaemia NOS (bortezomib: 12/44; dexamethasone: 15/56); peripheral neuropathy (bortezomib: 7/44); headache NOS (bortezomib: 5/44); anorexia (bortezomib: 13/44); cough (bortezomib: 6/44); paraesthesia (bortezomib: 10/44); insomnia (dexamethasone: 10/56); dyspnea NOS (dexamethasone: 11/56); hyperglycemia NOS (dexamethasone: 9/56); muscle cramps (dexamethasone: 5/56); bone pain (dexamethasone: 10/56); - At least one grade ≥ 3 AE (bortezomib: 30/44; dexamethasone: 44/56); Thrombocytopenia (bortezomib: 15/44; dexamethasone: 6/56); neutropenia (bortezomib: 4/44); anaemia NOS (bortezomib: 6/44; dexamethasone: 9/56); peripheral neuropathy (high level term; bortezomib: 4/44); diarrhoea NOS (bortezomib: 3/44); dyspnea NOS (bortezomib: 0/44); fatigue (bortezomib: 3/44); hyperglycemia (dexamethasone: 5/56); pneumonia NOS (dexamethasone: 4/56); - At least one SAE (bortezomib: 18/44; dexamethasone: 33/56); patients discontinuing treatment due to AE (bortezomib: 16/44; dexamethasone: 25/56); patients with dose reductions/interruptions due to AEs (bortezomib: 32/44; dexamethasone: 26/56). **And grouped together as CrCl ≤ 50:** **Myeloma response:** **-** Response-evaluable: Bortezomib: N = 58; Dexamethasone: N = 62 - Response rate (CR + PR): Bortezomib (40%), Dexamethasone (16%). - CR response rate: Bortezomib (7%), Dexamethasone (2%). - PR response rate: Bortezomib (33%), Dexamethasone (15%). - Median time to first response: Bortezomib (1.4 month), Dexamethasone (0.8 month) **Time-to-progression:** - Median [95% CI]: Bortezomib (4.9 months [4.2-7.7]), Dexamethasone (2.8 months [2.4-4.1]); p = 0.02. **Overall survival:** - Median [95% CI]: Bortezomib (22.8 months [18.2-NE]), Dexamethasone (12.6 months [9.8-27]); p = 0.09. **Adverse events:** - At least one AE of any grade(bortezomib: 61/61; dexamethasone: 67/67); diarrhoea NOS (bortezomib: 36/61; dexamethasone: 13/67); nausea (bortezomib: 35/61); constipation (bortezomib: 31/61; dexamethasone: 12/67); fatigue (bortezomib: 27/61; dexamethasone: 23/67); vomiting NOS (bortezomib: 25/61); thrombocytopenia (bortezomib: 21/61); pyrexia (bortezomib: 24/61; dexamethasone: 12/67); anaemia NOS (bortezomib: 17/61; dexamethasone: 19/67); peripheral neuropathy (bortezomib: 8/61); headache NOS (bortezomib: 12/61); anorexia (bortezomib: 18/61); cough (bortezomib: 13/61); paraesthesia (bortezomib: 11/61); insomnia (dexamethasone: 13/67); dyspnea NOS (dexamethasone: 13/67); hyperglycemia NOS (dexamethasone: 9/67); muscle cramps (dexamethasone: 8/67); bone pain (dexamethasone: 10/67); - At least one grade ≥ 3 AE (bortezomib: 44/61; dexamethasone: 53/67); Thrombocytopenia (bortezomib: 19/61; dexamethasone: 6/67); neutropenia (bortezomib: 4/61); anaemia NOS (bortezomib: 8/61; dexamethasone: 13/67); peripheral neuropathy (high level term; bortezomib: 4/61); diarrhoea NOS (bortezomib: 4/61); dyspnea NOS (bortezomib: 2/61); fatigue (bortezomib: 5/61); hyperglycemia (dexamethasone: 5/67); pneumonia NOS (dexamethasone: 6/67); - At least one SAE (bortezomib: 30/61; dexamethasone: 40/67); patients discontinuing treatment due to AE (bortezomib: 23/61; dexamethasone: 29/67); patients with dose reductions/interruptions due to AEs (bortezomib: 44/61; dexamethasone: 28/67).
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – RCT but no details provided - Performance bias (blinding of patients, personnel)? Unclear risk – no details reported - Detection bias (blinding of outcome assessor)? Unclear risk – no details reported - Attrition bias (missing data)? Data from all included patients available - Reporting bias? Low risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Scheid (2014).					
Pub year: 2014		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	Belgium, the Netherlands,	Inclusion: "patients with newly diagnosed symptomatic MM Durie	PAD: Induction treatment with	VAD: Vincristine,	Response

Scheid (2014).					
	Germany	and Salmon stage II or III aged between 18 and 65 years and with adequate performance status". "Renal function was assessed by serum creatinine level at study baseline (BLC) and classified using a cut-off BLC of 2 mg/dl". *Only data from patients with BLC ≥ 2 mg/dl are reported here.* Exclusion: "presence of systemic AL amyloidosis, non-secretory MM, neuropathy grade 2 or higher, a history of active malignancy during the past 5 yearsa, positivity for human immunodeficiency virus, or hepatic dysfunction." - <u>PAD (N=36):</u> Median age (range), years: 57 (38-64); gender not reported; median (range) creatinine (mg/dl): 3.32 (2.1-8.99); ISS stage II/III/unknown: 3/28/5; median (range) beta 2 MG (mg/L): 13.3 (4.2-44.8). - <u>VAD (N=45):</u> Median age (range), years: 57 (39-65); gender not reported; median (range) creatinine (mg/dl): 3.36 (2-18.3); ISS stage II/III/unknown: 3/38/4; median (range) beta 2 MG (mg/L): 13.3 (4.9-63). There were no significant differences between the VAD- and PAD-arms.	bortezomib, doxorubicin and dexamethasone, high dose melphalan/ASCT, followed by maintenance with bortezomib 1.3 mg/m^2 i.v. two-weekly for 2 years. High-dose melphalan was given at a dose of 200 mg/m^2 or 100 mg/m^2 in patients with creatinine clearance < 40 ml/min.	doxorubicin and dexamethasone induction therapy, intensification with high-dose melphalan and ASCT, followed by maintenance therapy with thalidomide 50 mg daily. High-dose melphalan was given at a dose of 200 mg/m^2 or 100 mg/m^2 in patients with creatinine clearance < 40 ml/min.	Progression-free survival Overall survival Adverse events
Design, period	RCT Study years not reported				
N	81				
Follow-up	Not reported				
Funding source	Dutch Cancer Foundation, the German Federal Ministry of Education and Research, Janssen-Cilag, Novartis, Amgen, Chugai and Roche.				
Results	**Treatment received:** - 80/81 patients received at least one cycle of induction treatment - Non-completion of induction treatment: VAD: N = 12; PAD: N = 6 - 57/81 patients received high-dose melphalan (VAD: N = 29; PAD: N = 28), to the full dose of 200 mg/m^2 in 39 patients, at 140 mg/m^2 to 1 patient and at 100 mg/m^2 in 17 patients. - After high-dose therapy 42/57 patients started maintenance therapy: VAD: N = 20; PAD: N = 22. **Adverse events:** "Within the patients with BLC ≥ 2 mg/dl there were no significant differences in the frequency and type of adverse events between the VAD-arm and the PAD-arm (all CTC grade 2: 3-% versus 39%, grade 3: 32% versus 31%, grade 4: 14% versus 19%). **Renal response:** - Renal function before high-dose therapy: - Median (range) creatinine level: VAD (1.41 (0.65-6.9) ml/mg) = PAD (1.1 (0.6-5.9) mg/dl), p = 0.43. - Median (range) creatinine clearance: VAD (51 (12-147) ml/min) = PAD (65 (11-180) mg/min), p = 0.42. - Renal response after 3 cycles of induction treatment: VAD (13 CR, 1 PR, 5 MR; overall response rate = 63%) = PAD (18 CR, 7 MR; overall response rate = 81%), p = 0.31. **Myelomal response:** - Response after 1-3 cycles of induction treatment: VAD (overall response rate = 36% with 9% of patients achieving at least a very good PR) < PAD (overall response rate = 75% with 33% of patients achieving at least a very good PR), p = 0.003. - Best response achieved any time during trial treatment: VAD (64% with 13% CR) < PAD (89% with 36% CR), p = 0.01. **Progression-free survival:** - 3-year: VAD (16%) < PAD (48%), p = 0.004. **Overall survival:** - 3-year: VAD (34%) < PAD (74%), HR = 0.33, 95% CI = 0.16-0.65, p < 0.001.				
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? Unclear risk – RCT but no details provided - Performance bias (blinding of patients, personnel)? Unclear risk – no details reported - Detection bias (blinding of outcome assessor)? Unclear risk – no details reported				

Scheid (2014).	
	- Attrition bias (missing data)? Data from all included patients available - Reporting bias? Low risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.

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Song (2012).					
Pub year: 2012		**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**
Country	South Korea	Inclusion: "Elderly MM patients having RI [renal impairment] (<90 ml/min/1.73 m2) in chronic kidney disease (CKD) classification calculated by the Modification of Diet in Renal Disease (MDRD) formula".. Exclusion: "MM patients receiving dialysis or CKD classification stage 5 (GFR <15 ml/min/1.73 m2). Therefore, CKD stages I and V were excluded, as well as MM patients with RI by other causes including MM patients having evidence of combined amyloidosis or light chain deposition disease, and MM patients having poor performance status such as Eastern Cooperative Oncology Group performance status≥2." - MPT (N=74): Median age, years (range): 69 (65-80); ≥ 75 years: N = 13; Gender male/female: 40/34; ISS stage I/II/III: 5/30/39; median serum β_2 MG, mg/l (range): 5.53 (2.2-23.1); median serum albumin, g/dl (range): 3.3 (2-4.6); median haemoglobin, g/dl (range): 9.7 (6.2-14); median serum creatinine, mg/dl (range): 1.3 (0.9-2.8); median serum calcium, mg/dl (range): 9.3 (7-13.8); median bone marrow plasma cell (range): 32.2% (12.1%-95.3%); median GFR, ml/min/1.73m^2 (range): 45 (16-84); M protein type: IgG/IgA/light chain only/others: 35/26/10/3; light chain type: κ: N = 32, λ: N = 42; renal impairment stage: Stage 2 (GFR, 60-89 ml/min/1.73m^2): 21, Stage 3 (GFR, 30-59 ml/min/1.73m^2): 36, Stage 4 (GFR, 15-29 ml/min/1.73m^2): 17. - TCD (N=83): Median age, years (range): 69 (65-85); ≥ 75 years: N = 15; Gender male/female: 50/33; ISS stage I/II/III: 9/28/46; median serum β_2 MG, mg/l (range): 5.7 (1.6-16.23); median serum albumin, g/dl (range): 3.2 (2.1-4.9); median haemoglobin, g/dl (range): 8.9 (6.3-14.8); median serum creatinine, mg/dl (range): 1.5 (0.8-5.4); median serum calcium, mg/dl (range): 9.2 (7.2-15.3); median bone marrow plasma cell (range): 30% (10%-98%); median GFR, ml/min/1.73m^2 (range): 41 (14-84); M protein type: IgG/IgA/light chain only/others: 43/27/9/4; light chain type: κ:	MPT: Cycles (unclear how many) of a 4-week cycle of oral melphalan 8 mg/m^2 on days 1-4, prednisone 80 mg/m^2 on days 1-4, and thalidomide 50 mg/day continuously Melphalan dose was not adjusted regardless of age and renal function.	TCD: Cycles (unclear how many) of a 4-week cycle of oral cyclophosphamide 150 mg/m^2 on days 1-4, oral dexamethasone 20 mg/m^2 on days 1-5 and 15-19, and thalidomide 50 mg/day continuously Cyclophosphamide dose was not adjusted regardless of age and renal function. During dexamethasone treatment trimethoprim/ sulfamethoxazole was administrated to prevent Pneumocystis carinii infection. Routine antiviral prophylaxis for herpes zoster infection was not administrated	Myeloma response Event-free survival Survival Adverse events
Follow-up	Median: 36 months				
Funding source	The national R & D program for Cancer Control , Ministry of Health, Welfare and Family Affairs, Republic of Korea, and Korean Health Technology R & D Project, Ministry of Health and Welfare, Republic of Korea				

Song (2012).					
		N = 40, λ: N = 43; renal impairment stage: Stage 2 (GFR, 60-89 ml/min/1.73m^2): 16, Stage 3 (GFR, 30-59 ml/min/1.73m^2): 37, Stage 4 (GFR, 15-29 ml/min/1.73m^2): 30. In both arms, transfusions of red blood cells and platelets and the administration of neutrophil growth factors or erythropoiesis-stimulating agents were permitted as required.			
Results	*The patients were subgrouped according to treatment and GRF: MPT-GFR ≥40 ml/min/1,73m^2 (N = 44), MPT-GFR <40 ml/min/1,73m^2 (N = 30), TCD-GFR ≥40 ml/min/1,73m^2 (N = 45), TCD-GFR <40 ml/min/1,73m^2 (N = 38),* **Myeloma response:** - CR: MPT-GFR ≥40 22.7%, MPT-GFR <40 3.3%, TCD-GFR ≥40 20%, TCD-GFR <40 21.1%, p = 0.15. - At least very good PR: MPT-GFR ≥40 38.6%, MPT-GFR <40 13.3%, TCD-GFR ≥40 42.2%, TCD-GFR <40 39.5%, p = 0.041. MPT-GFR < 40 ml worse than the other 3 groups. - At least PR: MPT-GFR ≥40 86.4%, MPT-GFR <40 40%, TCD-GFR ≥40 84.4%, TCD-GFR <40 78.9%, p < 0.001. MPT-GFR < 40 ml worse than the other 3 groups. **Serum creatinine:** - At GFR ≥40 there were no differences between the treatments at baseline or after the 2nd, 4th, 6th and 8th cycle. - At GFR <40 the baseline levels did not differ significantly between the treatments, but after after the 2nd, 4th, 6th and 8th cycle ther serum creatinine levels were significantly lower in the TCD group compared to MPT group. **Event-free survival:** - MPT-GFR < 40 ml worse than the other 3 groups, p < 0.001. **Overall survival:** - MPT-GFR < 40 ml worse than the other 3 groups, p < 0.001. **Haematologic adverse effect:** - Neutropenia: MPT-GFR ≥40 13.6%, MPT-GFR <40 36.7%, TCD-GFR ≥40 8.9%, TCD-GFR <40 15.8%, p = 0.016. MPT-GFR < 40 ml worse than the other 3 groups. - Anaemia: MPT-GFR ≥40 11.4%, MPT-GFR <40 30%, TCD-GFR ≥40 11.1%, TCD-GFR <40 18.4%, p = 0.14. - Thrombocytopenia: MPT-GFR ≥40 11.4%, MPT-GFR <40 26.7%, TCD-GFR ≥40 6.7%, TCD-GFR <40 18.4%, p = 0.089. **Non-haematologic adverse effect:** - Embolism: MPT-GFR ≥40 2.3%, MPT-GFR <40 3.3%, TCD-GFR ≥40 0%, TCD-GFR <40 10.5%, p = 0.082. - Peripheral neuropathy: MPT-GFR ≥40 27.3%, MPT-GFR <40 13.3%, TCD-GFR ≥40 40%, TCD-GFR <40 31.6%, p = 0.089. - Infection without neutropenia: MPT-GFR ≥40 2.3%, MPT-GFR <40 13.3%, TCD-GFR ≥40 11.1%, TCD-GFR <40 13.2%, p = 0.28. - Infection with febrile neutropenia: MPT-GFR ≥40 6.8%, MPT-GFR <40 33.3%, TCD-GFR ≥40 4.4%, TCD-GFR <40 7.9%, p < 0.001. MPT-GFR < 40 ml worse than the other 3 groups. Mortality due to these infections was also significantly higher in this subgroup compared to the other 3 groups. - Gastrointestinal adverse effect (nausea/vomiting): MPT-GFR ≥40 9.1%, MPT-GFR <40 10%, TCD-GFR ≥40 8.9%, TCD-GFR <40 10.5%, p = 0.88.				
Comments	- Patient selection bias (randomisation sequence, allocation concealment)? High risk – Unclear if it is a retrospective study or RCT; if RCT no details reported about patient selection/allocation methods - Performance bias (blinding of patients, personnel)? Unclear/High risk – No details reported/Retrospective study - Detection bias (blinding of outcome assessor)? Unclear/High risk – No details reported/Retrospective study - Attrition bias (missing data)? Data from all included patients available - Reporting bias? Unclear risk - Other bias? Unclear risk Unsure if patients have **acute** renal disease.				

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1 Health economic evidence

Myeloma: diagnosis and management of myeloma	**Economic evidence summary**

Topic: The management of renal disease for patients with myeloma

Key question: What is the optimal management of acute renal disease in patients with myeloma?

Population: Patients with myeloma who have myeloma-induced acute renal disease.

Intervention: Plasmapherisis, haemodialysis (including wide pore membrane dialysis), haemofiltration, CAPD, renal replacement therapy, systemic therapies/chemotherapy regimens.

Comparator: Each other, hydration and supportive management.

Outcomes: improvement in renal function, recovery from dialysis, rate of dialysis, overall survival, progression-free survival, health related quality of life, adverse events.

Summary

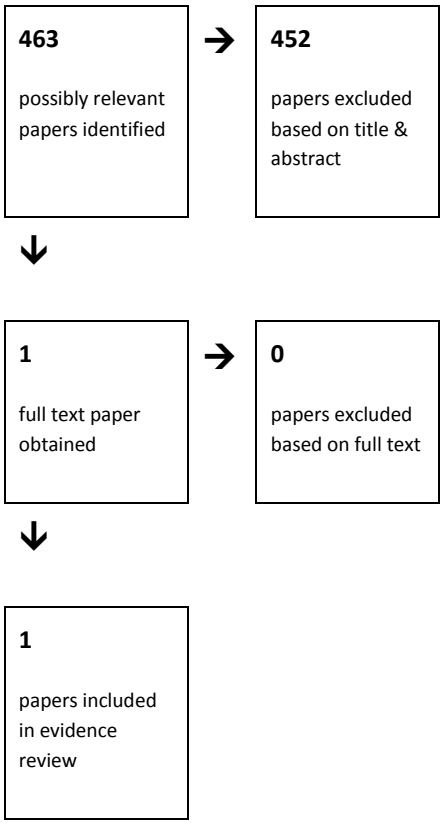
- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted from any OECD countries were considered (Guidelines Manual 2014).
- 463 possibly relevant papers were identified. Of these, 1 full paper relating to this topic was obtained for appraisal. This paper (Grima et al. 2011) was included in the current review of published economic evidence for this topic.
- The study was a cost-effectiveness analysis of high cut-off haemodialysis (HCO-HD) versus standard haemodialysis (HD) in patients with myeloma complicated by dialysis dependant renal failure secondary to myeloma kidney. The study reported the results in terms of cost per Quality Adjusted Life Year (QALY) gained and considered a NHS and Personal Social Services (PSS) perspective.
- Grima et al. is deemed directly applicable to the decision problem that we are evaluating. This is because it took a NHS and PSS perspective and reported health outcomes in terms of QALYs. Both costs and outcomes were discounted at an annual rate of 3.5%.
- Potentially serious limitations were identified with Grima et al. Most notably, a potential conflict of interest as the study was funded by a manufacturer of HCO-HD. Uncertainty around the effectiveness of HCO-HD compared to HD was also not adequately explored during sensitivity analysis. There was also inadequate exploration around other key parameters.
- The base case suggested that using HCO-HD over HD would lead to total cost savings of £6500 and 0.75 additional QALYs per patient (HCO-HD dominant). This result was robust to all but one of the deterministic sensitivity analyses although exploration around some key parameters was

inadequate.

- Probabilistic sensitivity analysis suggested the results were robust with 99.7% of iterations being cost effective at a threshold of £20,000 per QALY. Over 80% of iterations were also cost-saving and health improving.

Volume of evidence

- 463 possibly relevant papers were identified. Of these, one full paper relating to this topic was obtained for appraisal (Grima et al, 2011) and was included in the current review of published economic evidence for this topic.
- Grima et al. was a cost effectiveness analysis comparing HCO-HD to HD from a NHS and PSS perspective.



Selection criteria for included evidence:

- Studies that compare costs and health consequences of interventions were included (i.e. true cost-effectiveness analyses)
- Quality of life based outcomes were used as the measure of effectiveness in at least one of the analyses presented
- Studies conducted in OECD countries were included
- Studies that presented incremental results or presented enough information for incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO

Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations	Grima et al (2011)	
	Very serious limitations		

- Grima et al. is deemed directly applicable to the decision problem that we are evaluating. This is because the interventions considered were directly applicable to the PICO, the study considered a NHS+PSS perspective and reported health outcomes in terms of QALYs
- Potentially serious limitations were identified with all Grima et al. Most notably that some key parameters, including the effectiveness of HCO-HD, were not adequately explored during sensitivity analysis. There was also a potential conflict of interest as the study was funded by a manufacturer of HCO-HD.

Reference List

Grima DT, Airia P, Attard C et al. (2011) 'Modelled cost-effectiveness of high cut-off haemodialysis compared to standard haemodialysis in the management of myeloma kidney' **Current Medical Research & Opinion** 27(2): 383-391.

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Chapter 8: Preventing and managing bone disease

Preventing bone disease

Review Question:
What is the most effective method of preventing bone disease in patients with myeloma?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients diagnosed with symptomatic myeloma Patients diagnosed with asymptomatic myeloma Patients diagnosed with myeloma who have renal disease Patients with relapsed myeloma	• Bisphosphonates (including type of bisphosphonate, treatment duration and scheduling) • Calcium supplements • Vitamin D supplements • Osteoclast inhibition (RANKL inhibitors eg., denosumab) • Bone anabolic therapy • exercise	• placebo • no treatment • each other	• skeletal related events • Adverse events (e.g., ONJ, hypocalcaemia, renal impairment) • Quality of life • Overall survival • Progression-free survival • Pain • Need for radiotherapy • Hypercalcaemia

Evidence statements

Overall survival (OS)

Pooled results of 12 RCTs (2292 patients) in Mhaskar et al provide low quality evidence suggesting that bisphosphonates do not improve OS when compared with placebo or no treatment (HR 0.96; 95% CI 0.82 - 1.13). However, there was statistically significant heterogeneity among the included RCTs (I^2 = 55%, P = 0.01).

Results from network meta-analyses which included all studies that examined overall survival (12 RCTs comparing bisphosphonate with placebo or no treatment, and 2 RCTs with a different bisphosphonate as a comparator) demonstrated that zoledronate is superior to placebo and etidronate in improving OS. Meta-analyses of 14 RCTs (4766 patients) showed superior OS with zoledronate compared with etidronate (HR 0.43, 95% CI 0.16 to 0.86) and placebo (HR 0.61, 95% CI 0.28 to 0.98). However, there was no difference between zoledronate and other bisphosphonates.

Results from Henry et al provide moderate quality evidence of increased overall survival in myeloma patients receiving denosumab compared to those receiving zoledronic acid (HR 2.26; 95% CI 1.13 - 4.50).

Progression-free survival (PFS)

Pooled analysis of 4 RCTs (364 patients) in Mhaskar et al provide very low quality evidence suggesting that bisphosphonates do not improve PFS when compared with placebo or no treatment (HR 0.70; 95% CI 0.41 - 1.19).

Skeletal-related events (SRE)

Pooled analysis of 7 RCTs (1116 patients) in Mhaskar et al provides moderate quality evidence of a beneficial effect of bisphosphonates compared with placebo or no treatment in preventing pathological vertebral fractures (RR 0.74; 95% CI 0.62 - 0.89; p=0.001). Results also demonstrated an effect of bisphosphonates on the prevention of total skeletal-related events (7 RCTs, 1497 patients) (RR 0.80; 95% CI 0.72 - 0.89; p<0.0001). There was uncertainty whether bisphosphonates were more or less effective than placebo or no treatment in reducing nonvertebral fractures (6 RCTs, 1389 patients) (RR 1.03; 95% CI 0.68 - 1.56).

Results from network meta-analyses in Mhaskar et al found no evidence for superiority of any specific bisphosphonate for preventing skeletal related events. However, a head-to-head comparative study of the effects of zoledronic acid versus clodronic acid (Morgan et al., 2011) provides moderate quality evidence demonstrating that treatment with zoledronic acid is superior to clodronic acid with regards to preventing skeletal-related events. Fewer patients in the zoledronic acid group had vertebral fractures than did those in the clodronic acid group (5% *vs.* 9%, p=0.0008), other fractures (5% *vs.* 7%, p=0.04), and new osteolytic lesions (5% *vs.* 10%, p<0.0001).

Results from Henry et al provide moderate quality evidence that there is uncertainty about whether the time to first on-study SRE is longer with denosumab or zoledronic acid (HR 1.03; 95% CI 0.68 - 1.57).

Incidence of hypercalcemia (≥ 2.65 mmol/L)

Pooled analysis of 8 RCTs (1934 patients) in Mhaskar et al provide moderate quality evidence of uncertainty in relative effectiveness of bisphosphonates compared with placebo or no treatment in reducing hypercalcemia (RR 0.79; 95% CI 0.56 - 1.11). The 95% confidence interval of the effective estimate includes both significant benefit with bisphosphonates and no difference between the treatments.

Pain

Pooled analysis of 8 RCTs (1281 patients) in Mhaskar et al provide very low quality evidence that demonstrated a beneficial effect of bisphosphonates compared with placebo or no treatment on amelioration of pain (RR 0.75; 95% CI 0.60 - 0.95; p=0.01). However, there was statistically significant heterogeneity among the included RCTs (I2 = 63%, P = 0.008) more than likely due the variation in the pain reporting methods and quality of included.

Adverse events

Osteonectrosis of the jaw (ONJ)

ONJ was at reported a rate of 0.8% with bisphosphonate treatment but no cases were reported with placebo or no treatment in a systematic review of 3 RCTs including 736 patients (Mhaskar et al). The pooled results do not show a statistically significant increase in frequency of ONJ with the use of bisphosphonates compared with placebo or no treatment (RR 3.99; 95% CI 0.44 - 5.84), this was due to the very low event rate for ONJ in these studies which is why the evidence is considered low quality.

Two RCTs with bisphosphonate as the comparator also reported estimates of ONJ. In the RCT by Morgan et al (Morgan 2010), zoledronate was associated with higher rates of ONJ (35/983 (4%))

than clodronate (3/979 (< 1%)). In the RCT by Gimsing et al, ONJ was reported in 2 of 252 (0.79%) patients receiving 30mg of pamidronate compared with 8 of 250 (3.2%) patients receiving 90mg of pamidronate (Gimsing 2010).

Even though only 5 RCTs reported ONJ, a growing number of ONJ case reports and observational studies evaluating ONJ have been published in recent years and these studies were included in the data extracted for the Cochrane review which found that the rates of ONJ in observational studies (9 studies, 1400 patients) (table 5) ranged from 0% to 51% (the quality of this evidence is very low). The highest frequencies of ONJ were seen in studies that used a combination of pamidronate and zoledronate (range 5% to 51%). Zoledronate was associated with ONJ in 3% to 11% of cases. Pamidronate related frequencies of ONJ ranged from 0% to 18%.

Gastrointestinal symptoms

The pooled results (6 RCTs, 1689 patients) in Mhaskar et al provide low quality evidence that showed no statistically significant increase in frequency of gastrointestinal symptoms with the use of bisphosphonates compared with placebo or no treatment (RR 1.23; 95% CI 0.95 - 1.60), although the confidence intervals for the effect estimate include the possibility that bisphosphonates are associated with an increased rate of gastrointestinal symptoms.

One RCT with bisphosphonate as the comparator also reported estimates of GI symptoms (Morgan 2010). In this study 24 of 981 (2.4%) patients enrolled in the zoledronate arm had GI symptoms, and 30 of 979 (3.1%) patients receiving clodronate had GI symptoms.

Hypocalcaemia

The pooled results (3 RCTs, 1002 patients) in Mhaskar et al provide very low quality evidence of uncertainty about the relative frequency of hypocalcaemia with the use of bisphosphonates compared with placebo or no treatment (RR 2.19; 95% CI 0.49 - 9.74).

One RCT with bisphosphonate as the comparator also reported estimates of hypocalcaemia (Terpos 2003). In this study none of the 23 patients enrolled in the pamidronate arm had hypocalcaemia, while 2 of 19 patients receiving ibandronate did.

Renal dysfunction

The pooled results (2 RCTs, 414 patients) in Mhaskar et al provide low quality evidence of uncertainty about the relative frequency of renal dysfunction with the use of bisphosphonates compared with placebo or no treatment (the pooled mean difference in serum creatinine was -0.36 (95%CI -9.75 to 9.03).

One RCT with bisphosphonate as the comparator also reported estimates of renal failure (Morgan 2010). In this study 57 of 983 (5.8%) patients enrolled in the zoledronate arm had renal failure, while 60 of 979 (6.1%) patients receiving clodronate had renal failure.

The network meta-analysis in Mhaskar et al did not show any differences in the incidence of osteonecrosis of the jaw, hypocalcaemia, renal dysfunction and gastrointestinal toxicity between the bisphosphonates used.

The study by Henry et al reported on adverse events but these were reported for the whole population and not by tumour type and so there is no evidence from this study regarding occurrence of adverse events in myeloma patients. For the whole population patients in both treatment groups (denosumab or zoledronic acid) experienced similar rates of overall adverse events. Hypocalcaemia occurred more frequently with denosumab (10.8% vs. 5.8%), acute phase reactions after the first

dose occurred more frequently with ZA (14.5% vs. 6.9%), renal adverse events occurred more frequently with ZA (10.9% vs. 8.3%) and elevations in serum creatinine occurred more frequently with ZA (23.9% vs. 16.5%).

Need for radiotherapy

We did not find evidence for this outcome.

Quality life

We did not find evidence for this outcome.

Table 8.1*:* GRADE summary of findings table (benefits): What is the most effective method of preventing bone disease in patients with myeloma (bisphosphonates versus placebo or no treatment)? (from Mhaskar et al., 2012)

Note: not all studies included patients with lytic lesions or did not specify bone disease in inclusion criteria

Patient or population: patients with prevention of skeletal-related events in multiple myeloma
Intervention: Bisphosphonates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Bisphosphonates				
	Medium risk population					
Overall mortality 2292 patients	**530 per 1000**	**504 per 1000 (449 to 561)**	**HR 0.96** (0.82 to 1.13)	2292 (12 studies)	⊕⊕⊖⊖ **low**[1,2,3]	
	Medium risk population					
Progression-free survival 364 Patients	**350 per 1000**	**260 per 1000** (162 to 401)	**HR 0.70** (0.41 to 1.19)	364 (4 studies)	⊕⊖⊖⊖ **very low**[1,4]	
	Low risk population5					
	100 per 1000	**74 per 1000 (62 to 89)**				
	Medium risk population[5]					
	350 per 1000	**259 per 1000 (217 to 311)**				
	High risk population[5]					
Vertebral fractures 1116 Patients	**690 per 1000**	**511 per 1000 (428 to 614)**	**RR 0.74** (0.62 to 0.89)	1116 (7 studies)	⊕⊕⊕⊖ **moderate**[1,6]	
	Medium risk population					
Nonvertebral fractures 1389 patients	**140 per 1000**	**144 per 1000 (95 to 218)**	**RR 1.03** (0.68 to 1.56)	1389 (6 studies)	⊕⊕⊕⊖ **moderate**[1,7]	

	Low risk population[5]				
	240 per 1000	**194 per 1000** (173 to 221)			
	Medium risk population[5]				
	303 per 1000	**245 per 1000 (218 to 279)**			
	High risk population[5]				
Skeletal-related events 1497 patients	**860 per 1000**	**697 per 1000 (619 to 791)**	**RR 0.80** (0.72 to 0.89)	1497 (7 studies)	⨁⨁⨁⨀ **moderate**[1,8]
	Low risk population[5]				
	60 per 1000	**45 per 1000 (36 to 57)**			
	Medium risk population5				
	500 per 1000	**375 per 1000 (300 to 475)**			
	High risk population[5]				
Pain 1281 patients	**1000 per 1000**	**750 per 1000 (600 to 950)**	**RR 0.75** (0.6 to 0.95)	1281 (8 studies)	⨁⨀⨀⨀ **very low**[9,10]
	Medium risk population				
Hypercalcemia 1934 patients	**100 per 1000**	**87 per 1000 (61 to 124)**	**RR 0.79** (0.56 to 1.11)	1934 (8 studies)	⨁⨁⨁⨀ **moderate**[1]

The basis for the **assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
***CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio*

GRADE Working Group grades of evidence
***High quality:** Further research is very unlikely to change our confidence in the estimate of effect.*
***Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.*
***Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.*
***Very low quality:** We are very uncertain about the estimate.*

[1] *Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on allocation concealment and description of randomization method didn't change the estimates. Hence, the assessment of studies limitations may represent the poor*

quality of reporting rather than true biased estimates.
[2] *I^2 = 55%. The pooled estimate is driven by studies by Aviles et al and Belch et al; when we removed these RCTs pooled estimates remained the same but heterogeneity disappeared.*
[3] *The overall mortality data were extractable from 11 of 16 studies. Also, note that overall mortality data denotes the mortality rates, i.e. the number of events refers to the number of deaths.*
[4] *The progression-free survival data could be extracted from only 4 of 16 studies.*
[5] *We have denoted only medium risks in controls for statistically nonsignificant outcomes while denoting low, medium and high risks in controls for statistically significant outcomes.*
[6] *Data related to patients with vertebral fractures were extractable from only 7 of 16 RCTs.*
[7] *Data related to patients with nonvertebral fractures were extractable from only 6 of 16 RCTs.*
[8] *Skeletal-related events data were extractable from only 7 of 16 RCTs.*
[9] *Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment.*
[10] *There was variation in the pain scales used to measure pain.*

Table 8.2 GRADE summary of findings table (harms): What is the most effective method of preventing bone disease in patients with myeloma (bisphosphonates versus placebo or no treatment)? (from Mhaskar et al., 2012).

Note: not all studies included patients with lytic lesions or did not specify bone disease in inclusion criteria

Patient or population: patients with prevention of skeletal-related events in multiple myeloma
Intervention: Bisphosphonates

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Bisphosphonates				
Gastrointestinal toxicity **1689 patients**	**Medium risk population**					
	10%	**23 more per 1000 (from 5 fewer to 60 more)**	RR 1.23 (0.95 to 1.6)	6 RCTs (1689 patients)	++OO low	Limitations in design: serious [1] Serious imprecision [2]
	Number of observed gastrointestinal toxicities: 86/836 (10.3%)	**Number of observed gastrointestinal toxicities: 110/853 (12.9%)**				
Hypocalcemia **1002 patients**	**Medium risk population**					
	9%	**107 more per 1000 (from 46 fewer to 787 more)**	RR 2.19 (0.49 to 9.74)	3 RCTs (1002 patients)	+OOO very low	Limitations in design: serious [1] Very serious imprecision [3] Reporting bias [4]
	Number of patients with	**Number of patients with**				

	hypocalcemia: 2/451 (0.4%)	**hypocalcemia: 5/462 (1.1%)**			
	Number of patients with ONJ: 0/370 (0%)	**Number of patients with ONJ: 3/366 (0.8%)**	RR 3.99 (0.44 to 35.84)	3 RCTs (913 patients)	++OO low	Limitations in design: serious [1] Reporting bias [4]
Osteonecrosis of jaw **913 patients**	**ONJ incidence range: 0% to 51%**			9 Observational studies (1400 patients)	+OOO very low	reporting bias reduced effect for RR >> 1 or RR << 1[5] dose response gradient[6]
Renal dysfunction **414 patients**	**Mean difference: −0.36 (−9.75 to 9.03)**			2 RCTs (414 patients)	++OO low	Limitations in design: serious [1] Reporting bias [7]

The basis for the **assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*

[1] Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on allocation concealment and description of randomization method didn't change the estimates. Hence, the assessment of studies' limitations may represent the poor quality of reporting rather than true biased estimates. Nonetheless, it should be noted that some authors would not downgrade evidence regarding treatment-related harms based on quality of randomization process.

[2] The pooled estimate has a wide confidence interval.

[3] All the RCTs have estimates with wide confidence intervals.

[4] Data related to patients with hypocalcemia and ONJ was extractable from only 3 of 16 RCTs.

[5] ONJ was observed in case control, case series and prospective observational studies and RCTs. Very few studies included consecutive prospective cohort with clear diagnostic criteria and blinded assessment of radiological findings. Therefore, while ONJ is considered a real adverse event, the exact incidence or risk is difficult to assess.

[6] While some studies indicate dose response, it could be that ONJ is related to the type of bisphosphonate. So far, no ONJ has been observed in the studies of clodronate.

7 Data related to patients with renal dysfunction were extractable from only 2 of 16 RCTs.

CI: Confidence interval; RR: Risk ratio; ONJ: Osteonecrosis of the jaw

Table 8.3: GRADE profile: What is the most effective method of preventing bone disease in patients with myeloma (zoledronic acid versus clodronic acid?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**zoledronic acid**	**clodronic acid**	**Relative (95% CI)**	**Absolute**	**Quality**

incidence of skeletal related events (follow-up median 3.7 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	265/981 (27%)	346/979 (35.3%)	HR 0.74 (0.62 to 0.87)	78 fewer per 1000 (from 38 fewer to 117 fewer)	⊕⊕⊕O MODERATE

[1] Perfomance bias and detection bias as study is open-label and not blinded

Table 8.4: GRADE profile: What is the most effective method of preventing bone disease in patients with myeloma (denosumab versus zoledronic acid)?

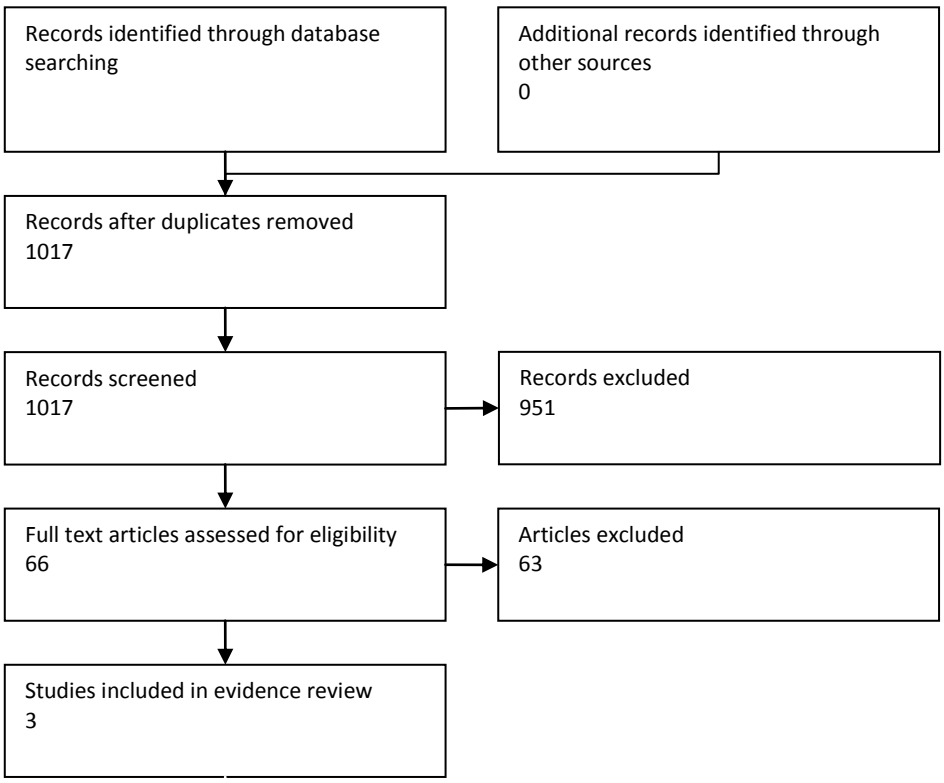
Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**denosumab**	**zoledronic acid**	**Relative (95% CI)**	**Absolute**	
time to first on-study SRE (Better indicated by higher values)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	93	87	HR of 1.03 95% CI, 0.68 to 1.5	Not reported	⊕⊕⊕O MODERATE
overall survival (Better indicated by lower values)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	93	87	HR of 2.26 (95% CI, 1.13 to 4.50	Not reported	⊕⊕⊕O MODERATE

[1] no absolute data reported for myeloma

Search Results

An RCT study design filter was applied to database searching for the interventions bisphosphonates and denosumab. For the other interventions included in the PICO table no study design filter was applied.

Figure 8.1: Screening results



Summary

Three studies investigating interventions for the prevention of bone disease in myeloma patients are included in the evidence review. One of these is a Cochrane systematic review and meta-analysis examining the effectiveness of bisphosphonates in myeloma (Mhaskar et al., 2012). The primary objective of the review was to determine whether adding bisphosphonates to standard therapy in myeloma improves OS and PFS, and decreases skeletal-related morbidity. The secondary objectives were to determine the effects of bisphosphonates on pain, quality of life, incidence of hypocalcaemia, and adverse events. Any RCT assessing the role of bisphosphonates and observational studies or case reports examining bisphosphonate-related osteonecrosis of the jaw in patients with MM were eligible for inclusion. 16 RCTs comparing bisphosphonates with either placebo or no treatment and 4 RCTs with a different bisphosphonate as a comparator were identified resulting in 20 RCTs with a total of 6692 patients. Analysis of the data concluded that the use of bisphosphonates reduces vertebral fractures and pain. In terms of type of bisphosphonate zoledronate appeared to be superior to etidronate and placebo. However, whether zoledronate is superior to pamidronate and other bisphosphonates remains to be determined.

The MRC myeloma IX trial is included in the Cochrane review but since the publication of the Cochrane review an updated paper of the MRC Myeloma IX trial reporting on the secondary outcomes relating to skeletal events has been published (Morgan et al., 2011). This study found fewer patients with skeletal-related events in the zoledronic acid group compared to the clodronic acid group.

Only 1 RCT was identified that studied the intervention denosumab in myeloma patients. This was a phase III trial comparing denosumab to zoledronic acid in patients with at least 1 osteolytic lesion (Henry et al., 2011). Patients were randomly assigned to receive 120mg subcutaneous denosumab and an intravenous placebo infusion every 4 weeks or intravenous zoledronic acid 4mg and a subcutaneous placebo every 4 weeks. The trial included patients with different cancers: non-small cell lung cancer n=702, other tumours, excluding breast and prostate n=904 and myeloma n=180.The primary end point was time to first on-study SRE comparing denosumab with ZA for noninferiority. Results for myeloma concluded that there was no difference in time to first on-study SRE when comparing denosumab with zoledronic acid. However patients on denosumab were found to have an increased overall survival. These findings warrant further investigation and currently there is an ongoing phase 3 study specifically in myeloma patients (NCT01345019). The trial will evaluate the efficacy and safety of denosumab compared with ZA in preventing skeletal complication in patients with myeloma. The primary endpoint will determine if denosumab is non-inferior to ZA in prevention of the first on-study SRE. If denosumab in found to be non-inferior to ZA, superiority in time to first on-study SRE and time to first and subsequent SRE will be assessed as secondary endpoints. Projected enrolment is 1520 patients with a 48 month study period. Results are expected in 2016.

There were no studies identified that examined the interventions calcium supplements, vitamin D supplements, bone anabolic therapy or exercise for preventing bone disease in myeloma patients.

References of included studies

1. Henry, D. H., Costa, L., Goldwasser, F., Hirsh, V., Hungria, V., Prausova, J., Scagliotti, G. V., Sleeboom, H., Spencer, A., Vadhan, R. S., Moos, R., Willenbacher, W., Woll, P. J., Wang, J., Jiang, Q., Jun, S., Dansey, R. & Yeh, H. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of clinical oncology,* 29: 1125-1132.
2. Mhaskar, R., Redzepovic, J., Wheatley, K., Clark, O. A., Miladinovic, B., Glasmacher, A., Kumar, A. & Djulbegovic, B. (2012) Bisphosphonates in multiple myeloma: a network meta-analysis. [Review][Update of Cochrane Database Syst Rev. 2010;(3):CD003188; PMID: 20238320]. *Cochrane Database of Systematic Reviews,* 5: CD003188.
3. Morgan, G. J., Child, J. A., Gregory, W. M., Szubert, A. J., Cocks, K., Bell, S. E., Navarro, C. N., Drayson, M. T., Owen, R. G., Feyler, S., Ashcroft, A. J., Ross, F. M., Byrne, J., Roddie, H., Rudin, C., Cook, G., Jackson, G. H., Wu, P. & Davies, F. E. (2012) Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. *The.lancet oncology,* 12: 743-752.

Evidence table

Paper	Study type	Population	Intervention	Comparison	Outcomes	Results
Mhaskar et al., 2012	Cochrane systematic review and meta-analysis	6692 myeloma patients	bisphosphonates	- placebo - no treatment - different bisphosphonate	- OS - PFS - skeletal-related events - pain - quality of life - incidence of hypercalcemia - adverse events • gastrointestinal toxicities • osteonecrosis of jaw • hypocalcemia • renal dysfunction	The use of BPs reduces vertebral fractures, SREs and pain. There were no significant adverse events associated with the administration of BPs.
Morgan, et al., 2012	RCT	1960 myeloma patients	zoledronic acid (n=981)	clodronic acid (n=979)	- time to first skeletal-related event - incidence of skeletal related events	Treatment with zoledronic acid was associated with a significant reduction in the proportion of patients with skeletal-related events (27% ***vs.*** 35% with clodronic acid HR = 0.74 , CI 0.62-0.87, p=0.0004
Henry et al., 2011	RCT	180 myeloma patients	denosumab (n=87)	zoledronic acid (n=93)	time to first on-study SRE	The effect of denosumab on time to first on-study SRE relative to zoledronic acid resulted in an HR of 1.03 (95% CI: 0.68 to 1.57). An ad hoc analysis examining overall survival demonstrated an HR of 2.26 (95% CI: 1.13 to 4.50).

Table 8.5: RCTs included in Cochrane review

Study	Methods	Inclusion criteria –	Other inclusion criteria	Participants	Interventions	Outcomes	Notes

		stage (Durie 2005)					
Attal 2006	Not double-blind; placebo-controlled; ITT: yes.	I-III	Osteolytic lesion: not required Creatinine: not specified Calcium: not specified Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled 196, analyzed 196. Bisphosphonates + thalidomide: enrolled 201, analyzed 201. Placebo: enrolled 200, analyzed 200.	Pamidronate 90 mg IV, every 4 weeks; control 1: pamidronate and thalidomide, po a minimum dose reduction of 50 mg for treatment-related toxicity	Total skeletal-related events; total mortality; response rates; ONJ	SRE: bone lesion requiring a specific therapy (chemotherapy, irradiation or surgery)
Aviles 2007	Not double-blind; not placebo-controlled; ITT: yes.	III	Osteolytic lesion: at least one Creatinine: not specified Calcium: not specified Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled 46, analyzed 46. Control: enrolled 48, analyzed 48.	Zoledronate 4 mg IV, every 4 weeks.	Total mortality; progression-free survival.	SRE: appearance of a new lytic lesion (excluding skull), after patient began zoledronate or progression of previous bone lesion according to criteria of Union Internationale Centre le Cancer
Belch 1991	Double-blind; placebo-controlled; ITT: no.	I-III	Osteolytic lesion: not required Creatinine: < 3 mg/dL Calcium: normal or elevated Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled 98, analyzed 92. Placebo: enrolled 78, analyzed 74.	Etidronate capsules (20mg/kg x 28 days), (then 5mg/kg) until death or discontinuation. Placebo: identical appearance.	Vertebral index; total mortality*; pain; calcium.***	SRE = bone progression (appearances of new lesions or worsening of existing ones)$; mortality* (fromthe date of randomization); calciumreported as a dichotomous variable
Berenson 1998	Double-blind; placebo-controlled; ITT: no.	III only	Osteolytic lesion: at least one Creatinine: < 5 mg/dL Calcium: not specified Other criteria: no bone specific treatment prior to entry	Bisphosphonates: enrolled 205, analyzed 198. Placebo: enrolled 187, analyzed 179.	Pamidronate 90 mg in 500 mL of 5% dextrose in water, every 4 weeks for 21 months; identical placebo in 5% dextrose.	SRE (total); vertebral fractures; nonvertebral fractures; total mortality (#); calcium***; pain; adverse events.	SRE: pathologic fracture or radiation treatment/surgery on bone or spinal cord compression
Brincker 1998	Double-blind; placebo-controlled; ITT: yes.	II-III	Osteolytic lesion: not specified Creatinine: < 2.8 mg/dL Calcium: normal or elevated Other criteria: no cytotoxic chemotherapy prior to entry	Total enrolled: 304. Bisphosphonates: enrolled 152, analyzed 152. Placebo: enrolled 148, analyzed 148.	Pamidronate 75 mg capsules po bid; identical placebo; duration at least 2 years.	Total mortality*$; SRE; pain; calcium(&); adverse events.	SRE: bone fracture other than vertebral or surgery or increase in number of osteolytic lesions + vertebral collapse; pain reported as the number of events, not as the number of patients experiencing pain
Daragon	Double-blind;	II-III	Osteolytic lesion: not specified	Bisphosphonates: enrolled	Etidronate 10 mg/kg po	Total mortality *$	SRE: new extraspinal

1993	placebo-controlled; ITT: no.		Creatinine: < 2mg/dL Calcium: normal or elevated Other criteria: no cytotoxic chemotherapy prior to entry	49, analyzed 39. Placebo: enrolled 45, analyzed 39.	qd; identical placebo; duration 4 months.	;SRE (total); total fractures; vertebral fractures; nonvertebral fractures; vertebral index; total mortality; pain; calcium; adverse events.	osteolytic bone lesions or fractures or vertebral index; total mortality: total number of deaths reported in the text; pain recorded as the number of patients taking class 2 and 3 narcoanalgesics
Delmas 1982	Double-blind; placebo-controlled; ITT: no.	Not specified	Osteolytic lesion: not specified Creatinine: < 1.8 mg/dL Calcium: not specified Other criteria: n/a	Bisphosphonates: enrolled 7, analyzed 7. Placebo: enrolled 6, analyzed 6.	Clodronate 1600 mg/d po; identical placebo; duration 18 months.	SRE; total fractures; vertebral fracture; nonvertebral fractures; total mortality; pain; calcium; adverse events.	SRE: new osteolytic lesions or fractures or vertebral index ($); vertebral fractures for control group not reported; total mortality reported for clodronate group only; adverse events stated only (data could not be extracted).
Gimsing 2010	Double-blind; Comparing 30 mg versus 90 mg pamidronate; ITT: no.	I-III	Osteolytic lesion: not specified Creatinine: < 400 umol/L Calcium: not specified Other criteria: no prior treatment with bisphosphonates	Pamidornate 30 mg: enrolled 252, analyzed 198. Pamidronate 90 mg: enrolled 252, analyzed 179.	Pamidronate 90 mg in 500 mL of 5% dextrose in water, every 4 weeks for 21 months; identical placebo in 5% dextrose.	SRE (total); vertebral fractures; nonvertebral fractures; total mortality (#); calcium***; pain; adverse events.	SRE: pathologic fracture or radiation treatment/surgery on bone or spinal cord compression
Heim 1995	Not double-blind; placebo-controlled; ITT: no.	I-III	Osteolytic lesion: not required Creatinine: < 2.5mg/dL Calcium: not specified Other criteria: n/a	Total: 170; 13 withdrawn after treatment. premature termination in additional 75. Bisphosphonates: analyzed: 39. Placebo: analyzed: 32.	Clodronate 1600 mg/d po; control: no treatment; duration 12 months.	SRE; pain; total fractures; calcium; adverse events.	SRE: bone progression ($); effect on pain characterized as the number of patientswithout pain or no need for therapy
Kraj 2000	Not double-blind; placebo-controlled; ITT: no.	II-III	Osteolytic lesion: not required Creatinine: unclear Calcium: not specified Other criteria: n/a	Bisphosphonates: analyzed 23; Placebo: analyzed 23.	Pamidronate 60 mg IV, every 4 weeks; control: no treatment.	Total mortality, vertebral fractures.	
Lahtinen	Double-blind;	Not specified	Osteolytic lesion: not required	Bisphosphonates: enrolled	Clodronate 400 mg	SRE (total); total	Total mortality reported as

1992	placebo-controlled; ITT: yes.		Creatinine: any Calcium: normal or elevated Other criteria: newly diagnosed and previously untreated patients	168, analyzed 168. Placebo: enrolled 168, analyzed 168.	capsules po tid; identical placebo; duration 24 months.	mortality; vertebral fractures; nonvertebral fractures; calcium.**	a total number of deaths.
Leng 2002	Not double-blind, not placebo-controlled; ITT: unclear.	II-III	Osteolytic lesion: not specified Creatinine: not specified Calcium: not specified Other criteria: verbal rating scale > II	Bisphosphonates: analyzed 16. Placebo: analyzed 18.	Pamidronate 90 mg IV OD; duration 2 days; identical placebo; duration 2 days.	Pain (continuous data).	
McCloskey 2001	Double-blind; placebo-controlled; ITT: no	II-III	Osteolytic lesion: at least one Creatinine: any Calcium: normal or elevated Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled/analyzed 264. Placebo: enrolled/analyzed 272.	Clodronate 400 mg capsules po qid; identical placebo; duration 24 months.	Total mortality*; SRE; total fractures; vertebral fractures; nonvertebral fracture; pain; calcium.***	SRE: event-free survival (pathological fractures or hypercalcemia), calculated from survival curves; outcome on calcium also reported as a dichotomous variable on the number of patients with hypercalcemia; pain calculated as the number of patients with maximal pain over 24 months
Menssen 2002	Double-blind; placebo-controlled; ITT: yes.	I-III	Osteolytic lesion: at least one Creatinine: < 3mg/dL Calcium: normal Other criteria: no bone specific treatment prior to entry	Bisphosphonates: enrolled 107, analyzed 99. Placebo: enrolled 107, analyzed 99.	Ibandronate 2 mg IV every month; identical placebo, duration 24 months.	SRE (total)/year; mortality;* vertebral fractures (!); nonvertebral fractures (!); hypercalcemia (!); pain (!).	SRE: pathological fractures or vertebral fractures, hypercalcemia, severe bone pain, and bone radiotherapy or surgery
Morgan 2010	Open label; Comparing zoledronate versus clodronate; ITT: yes.	I-III (ISS)	Osteolytic lesion: not specified Creatinine: < 5.65 mg/dL Calcium: not specified Other criteria: no previous or	zoledronate: analyzed 981. clodronate: analyzed 979.	zoledronate: 4 mg IV every 3 to 4 weeks clodronate: 1600 mg orally daily	Mortality; SREs; complete response; vertebral fractures, other fractures; hypercalcemia; renal failure; very good partial	SRE: vertebral fractures, other fractures, spinal cord compression, need for radiation or surgery to bone lesions, and new osteolytic bone lesions were recorded until

			concurrent active malignancies. No acute renal failure (serum creatinine > 500 umol/L and unresponsive to 72 hours of rehydration.			response; treatment-related toxicities.	disease progression. Complete response: negative immunofixation (100%M-protein reduction) very good partial response: at least 90% M-protein reduction with positive immunofixation
Musto 2003	Not double-blind; not placebo-controlled; ITT: no.	I-II	Osteolytic lesion: any Creatinine: not specified Calcium: not specified Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled 45, analyzed 40. Control: enrolled 45, analyzed 41.	Zoledronate 4 mg IV, every 4 weeks, duration 12 months.	Total skeletal related events; PFS.	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia
Musto 2008	Not double-blind; not placebo-controlled; ITT: yes.	I(ISS)	Osteolytic lesion: any Creatinine: < 1.2 mg/dL Calcium: < 10 mg/dL Other criteria: no cytotoxic chemotherapy prior to entry	Bisphosphonates: enrolled 81, analyzed 81. Control: enrolled 82, analyzed 82.	Zoledronate 4 mg IV, every 4 weeks; duration 12 months.	SRE (total); PFS; ONJ.	SRE: single/multiple osteolytic lesions, pathological fractures and/or hypercalcemia The trial was prematurely stopped due to ONJ case in patient receiving zoledronate
Rosen 2003	Double-blinded; double dummy; stratified; not placebo-controlled; ITT: yes.	III	Osteolytic lesion: at least one Creatinine: < 3 mg/dL Calcium: > 12 mg/dL Other criteria: serim bilirubin < 2.5 mg/dL. No prior treatmenr with bisphosphonates within 12 months of the screening visit.	Zoledronate: enrolled 564, analyzed 561 Pamidronate: enrolled 558, analyzed 555	Zoledronate 4 mg IV, every 4 weeks, duration 24 months. Pamidronate 90 mg IV, every 4 weeks, duration 24 months.	SREs	SREs were defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone Data for MM and breast carcinoma patients were reported in combined manner for all outcomes except SREs
Terpos 2000	Not double-blind; not placebo-controlled; ITT: yes.	I-III	Osteolytic lesion: not specified Creatinine: < 5 mg/dL Calcium: not specified Other criteria: n/a	Bisphosphonates: enrolled/analyzed 32. Control: enrolled/analyzed 30.	Pamidronate 90 mg IV, every 4 weeks; duration 14 months.	Total mortality;* total fractures; vertebral fractures; nonvertebral fracture; pain; hypercalcemia; abdominal pain.	Data provided by the authors of the article.
Terpos 2003	Not double-blind, not	II	Osteolytic lesion: at least one	Pamidronate: enrolled 23, analyzed 23.	Pamidronate 90 mg IV, every 4 weeks, duration 4	Hypocalcemia, hypercalcemia.****	

	placebo-controlled; ITT: no.		Creatinine: < 4 mg/dL Calcium: not specified Other criteria: no bone specific treatmemt within 2 months prior to study entry	Ibandronate: enrolled 21, analyzed 20.	months. Ibandronate 4 mg IV, every 4 weeks, duration 4 months.		

ITT = intention to treat
IV = intravenous
ONJ = osteonecrosis of the jaw
po = oral (by mouth)
qd = every day
SRE = skeletal-related events
tid = three times daily
** mortality data obtained from authors; *$ mortality data derived using the Tierney method*
 # total number of deaths reported in Berenson 1996
$ defined by reviewers
***hypercalcemia defined as > 2.65 mmol/L*
&hypercalcemia defined as > 2.75 mmol/L
****hypercalcemia defined as > 3.00 mmol/L*
***** hypercalcemia defined as presence of symptoms or serum calcium concentration, corrected for the serum albumin concentration, of at least 12.0 mg/dL or 3.0 mmol/L*
! Data obtained from (author Fontana et al) and data from previous publication (abstract) were used

1
2 ***Table 8.6Summary of results from Cochrane review Mhaskar et al., 2012***

Outcome	Number of RCTs	Number of patients	conclusion	HR or RR	heterogeneity	
Overall survival	12	2292	no improvement in OS with use of bisphosphonates compared with placebo or no treatment	0.96 95%CI 0.82 to 1.13 P = 0.64	I2 = 55% P = 0.01	Analysis 1.1
progression-free survival	4	364	No improvement in PFS with use of bisphosphonates compared with placebo or no treatment	0.70 95% CI 0.41 to 1.19 P = 0.18	I2 = 35% P = 0.20	Analysis 1.2
vertebral fractures	7	1116	statistically significant improvement in reducing vertebral fractures with use of bisphosphonates compared with placebo or no treatment	0.74 95%CI 0.62 to 0.89 P = 0.001	I2 = 7% P = 0.38	Analysis 1.3
nonvertebral fractures	6	1389	no improvement in reducing nonvertebral fractures with use of bisphosphonates compared with placebo or no treatment	1.03 95% CI 0.68 to 1.56 P = 0.90	I2 = 54% P = 0.07	Analysis 1.4
total skeletal-related events	7	1497	statistically significant improvement in reducing SREs with use of bisphosphonates compared with placebo or no treatment	0.80 95% CI 0.72 to 0.89 P < 0.0001	I2 = 2% P = 0.41	Analysis 1.5
incidence of hypercalcemia (≥ 2.65 mmol/L)	8	1934	no improvement in reducing hypercalcemia with use of bisphosphonates compared with placebo or no treatment	0.79 95% CI 0.56 to 1.11 P = 0.17	I2 = 24% P = 0.24	Analysis 1.6
pain	8	1281	statistically significant beneficial effect in amelioration of pain with use of bisphosphonates compared with placebo or no treatment	0.75 95% CI 0.60 to 0.95 P =0.01	I2 = 63% P = 0.008	Analysis 1.7
Adverse events: Gastrointestinal symptoms	6	1689	no statistically significant increase in frequency of GI symptoms with use of bisphosphonates compared with placebo or no treatment	1.23 95% CI 0.95 to 1.60 P =0.11	I2 = 0% P = 0.90	Analysis 2.1
Adverse events: Hypocalcemia	3	1002	no statistically significant increase in frequency of hypocalcemia with use of bisphosphonates compared with placebo or no treatment	2.19 95% CI 0.49 to 9.74 P =0.30	I2 = 0% P = 0.88	Analysis 2.2
Adverse events: Osteonecrosis of the jaw (ONJ)	3	736	no statistically significant increase in frequency of ONJ with use of bisphosphonates	3.99 95% CI 0.44 to 5.84	I2 = 0% P = 0.82	Analysis 2.3

			compared with placebo or no treatment	P = 0.22		
Advese events: Renal dysfunction	2	414	no statistically significant increase in the frequency of elevated serum creatinine with the use of bisphosphonates compared with placebo or no treatment	pooled mean difference in serum creatinine = −0.36 95% CI −9.75 to 9.03 P = 0.94	I2 = 18% P = 0.27	Analysis 2.4

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2
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Figure 8.2: Methodological quality summary of RCTs included in Cochrane review

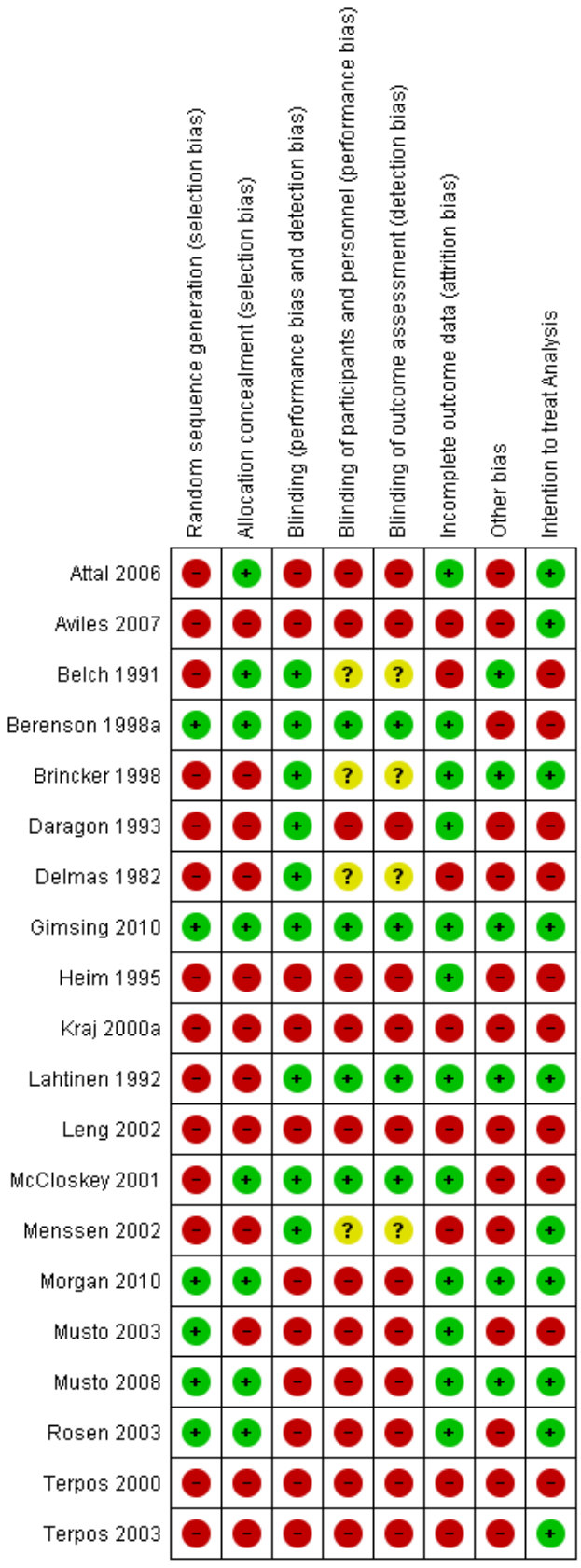


Table 8.7: ONJ observational studies included in Cochrane review Mhaskar et al 2012

Study	Study design	Type of bisphosphonate	Total number of patients	Number of patients with ONJ	Route, dose, frequency	Treatment duration	ONJ frequency

Badros 2006	Retrospective study	Pamidronate	17	3	Not reported	Not reported	17.65%
		Zoledronate	34	2			5.88%
		Pamidronate + zoledronate	33	17			51.51%
Berenson 2011	Retrospective study	Zoledronate	300	14	Not clear	Median: 18 months Range: 1-121 months	5%
Calvo-Villas 2006	Not clear	Zoledronate	64	7	Not reported	Not clear	9%
Cetiner 2009	Prospective study	Zoledronate	32	5	15 minute infusion of 4 mg IV zoledronate once a month	Mean duration: 26.5 months, SD 18.7 months	15%
Corso 2007	Retrospective study	Pamidronate	20	0	Not clear	23 months	0%
		Zoledronate	37	5	Not clear	28 months	11.9%
		Pamidronate + zoledronate	42	2	Not clear	47 months	4.55%
Dimopoulos 2006		Pamidronate	93	7	Not reported	39 months ONJ patients (11-76) vs 28 (4.5-123) months without ONJ	7.5%
		Zoledronate	33	1			3%
		Pamidronate + zoledronate	66	6			9.1%
		Ibandronate	1	0			0%
		Ibandronate + zoledronate	4	1			25%
		Clodronate + zoledronate	1	0			0%
		Alendronate + zoledronate	1	0			0%
Garcia-Garay 2006	Retrospective study	Pamidronate	49	1	90 mg monthly	28 months	2%
		Zoledronate	64	6	4 mg monthly	12 months (7-28)	9.3%
		Pamidronate + zoledronate	30	7		43.5 months (24-59)	23.3%
Tosi 2006b	Retrospective study	Zoledronate	225	6	Not reported	10 months (4-35)	2.7%
Zervas 2006	Retrospective study from 1991, prospective from 2001-2006	Pamidronate	78	1	90 mg	24 months (4-120)	1.28%
		Pamidronate	91	6	4 mg 4-6 weeks		6.59%
		Pamidronate + zoledronate	85	21			24.71%

1

2

1 ***Excluded papers (after checking full text)***

Paper	Intervention	Reasons for exclusion
1. Attal, M., Harousseau, J. L., Leyvraz, S., Doyen, C., Hulin, C., Benboubker, L., Yakoub, A., I, Bourhis, J. H., Garderet, L., Pegourie, B., Dumontet, C., Renaud, M., Voillat, L., Berthou, C., Marit, G., Monconduit, M., Caillot, D., Grobois, B., Avet-Loiseau, H., Moreau, P., Facon, T. & Inter-Group (2006) Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood,* 108: 3289-3294.	Bisphophonate - pamidronate	included in cochrane review Mhaskar et al 2012
2. Avilés, A., Nambo, M. J., Neri, N., Castañeda, C., Cleto, S. & Huerta, G. J. (2007) Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Medical.oncology,* 24: 227-230.	bisphosphonate -zoledronic acid	included in cochrane review Mhaskar et al 2012
3. Belch, A. R., Bergsagel, D. E., Wilson, K., O'Reilly, S., Wilson, J., Sutton, D., Pater, J., Johnston, D. & Zee, B. (1991) Effect of daily etidronate on the osteolysis of multiple myeloma. *Journal of clinical.oncology,* 9: 1397-1402.	bisphosphonate -etidronate disodium	included in cochrane review Mhaskar et al 2012
4. Berenson, J. R., Lichtenstein, A., Porter, L., Dimopoulos, M. A., Bordoni, R., George, S., Lipton, A., Keller, A., Ballester, O., Kovacs, M., Blacklock, H., Bell, R., Simeone, J. F., Reitsma, D. J., Heffernan, M., Seaman, J. & Knight, R. D. (1998) Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *Journal of clinical.oncology,* 16: 593-602.	Bisphophonate - pamidronate	included in cochrane review Mhaskar et al 2012
5. Brincker, H., Westin, J., Abildgaard, N., Gimsing, P., Turesson, I., Hedenus, M., Ford, J. & Kandra, A. (1998) Failure of oral pamidronate to reduce skeletal morbidity in multiple myeloma: a double-blind placebo-controlled trial. Danish-Swedish co-operative study group. *British.journal of haematology.,* 101: 280-286.	Bisphophonate - pamidronate	included in cochrane review Mhaskar et al 2012
6. Daragon, A., Humez, C., Michot, C., Loet, X., Grosbois, B., Pouyol, F., Euller, Z. L., Azais, I., Bernard, J. F. & Menard, J. F. (1993) Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. Groupe d'Etudes et de Recherches sur le Myélome (GERM). *European.journal of medicine,* 2: 449-452.	bisphosphonate -etidronate disodium	included in cochrane review Mhaskar et al 2012

Paper	Intervention	Reasons for exclusion
7. Delmas, P. D., Charhon, S., Chapuy, M. C., Vignon, E., Briancon, D., Edouard, C. & Meunier, P. J. (1982) Long-term effects of dichloromethylene diphosphonate (Cl2MDP) on skeletal lesions in multiple myeloma. *Metabolic.bone disease.& related.research.,* 4: 163-168.	bisphosphonate - dichloromethylene diphosphonate (Cl2MDP)	included in cochrane review Mhaskar et al 2012
8. Gimsing, P., Carlson, K., Turesson, I., Fayers, P., Waage, A., Vangsted, A., Mylin, A., Gluud, C., Juliusson, G., Gregersen, H., Hjorth, H. H., Nesthus, I., Dahl, I. M., Westin, J., Nielsen, J. L., Knudsen, L. M., Ahlberg, L., Hjorth, M., Abildgaard, N., Andersen, N. F., Linder, O. & Wisløff, F. (2010) Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. *Lancet oncology,* 11: 973-982.	Bisphophonate - pamidronate	included in cochrane review Mhaskar et al 2012
9. Heim, M. E., Clemens, M. R., Queisser, W., Pecherstorfer, M., Boewer, C., Herold, M., Franke, A., Herrmann, Z., Loose, R. & Edler, L. (1995) Prospective randomized trial of dichloromethylene bisphosphonate (clodronate) in patients with multiple myeloma requiring treatment. A multicenter study. *Onkologie.,* 18: 439-448.	bisphosphonate -clodronate	included in cochrane review Mhaskar et al 2012
10. Kraj, M., Poglod, R., Pawlikowski, J. & Maj, S. (2000) The effect of long-term pamidronate treatment on skeletal morbidity in advanced multiple myeloma. *Acta Haematologica Polonica,* 31: 379-389.	Bisphosphonate - pamidronate	included in cochrane review Mhaskar et al 2012
11. Lahtinen, R., Laakso, M., Palva, I., Virkkunen, P. & Elomaa, I. (1992) Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group.[Erratum appears in Lancet 1992 Dec 5;340(8832):1420]. *Lancet,* 340: 1049-1052.	Bisphosphonate – clodronate	included in cochrane review Mhaskar et al 2012
12. Leng, Y., Chen, S. L. & Shi, H. Z. (2002) [Effects of pamidronate disodium (Bonin) combined with chemotherapy on bone pain in multiple myeloma]. *Hang.tian.yi.xue.yu yi.xue.gong.cheng [Space medicine & medical.engineering.],* 15: 377-378.	Bisphosphonate - pamidronate	included in cochrane review Mhaskar et al 2012
13. McCloskey, E. V., Dunn, J. A., Kanis, J. A., MacLennan, I. C. & Drayson, M. T. (2001) Long-term follow-up of a prospective, double-blind, placebo-controlled randomized trial of clodronate in multiple myeloma. *British.journal of haematology.,* 113: 1035-1043.	Bisphosphonate – clodronate	included in cochrane review Mhaskar et al 2012
14. Menssen, H. D., Sakalová, A., Fontana, A., Herrmann, Z., Boewer, C., Facon, T., Lichinitser, M. R., Singer, C. R., Euller, Z. L., Wetterwald, M.,	Bisphosphonate – ibandronate	included in cochrane review Mhaskar et al 2012

Paper	Intervention	Reasons for exclusion
Fiere, D., Hrubisko, M., Thiel, E. & Delmas, P. D. (2002) Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *Journal of clinical.oncology,* 20: 2353-2359.		
15. Morgan, G. J., Davies, F. E., Gregory, W. M., Cocks, K., Bell, S. E., Szubert, A. J., Navarro, C. N., Drayson, M. T., Owen, R. G., Feyler, S., Ashcroft, A. J., Ross, F., Byrne, J., Roddie, H., Rudin, C., Cook, G., Jackson, G. H. & Child, J. A. (2010) First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet,* 376: 1989-1999.	bisphosphonates – zoledronic acid versus clodronic acid	included in cochrane review Mhaskar et al 2012
16. Musto, P., Petrucci, M. T., Bringhen, S., Guglielmelli, T., Caravita, T., Bongarzoni, V., Andriani, A., D'Arena, G., Balleari, E., Pietrantuono, G., Boccadoro, M., Palumbo, A. & GIMEMA (Italian Group for Adult Hematologic Diseases) (2008) A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma.[Erratum appears in Cancer. 2008 Nov 15;113(10):2835]. *Cancer,* 113: 1588-1595.	bisphosphonates – zoledronic acid	included in cochrane review Mhaskar et al 2012
17. Musto, P., Falcone, A., Sanpaolo, G., Bodenizza, C., Cascavilla, N., Melillo, L., Scalzulli, P. R., Dell'Olio, M., Sala, A., Mantuano, S., Nobile, M. & Carella, A. M. (2003) Pamidronate reduces skeletal events but does not improve progression-free survival in early-stage untreated myeloma: results of a randomized trial. *Leukemia & Lymphoma,* 44: 1545-1548.	bisphosphonates – Pamidronate	included in cochrane review Mhaskar et al 2012
18. Rosen, L. S., Gordon, D., Kaminski, M., Howell, A., Belch, A., Mackey, J., Apffelstaedt, J., Hussein, M. A., Coleman, R. E., Reitsma, D. J., Chen, B. L. & Seaman, J. J. (2003) Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer,* 98: 1735-1744.	bisphosphonates – zoledronic acid compared with pamidronate disodium	included in cochrane review Mhaskar et al 2012
19. Terpos, E., Palermos, J., Tsionos, K., Anargyrou, K., Viniou, N., Papassavas, P., Meletis, J. & Yataganas, X. (2000) Effect of pamidronate administration on markers of bone turnover and disease activity in multiple myeloma. *European.journal of haematology.,* 65: 331-336.	bisphosphonates – Pamidronate	included in cochrane review Mhaskar et al 2012

Paper	Intervention	Reasons for exclusion
20. Terpos, E., Viniou, N., Fuente, J., Meletis, J., Voskaridou, E., Karkantaris, C., Vaiopoulos, G., Palermos, J., Yataganas, X., Goldman, J. M. & Rahemtulla, A. (2003) Pamidronate is superior to ibandronate in decreasing bone resorption, interleukin-6 and beta 2-microglobulin in multiple myeloma. *European.journal of haematology.,* 70: 34-42.	bisphosphonates - Pamidronate ibandronate	included in cochrane review Mhaskar et al 2012
21. Richardson, P. G., Laubach, J. P., Schlossman, R. L., Ghobrial, I. M., Mitsiades, C. S., Rosenblatt, J., Mahindra, A., Raje, N., Munshi, N. & Anderson, K. C. (2012) The Medical Research Council Myeloma IX trial: the impact on treatment paradigms. [Review]. *European Journal of Haematology,* 88: 1-7.	Bisphosphonates - zoledronic acid vs. clodronate	Review of MRC myeloma IX trial: Morgan et al. (2010)
22. Morgan, G. J., Davies, F. E., Gregory, W. M., Szubert, A. J., Bell, S. E., Drayson, M. T., Owen, R. G., Ashcroft, A. J., Jackson, G. H. & Child, J. A. (2013) Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial. *Blood,* 119: 5374-5383.	bisphosphonates	Follow up from MRC myeloma IX trial. Bisphosphonate maintenance therapy. Maintenance therapy not covered in scope and not relevant for question.
23. Morgan, G. J. (2013) Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. *Clinical Cancer Research,* 19: 6030-6038.	bisphosphonates	Extended long term follow up from MRC myeloma IX trial. Confirms results from initial study. And looks at new/different outcomes. Not relevant for the review question. Not prevention of bone disease.
24. Aviles, A., Neri, N., Huerta, G. J. & Nambo, M. J. (2013) Randomized clinical trial of zoledronic acid in multiple myeloma patients undergoing high-dose chemotherapy and stem-cell transplantation. *Current.Oncology,* 20: e13-e20.	bisphosphonate -zoledronic acid	Extension of Aviles 2007. Randomized controlled phase iii trial to evaluate the effect of zol on overall survival and progression-free survival to assess the anticancer activity of ZOL. Not relevant to review question – does not look at preventing bone disease.
25. Lee, S.-H. (2014) Use of bisphosphonates and the risk of osteonecrosis among cancer patients: A systemic review and meta-analysis of the observational studies. *Supportive Care in Cancer,* 22: 533-560.	bisphosphonates	Not specific to myeloma
26. Palmieri, C., Fullarton, J. R. & Brown, J. (2013) Comparative efficacy of bisphosphonates in metastatic breast and prostate cancer and multiple myeloma: a mixed-treatment meta-analysis. *Clinical Cancer Research,* 19: 6863-6872.	bisphosphonates	Mixed-Treatment Meta-analysis. Studies for myeloma already included in Cochrane review.

Paper	Intervention	Reasons for exclusion
27. Berenson, J. R., Boccia, R., Lopez, T., Warsi, G. M., Argonza, A. E., Lake, S., Ericson, S. G. & Collins, R. (2011) Results of a multicenter open-label randomized trial evaluating infusion duration of zoledronic acid in multiple myeloma patients (the ZMAX trial). *Journal of Supportive.Oncology,* 9: 32-40.	bisphosphonate -zoledronic acid	This study was designed to assess whether prolonging the infusion time of zoledronic acid from the recommended 15 to 30 minutes would improve kidney safety in MM patients, assessed by pharmacokinetics measuring serum creatinine levels.
28. Kraj, M. (2004) The effects of 8-year pamidronate treatment on skeletal morbidity in patients with advanced multiple myeloma. *Nowotwory,* 54: 570-577.	Bisphosphonate - pamidronate	Follow up from Kraj et al 2000. Confirms results from initial study. Not relevant for the review question.
29. Pepe, J., Petrucci, M. T., Mascia, M. L., Piemonte, S., Fassino, V., Romagnoli, E. & Minisola, S. (2008) The effects of alendronate treatment in osteoporotic patients affected by monoclonal Gammopathy of undetermined significance. *Calcified Tissue International,* 82: 418-426.	Bisphosphonate - alendronate	MUGS - not in PICO. Management of MGUS not in scope.
30. Ria, R., Reale, A., Moschetta, M., Mangialardi, G., Dammacco, F. & Vacca, A. (2013) A retrospective study of skeletal and disease-free survival benefits of zoledronic acid therapy in patients with multiple myeloma treated with novel agents. *International Journal of Clinical and Experimental Medicine,* 6: 30-38.	Bisphosphonate - zoledronic acid	Retrospective study. Not RCT.
31. Kraj, M., Poglod, R., Maj, S., Pawlikowski, J., Sokolowska, U. & Szczepanik, J. (2004) Long-term efficacy and safety of zoledronic acid compared with pamidronate in the treatment of myeloma bone disease. *Acta Haematologica Polonica,* 35: 227-241.	Bisphosphonate - zoledronic acid compared with pamidronate	Only 9 patients in the study. 3 patients in each arm.
32. Berenson, J. R., Hillner, B. E., Kyle, R. A., Anderson, K., Lipton, A., Yee, G. C., Biermann, J. S. & American Society of Clinical Oncology Bisphosphonates Expert Panel. (2002) American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *Journal of Clinical Oncology,* 20: 3719-3736.	Bisphosphonates	Evidence based review and guidelines 2002. 4 RCTs identified. Evidence is included and updated in cochrane review Mhaskar et al 2012.
33. Bloomfield, D. J. (1998) Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers: an evidence-based review (Structured abstract). *Journal of clinical.oncology,* 16: 1218-1225.	Bisphosphonates	Evidence based review 1998. 3 myeloma RCTs identified. Evidence is included and updated in cochrane review Mhaskar et al 2012.
34. Ibrahim, A., Scher, N., Williams, G., Sridhara, R., Li, N., Chen, G., Leighton, J., Booth, B., Gobburu, J. V., Rahman, A., Hsieh, Y., Wood, R., Vause, D. & Pazdur, R. (2003) Approval summary for zoledronic	bisphosphonate -zoledronic acid	Summarizes data submitted to the United States Food and Drug Administration for marketing approval of zoledronic acid. 2003.

Paper	Intervention	Reasons for exclusion
acid for treatment of multiple myeloma and cancer bone metastases. *Clinical.cancer research.,* 9: 2394-2399.		Includes 1 RCT for myeloma –Berenson et al 1998
35. Terpos, E., Sezer, O., Croucher, P. I., Garcia-Sanz, R., Boccadoro, M., San, M. J., Ashcroft, J., Blade, J., Cavo, M., Delforge, M., Dimopoulos, M. A., Facon, T., Macro, M., Waage, A., Sonneveld, P. & European, M. N. (2009) The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. [Review] [193 refs]. *Annals of Oncology,* 20: 1303-1317.	bisphosphonates	Evidence review and recommendations. 2009. Evidence is included and updated in cochrane review Mhaskar et al 2012.
36. Terpos, E., Morgan, G., Dimopoulos, M. A., Drake, M. T., Lentzsch, S., Raje, N., Sezer, O., Garcia-Sanz, R., Shimizu, K., Turesson, I., Reiman, T., Jurczyszyn, A., Merlini, G., Spencer, A., Leleu, X., Cavo, M., Munshi, N., Rajkumar, S. V., Durie, B. G. M. & Roodman, G. D. (2013) International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma-Related Bone Disease. *Journal of Clinical Oncology,* 31: 2347-U179.	bisphosphonates	Evidence review and recommendations. 2013. Included papers are in our list and will be assessed in our own evidence review.
37. Terpos, E., Kastritis, E. & Dimopoulos, M. (2012) Prevention and Treatment of Myeloma Bone Disease. *Current Hematologic Malignancy Reports,* 7: 249-257.	Bisphosphonates	Expert review
38. Terpos E., K. (2013) Skeletal-related events in patients with multiple myeloma in the era of novel agents: Low incidence of pathological fractures after treatment. *Blood,* Conference: 21.	bisphosphonates	Conference poster abstract. Retrospective analysis of incidence of SREs.
39. Imrie, K. (2005) Role of bisphosphonates in the management of skeletal complications in patients with multiple myeloma. *Current Oncology,* 12: 3-17.	bisphosphonates	Evidence review and recommendations. 2005. Evidence is included and updated in cochrane review Mhaskar et al 2012.
40. Kuhl, S., Walter, C., Acham, S., Pfeffer, R. & Lambrecht, J. T. (2012) Bisphosphonate-related osteonecrosis of the jaws - A review. *Oral Oncology,* 48: 938-947.	Bisphosphonates	Review of bisphosphonate-related osteonecrosis of the jaws. Not specific to myeloma.
41. Kumar, A., Galeb, S. & Djulbegovic, B. (2011) Treatment of patients with multiple myeloma: an overview of systematic reviews. [Review]. *Acta Haematologica,* 125: 8-22.	Bisphosphonates	Summary off 11 systematic reviews on treatment of myeloma. For bisphospohonates – 1 review - cochrane review Mhaskar et al 2010 version.
42. Kyle, R. A., Yee, G. C., Somerfield, M. R., Flynn, P. J., Halabi, S., Jagannath, S., Orlowski, R. Z., Roodman, D. G., Twilde, P. & Anderson,	Bisphosphonates	Update of American society of clinical oncology guidelines on the role of bisphosphonates in myeloma published in 2002.

Paper	Intervention	Reasons for exclusion
K. (2007) American society of clinical oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *Journal of clinical oncology,* 25: 2464-2472.		Evidence is included and updated in cochrane review Mhaskar et al 2012.
43. Kyle, R. A. (2007) ASCO 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma: Guideline summary. *Journal of Oncology Practice,* 3: 236.	Bisphosphonates	Comment/editorial/summary on Kyle et al 2007 reference above
44. Ross, J. R., Saunders, Y., Edmonds, P. M., Patel, S., Wonderling, D., Normand, C. & Broadley, K. (2004) A systematic review of the role of bisphosphonates in metastatic disease. [Review] [335 refs]. *Health Technology Assessment (Winchester, England),* 8: 1-176.	bisphosphonates	Review of the role of bisphosphonates in metastatic disease. Not specific to myeloma. 2004. Myeloma references included in cochrane review Mhaskar et al 2012.
45. Yao, X.-J. (2010) Bisphosphonates for multiple myeloma: A systematic review. *Chinese Journal of Evidence-Based Medicine,* 10: 1188-1193.	Bisphosphonates	Paper not in English Papers in review are included in cochrane review Mhaskar et al 2012
46. Macro, M. (2008) New guidelines for the use of bisphosphonates in multiple myeloma. *Hematologie,* 14: 244-247.	bisphosphonates	Paper not in english
47. Lipton, A. (1998) Markers of bone resorption in patients treated with pamidronate. *European Journal of Cancer,* 34: 2021-2026.	Bisphosphonate - pamidronate	Mixed population: breast cancer and myeloma.
48. Poon, M., et al (2013) Incidence of skeletal morbidity rates over time in patients with multiple myeloma-related bone disease as reported in randomized trials employing bone-modifying agents. *Journal of Comparative Effectiveness Research,* 2: 69-76.	bisphosphonates	Review of skeletal morbidity rates. 8 RCTs included, but these are included in cochrane review Mhaskar et al 2012
49. Peddi, P., Lopez-Olivo, M. A., Pratt, G. F. & Suarez-Almazor, M. E. (2013) Denosumab in patients with cancer and skeletal metastases: A systematic review and meta-analysis. *Cancer Treatment Reviews,* 39: 97-104.	Denosumab	Systematic review. Denosumab in patients with cancer and skeletal bone metasates. 6 RCTs. Mix of cancers. All analysed together. No specific analysis/results for myeloma.
50. Body, J. J., Facon, T., Coleman, R. E., Lipton, A., Geurs, F., Fan, M., Holloway, D., Peterson, M. C. & Bekker, P. J. (2006) A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clinical.cancer research.,* 12: 1221-1228.	denosumab	Phase II trial. Randomized, double-blind, active-controlled multicenter study to determine the safety, pharmacokinetics and pharmacodynamics of denosumab in patients with breast cancer (n = 29) or multiple myeloma (n = 25).
51. Qiao, G.-L. (2013) Comparison of efficacy and safety of denosumab versus zoledronic acid for treating skeletal-related events caused by bone metastasis in patients with maligmant solid tumors and multiple myeloma: A Meta-analysis of randomized controlled trials. *Tumor,* 33:	denosumab versus zoledronic acid	Paper not in English. Also mixed cancer population – not specific to myeloma.

Paper	Intervention	Reasons for exclusion
48-57.		
52. Sun, L. & Yu, S. (2013) Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systematic review and meta-analysis. [Review]. *American Journal of Clinical Oncology,* 36: 399-403.	denosumab versus zoledronic acid	Systematic review. Denosumab vs. zoledronic acid in patients with bone metasates secondary to malignancy. 3 RCTs. Mix of cancers. All analysed together. No specific analysis/results for myeloma.
53. von, M. R. (2010) Results froma phase 3 randomized, double-blind, double-dummy clinical trial comparing denosumab with zoledronic acid for the management of bone metastases in patients with advanced solid tumors or multiple myeloma. *Bone,* 46: S44.	denosumab zoledronic acid	Conference abstract so limited details. For full paper see Henry et al 2011
54. Burkiewicz, J. S., Scarpace, S. L. & Bruce, S. P. (2009) Denosumab in osteoporosis and oncology. [Review] [35 refs]. *Annals of Pharmacotherapy,* 43: 1445-1455.	denosumab	Review of denosumab in osteoporosis and oncology. Only phase 3 trial of denosumab with published results in patients with cancer is an RCT in patients with breast cancer. Data for myeloma limited to phase 1 and 2 trials.
55. Ford, J. (2013) Systematic review of the clinical effectiveness and cost-effectiveness, and economic evaluation, of denosumab for the treatment of bone metastases from solid tumours. *Health Technology Assessment,* 17: 1-385.	denosumab	Evidence review for NICE TA265. Possible conflict here? The aim of this review was to assess the clinical effectiveness and cost-effectiveness of denosumab, within its licensed indication, for the prevention of SREs in patients with bone metastases from solid tumours. Denosumab (Xgeva®, Amgen) for the prevention of SREs in bone metastases from solid tumours was granted marketing authorisation in July 2011. Multiple myeloma was not included within the marketing authorisation and therefore has been removed from the decision problem chapter of the report.
56. Ford, J. A. (2013) Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis. *European Journal of Cancer,* 49: 416-430.	Denosumab	Summary of Ford 2013 health technology assessment
57. Hageman, K., Patel, K. C., Mace, K. & Cooper, M. R. (2013) The role of denosumab for prevention of skeletal-related complications in multiple myeloma. [Review]. *Annals of Pharmacotherapy,* 47: 1069-1074.	denosumab	Review. Included papers have been screened individually.
58. Fizazi, K., Lipton, A., Mariette, X., Body, J. J., Rahim, Y., Gralow, J. R., Gao, G., Wu, L., Sohn, W. & Jun, S. (2009) Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer,	denosumab	A phase II trial comparing denosumab to bisphosphonate continuation in patients with elevated urinary N-telopeptide levels (uNTX) despite bisphosphonate therapy.

Paper	Intervention	Reasons for exclusion
breast cancer, or other neoplasms after intravenous bisphosphonates. *Journal of clinical.oncology,* 27: 1564-1571.		111 patients. Mixed cancer. Only 9 patients with myeloma. Small sample size limits the generalizability to the myeloma population. Primary outcome of the study was bone marker turnover.
59. Palumbo, A., Durie, B. G., Raje, N., Sanz, R. G., Sezer, O., Shimizu, K., Terpos, E., Willenbacher, W., Qian, Y. & Balakumaran, A. (2012) Denosumab Compared with Zoledronic Acid for Preventing Skeletal Complications in Patients with Multiple Myeloma: A Randomized, Phase 3, Double-Blind, Double-Dummy Trial. *Annals of Oncology,* 23: 360.	Denosumab Vs Zoledronic Acid	Abstract for ongoing phase 3 study. So no results yet. This randomised, double-blind, double-dummy, global multicentre study compares denosumab to zoledonic acid in patients with newly diagnosed myeloma with evidence of 1 radiographic bone lesion (NCT01345019) Results are expected 2016.
60. Vadhan, R. S., Moos, R., Fallowfield, L. J., Patrick, D. L., Goldwasser, F., Cleeland, C. S., Henry, D. H., Novello, S., Hungria, V., Qian, Y., Feng, A., Yeh, H. & Chung, K. (2012) Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid. *Annals.of oncology,* 23: 3045-3051.	Denosumab Vs Zoledronic Acid	Extension of Henry et al. to analyse additional end points from the trial (But not powered for these end points as not primary outcomes). Analysis done on whole population not separated by tumour type. So no specific results reported for myeloma.
61. Golombick, T., Diamond, T. H., Manoharan, A. & Ramakrishna, R. (2012) Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. *American Journal of Hematology,* 87: 455-460.	curcumin	19 MGUS patients and 17 asymptomatic myeloma patients –all analysed together. MGUS not covered in scope. Outcomes different to those in PICO – no clinical outcomes.
62. Li, X., Ling, W., Khan, S. & Yaccoby, S. (2012) Therapeutic effects of intrabone and systemic mesenchymal stem cell cytotherapy on myeloma bone disease and tumor growth. *Journal of Bone and Mineral Research,* 27: 1635-1648.	mesenchymal stem cell cytotherapy	Proof-of-concept mouse model study
63. Wang, Z. Y., Qiao, D., Lu, Y. H., Curtis, D., Wen, X. T., Yao, Y. et al. (2015). Systematic Literature Review and Network Meta-Analysis Comparing Bone-Targeted Agents for the Prevention of Skeletal-Related Events in Cancer Patients With Bone Metastasis. The Oncologist, 20, 440-449.	Bone-targeted agents.	Systematic review, only one of the included trials had patients with myeloma, and they were in the minority in that trial.

Health economic evidence

Myeloma: diagnosis and management of myeloma	Economic evidence summary

Topic: The prevention and management of bone disease, including spinal bone disease, for patients with myeloma.

Key question: What is the most effective method of preventing bone disease in patients with myeloma?

Population: Patients diagnosed with symptomatic myeloma, Patients diagnosed with asymptomatic myeloma, Patients diagnosed with myeloma who have renal disease, Patients with relapsed myeloma.
Intervention: Bisphosphonates, calcium supplements, vitamin D supplements, osteoclast inhibition, bone anabolic therapy, exercise.

Comparator: Placebo, no treatment, each other

Outcomes: Skeletal related events, adverse events, quality of life, overall survival, Progression-free survival, pain, need for radiotherapy, hypercalcaemia.

Summary

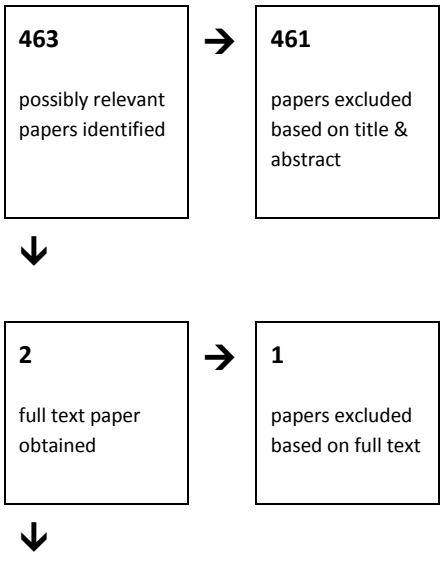
- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted from any OECD countries were considered (Guidelines Manual 2014).
- 463 possibly relevant papers were identified. Of these, 2 full papers relating to this topic were obtained for appraisal. Both papers identified used nearly identical models with differing costs to represent the perspective of a UK and a Canadian healthcare system. Therefore only one paper (Delea et al. 2012) was included in the current review of published economic evidence for this topic.
- The study was a cost-effectiveness analysis of zoledronic acid (ZOL) versus clodronic acid (CLO) for patients receiving first-line treatment for Stage I-III myeloma. The study reported the results in terms of cost per Quality Adjusted Life Year (QALY) gained and considered a NHS and Personal Social Services (PSS) perspective.
- Delea et al. is deemed directly applicable to the decision problem that we are evaluating. This is because it took a NHS+PSS perspective and reported health outcomes in terms of QALYs. In addition, quality of life states were scored directly by the relevant patient group using the EQ-5D

health questionnaire and valued using UK population preferences.

- Potentially serious limitations were identified with Delea et al. Most notably, a potential conflict of interest was identified as the study was funded by and the majority of authors owned stock options in the manufacturer of ZOL (Novartis Pharmaceuticals Corporation).Uncertainty around the utility values for both ZOL and CLO were also not appropriately captured in sensitivity analyses and the range of deterministic sensitivity analyses performed was inadequate.
- The base case suggested that treating with ZOL over CLO would cost £5443 per QALY gained although this varied from ZOL being dominant (less costly, more effective) to £19,378 per QALY gained during deterministic sensitivity analysis.
- Deterministic and probabilistic sensitivity analyses suggested this result was robust with ZOL having a 90% and 94% probability of being cost-effective at a willingness to pay threshold of £20000 and £30000 respectively although uncertainty around utility values for the interventions were not adequately captured.

Volume of evidence

- 463 possibly relevant papers were identified. Of these, 2 full papers relating to this topic were obtained for appraisal. Both papers reported a near identical model from a Canadian and UK healthcare system perspective. Only the paper from the NHS + PSS perspective (Delea et al, 2012) was included in the current review of published economic evidence for this topic.
- Delea et al was a cost-effectiveness analysis, conducted from a NHS and PSS perspective using effectiveness and utility data from a UK RCT
- The study reported cost-effectiveness results in terms of cost per QALY gained measured using the EQ-5D health questionnaire.



Selection criteria for included evidence:

- Studies that compare costs and health consequences of interventions were included (i.e. true cost-effectiveness analyses)
- Quality of life based outcomes were used as the measure of effectiveness in at least one of the analyses presented
- Studies conducted in OECD countries were included
- Studies that presented incremental results or presented enough information for incremental results to be derived
- Studies that matched the population, interventions,

	1 papers included in evidence review	comparators and outcomes specified in PICO • Studies not considering a UK NHS+PSS perspective which presented identical or similar economic models to a study which did were excluded

Quality and applicability of the included studies

		Applicability	
		Directly applicable	**Partially applicable**
Methodological quality	**Minor limitations**		
	Potentially serious limitations	Delea et al. 2012	
	Very serious limitations		

- Delea et al. is deemed directly applicable to the decision problem that we are evaluating. This is because the study considered a NHS+PSS perspective and reported health outcomes in terms of QALYs. In addition, quality of life values were scored directly from the patient group and valued using UK population preferences.
- Potentially serious limitations were identified with Delea et al. Most notably, a potential conflict of interest was identified as the study was funded by and the majority of authors owned stock options in the manufacturer of zoledronic acid (Novartis Pharmaceuticals Corporation).Uncertainty around the utility values for both ZOL and CLO were also not adequately captured in sensitivity analyses.

1. Delea TE, Rotter J, Taylor M, Chandiwana D et al. 'Cost-effectiveness of zoledronic acid vs clodronic acid for newly-diagnosed multiple myeloma from the United Kingdom healthcare system perspective.' **Journal of Medical Economics** 15 (2012): p454-64.

Managing non-spinal bone disease

Review Question:

What are the most effective treatments (other than chemotherapy) for non-spinal bone disease in patients with myeloma (including radiotherapy and surgical intervention)?

Question in PICO format

Population	Intervention	Comparator	Outcomes
myeloma patients with non-spinal bone disease	• orthopaedic surgery (Pinning, plating, bone grafting. Prophylactic vs. therapeutic intervention.) • Radiotherapy (including dose) • Interventional pain management • Bisphosphonates • Denosumab • Supportive care	• Each other • Conservative management	• Health related quality of life • Progression free survival • Overall survival • Adverse events (e.g., ONJ) • pain control • Mobility/dependency • Patient expectation

Evidence statements

Radiotherapy

Very low quality evidence came from one observational study of radiotherapy for non-spinal bone disease in 27 patients with multiple myeloma (Catell et al., 1998). The study aimed to examine the effectiveness of radiotherapy to the symptomatic portion of a long bone for palliation. The outcome assessed was progressive disease and it was found that 15% of patients developed progressive disease.

Surgery

Very low quality evidence came from three observational studies of surgery for non-spinal bone disease in patients with multiple myeloma (Chang et al., 2001; Natarajan et al., 2007; Papagelopoulos et al., 1997). Using data from all 3 studies the complication rate from surgery was 25.9%; the main issues being intra-operative complications and wound related complications. From 2 studies the implant failure rate was low (6.9%) and there was improvement in both pain (45 – 91% of patients reporting complete pain relief) and ambulatory status (40 – 64% of patients not requiring support for moving around/walking).

Two studies assessed overall survival post surgery. One study of 22 patients (Chang et al, 2001) found the mean overall survival to be 19 months (range 3 – 60 months). Another study of 46 patients (Papagelopoulos et al., 1997) found the median overall survival to be 18 months (range 7 days – 19.9 years).

One study of 9 patients (Natarajan et al., 2007) assessed functional outcome which was determined to be good or excellent in 67% of patients.

Interventional pain management, Bisphosphonates, Denosumab and Supportive care

We did not find evidence for these interventions.

Table 8.8: GRADE profile: What are the most effective treatments for non-spinal bone disease in patients with myeloma (radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	radiotherapy	control	Relative (95% CI)	Absolute	
progressive disease											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/27 (14.8%)	n/a	-	-	⊕OOO VERY LOW

[1] *retrospective case series (no comparator);* [2] *small sample size limits precision of results*

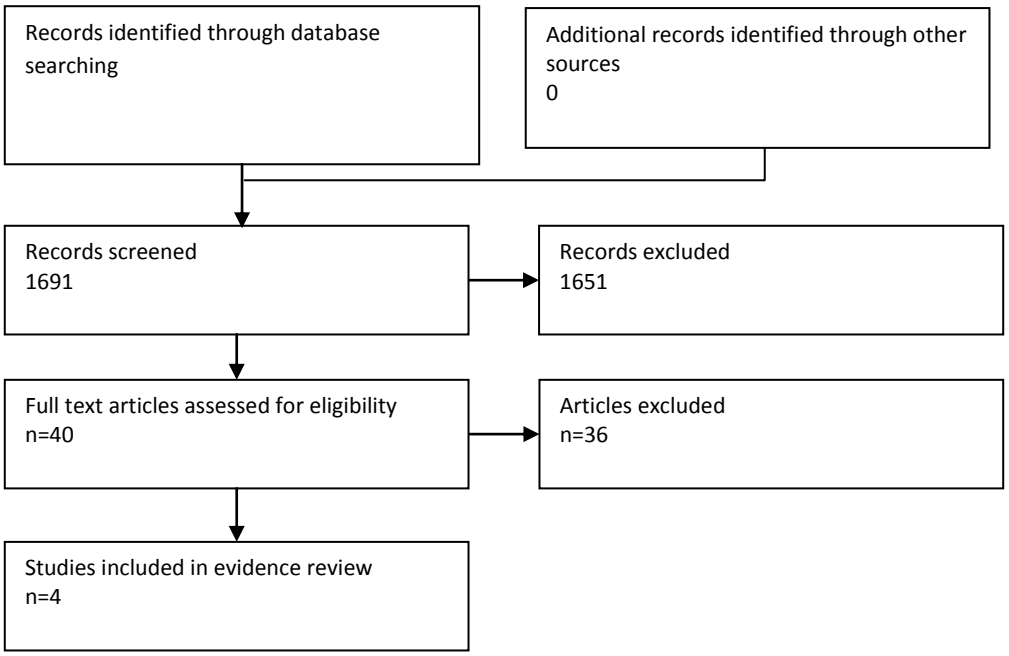
Table 8.9:: GRADE profile: What are the most effective treatments for non-spinal bone disease in patients with myeloma (orthopaedic surgery)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	orthopedic surgery	control	Relative (95% CI)	Absolute	
overall survival											
2	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	68	n/a	-	Study 1 (n=22): mean overall survival 19 months (range 3 – 60 months) Study 2 (n=46): median overall survival 18 months (range 7 days – 19.9 years)	⊕OOO VERY LOW
implant failure											
2	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	5/72 (6.9%)	n/a	-	-	⊕OOO VERY LOW
complication rate											
3	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	21/81 (25.9%)	n/a	-	-	⊕OOO VERY LOW
pain relief											
2	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	67	n/a	-	Complete pain relief: 45 – 91%	⊕OOO VERY LOW
ambulatory status											
2	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	57	n/a	-	Full weight bearing/used no support: 40 – 64%	⊕OOO VERY LOW
functional outcome											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	9	n/a	-	Functional outcome was good or excellent in 67% of patients	⊕OOO VERY LOW

[1] *retrospective case series (no comparator);* [2] *the different studies use different surgical methods;* [3] *small sample size limits precision of results*

Search Results

Figure 8.3: Screening results



Evidence table

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Catell et al., 1998</td><td>Retrospective case series

USA</td><td>27 myeloma patients

Mean age
63 years
12 female: 15 male</td><td>The symptomatic lesion plus a margin of 1-2cm was irradiated

Mean radiation dose 27.82 Gy (range 6.00 – 44.90 Gy)

All patients were treated with megavoltage therapy, usually ^{60}Co.</td><td>No comparator</td><td>27 patients received treatment to a long bone with 41 siteS irradiated
<table>
<tr><th>Site</th><th>No. treated</th><th>Mean length of field

absolute length (cm)</th><th>Mean length of field

relative length (% of total length of bone)</th></tr>
<tr><td>humerus</td><td>17</td><td>20</td><td>68</td></tr>
<tr><td>femur</td><td>22</td><td>18</td><td>42</td></tr>
<tr><td>radius</td><td>1</td><td></td><td></td></tr>
<tr><td>ulna</td><td>1</td><td></td><td></td></tr>
</table>
Progressive disease developed in 4 patients/sites.
In 3 patients the recurrence involved both the previously irradiated and adjacent unirradiated tissue.
In 1 patient the previously irradiated site remained under control while disease progressed further along the bone.</td><td>Non-comparative study</td></tr>
</table>

<table>
<tr>
<td>Chang et al., 2001</td>
<td>Retrospective case series

Taiwan</td>
<td>22 myeloma patients with long bone fractures

Mean age 65 years
13 female: 9 male</td>
<td>Surgery:
Open reduction and internal fixation either with plates or intra-medullary nailing.
Cement augmentations were performed in 20/22 of cases.</td>
<td>No comparator</td>
<td>
<table>
<tr><th>Site</th><th>No. treated</th></tr>
<tr><td>humerus</td><td>6</td></tr>
<tr><td>femur</td><td>13</td></tr>
<tr><td>tibia</td><td>2</td></tr>
<tr><td>patella</td><td>1</td></tr>
</table>

Follow up period 3 – 85 months (mean 18 months)

Implant failure: 3/22 (13.6%) (all were treated by open reduction with plates)

Complication rate: 2/22 (9%) – superficial wound infections

Mean post operative survival time: 19 months (range 3 – 60 months)

<table>
<tr><th>Pain relief</th><th>No.</th></tr>
<tr><td>excellent</td><td>10</td></tr>
<tr><td>good</td><td>10</td></tr>
<tr><td>fair</td><td>2</td></tr>
<tr><td>poor</td><td>0</td></tr>
</table>

<table>
<tr><th>Ambulatory status</th><th>%</th></tr>
<tr><td>Full weight bearing</td><td>40</td></tr>
<tr><td>Partial weight bearing</td><td>33</td></tr>
<tr><td>Wheelchair bound</td><td>20</td></tr>
<tr><td>Confined to bed</td><td>7</td></tr>
</table>
</td>
<td>Non-comparative study

An objective evaluation of pain relief was made based on the amount of analgesics required
Excellent - no regular NSAID used
good - regular NSAID used
fair- regular NSAID but no regular narcotic
poor - regular narcotics for pain relief</td>
</tr>
</table>

<table>
<tr>
<td>Natarajan et al., 2007</td>
<td>Retrospective case series

India</td>
<td>9 myeloma patients with pathological fractures

Mean age 47.7 years
5 female: 4 male</td>
<td>Resection and reconstruction with custom made prosthesis

8: 316L stainless steel
1:titanium alloy</td>
<td>No comparator</td>
<td>
<table>
<tr><th>Site</th><th>No. treated</th></tr>
<tr><td>Proximal femur</td><td>3</td></tr>
<tr><td>Femoral shaft</td><td>3</td></tr>
<tr><td>Distal femur</td><td>1</td></tr>
<tr><td>Proximal humerus</td><td>1</td></tr>
<tr><td>Humeral shaft</td><td>1</td></tr>
</table>

Long term follow up annually.
Follow up period 60 – 166 months (mean 88.2 months)

Complications: 4
Intra-operative bleeding
Superficial skin necrosis
Deep infection
Periprosthetic fracture

5 year survival rate 66.7%

Functional outcome assessed using Enneking’s modified system of functional evaluation of surgical management of musculoskeletal tumours.
<table>
<tr><th>Functional outcome</th><th>No.</th></tr>
<tr><td>excellent</td><td>3</td></tr>
<tr><td>good</td><td>3</td></tr>
<tr><td>fair</td><td>2</td></tr>
<tr><td>poor</td><td>1</td></tr>
</table>
All patients had improved functional outcome
</td>
<td>Non-comparative study.

Lower average age than reported in literature.</td>
</tr>
</table>

<table>
<tr>
<td>Papagelopoulos et al., 1997</td>
<td>Retrospective case series

USA</td>
<td>46 myeloma patients

Mean age 65 years

Stage I: 7
Stage II: 31
Stage III: 8</td>
<td>Prosthetic hip replacement</td>
<td>No comparator</td>
<td>Probability of survival was 43% at 2 years and 13% at 5 years after the hip operation.

Median survival after hip replacement was 18 months (range: 7 days – 19.9 years).

Results for whole sample:
46 myeloma + 4 solitary plasmocytoma (2 of which developed myeloma later)

Follow up period 7 days – 19.9 years (mean 32.6 months)

Implant failure: 2 (4%)

Complications: 15
2 intra-operative complications
- distress pulmonary syndrome
- blood loss
1 cerebral infarction - death
1 septicemia -death
1 acute renal failure – death
6 wound related complications
1 superficial infection
4 persistent wound drainage
1 hematoma
1 late deep infection
1 Deep vein thrombosis
1 Sciatic nerve palsy
1 Recurrent dislocation
1 Aseptic loosening and medial migration of acetabular component

<table>
<tr><th>Pain relief</th><th>No. (%)</th></tr>
<tr><td>Complete hip pain relief</td><td>41 (91%)</td></tr>
<tr><td>Mild pain</td><td>3 (7%)</td></tr>
<tr><td>Moderate pain</td><td>1 (2%)</td></tr>
</table>
<table>
<tr><th>Ambulatory status</th><th>No. (%)</th></tr>
<tr><td>Used no support</td><td>29 (64%)</td></tr>
<tr><td>Occasionally used a cane</td><td>6 (13%)</td></tr>
</table>
</td>
<td>Non-comparative study</td>
</tr>
</table>

References of included studies

1. Catell, D., Kogen, Z., Donahue, B. & Steinfeld, A. (1998) Multiple myeloma of an extremity: must the entire bone be treated? *International Journal of Radiation Oncology, Biology, Physics,* 40: 117-119.
2. Chang, S. A., Lee, S. S., Ueng, S. W., Yuan, L. J. & Shih, C. H. (2001) Surgical treatment for pathological long bone fracture in patients with multiple myeloma: a retrospective analysis of 22 cases. *Chang Gung Medical Journal,* 24: 300-306.
3. Natarajan, M. V., Mohanlal, P. & Bose, J. C. (2007) The role of limb salvage surgery and custom mega prosthesis in multiple myeloma. *Acta Orthopaedica Belgica,* 73: 462-467.
4. Papagelopoulos, P. J., Galanis, E. C., Greipp, P. R. & Sim, F. H. (1997) Prosthetic hip replacement for pathologic or impending pathologic fractures in myeloma. *Clinical Orthopaedics and Related Research,* 192-205.

Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. Abruzzese, E., Iuliano, F., Trawinska, M. M. & Di Maio, M. (2008) (SM)-S-153: its use in multiple myeloma and report of a clinical experience. *Expert Opinion on Investigational Drugs,* 17: 1379-1387.	Expert review that includes a report on a case series of 10 myeloma patients treated with ^{153}Sm-EDTMP. Reduction in pain was reported after treatment. ^{153}Sm not in PICO. Patients also were treated with zoledronic acid at the same time. Patients had severe bone disease. Unclear if spinal and/or non-spinal.
2. Adamczyk-Cioch, M. (1996) Clodronate in the treatment of bone lesions and pseudo-rheumatic complains in multiple myeloma. *Reumatologia,* 34: 700-704.	Paper not in English.
3. Addeo, R., Nocera, V., Faiola, V., Vincenzi, B., Ferraro, G., Montella, L., Guarrasi, R., Rossi, E., Cennamo, G., Tonini, G., Capasso, E., Santini, D., Caraglia, M. & Del, P. S. (2008) Management of pain in elderly patients receiving infusion of zoledronic acid for bone metastasis: a single-institution report. *Supportive Care in Cancer,* 16: 209-214.	Mixed cancer population. Not specific to myeloma.
4. Alegre, A., Gironella, M., Bailen, A. & Giraldo, P. (2014) Zoledronic acid in the management of bone disease as a consequence of multiple myeloma: a review. *European Journal of Haematology,* 92: 181-188.	Expert review
5. Ali, N. (2013) Improved outcome of myeloma related bone pain with oral analgesics and bisphosphonate therapy: A single-center experience from Pakistan. *Progress in Palliative Care,* 21: 337-340.	Not specific to non-spinal bone disease. 125 myeloma patients - 89 with bone pain – spinal + non-spinal
6. Alvi, H. M. & Damron, T. A. (2013) Prophylactic stabilization for bone metastases, myeloma, or lymphoma: do we need to protect the entire bone? *Clinical Orthopaedics & Related Research,* 471: 706-714.	Mixed cancer population. Not specific to myeloma.
7. Avilés, A., Nambo, M. J., Neri, N., Castañeda, C., Cleto, S. & Huerta, G. J. (2007) Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Medical.oncology,* 24: 227-230.	Unclear if spinal bone disease also included. Not mentioned. Not specifically excluded so population is probably a mix of spinal and non-spinal bone disease?
8. Aviles, A., Neri, N., Huerta, G. J. & Nambo, M. J. (2013) Randomized clinical trial of zoledronic acid in multiple	Unclear if spinal bone disease also included. Not mentioned. Not specifically excluded so population

	myeloma patients undergoing high-dose chemotherapy and stem-cell transplantation. *Current.Oncology,* 20: e13-e20.	is probably a mix of spinal and non-spinal bone disease?
9.	Balducci, M., Chiesa, S., Manfrida, S., Rossi, E., Za, T., Frascino, V., De, B. B., Hohaus, S., Cellini, F., Mantini, G., D'Agostino, G. R., Gambacorta, M. A., Leone, A., Valentini, V. & De, S., V (2011) Impact of radiotherapy on pain relief and recalcification in plasma cell neoplasms: long-term experience. *Strahlentherapie und Onkologie,* 187: 114-119.	Not specific for myeloma: 42 (81%) myeloma, 10 (19%) solitary plasmacytoma (not in scope). Not specific to non-spinal bone disease: 35 (68% spinal); 15 (32%) non-spinal.
10.	Basile, A., Tsetis, D., Cavalli, M., Fiumara, P., Di, R. F., Coppolino, F., Coppolino, C., Mundo, E., Desiderio, C., Granata, A. & Patti, M. T. (2010) Sacroplasty for local or massive localization of multiple myeloma. *Cardiovascular & Interventional Radiology,* 33: 1270-1277.	Small case series. n=8. Spinal bone disease.
11.	Berenson, J. R., Lichtenstein, A., Porter, L., Dimopoulos, M. A., Bordoni, R., George, S., Lipton, A., Keller, A., Ballester, O., Kovacs, M. J., Blacklock, H. A., Bell, R., Simeone, J., Reitsma, D. J., Heffernan, M., Seaman, J. & Knight, R. D. (1996) Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *New England.journal of medicine,* 334: 488-493.	Not specific to non-spinal bone disease. There were 50 vertebral and 20 nonvertebral fractures in the pamidronate group, as compared with 91 and 44, respectively, in the placebo group
12.	Berenson, J. R., Lichtenstein, A., Porter, L., Dimopoulos, M. A., Bordoni, R., George, S., Lipton, A., Keller, A., Ballester, O., Kovacs, M., Blacklock, H., Bell, R., Simeone, J. F., Reitsma, D. J., Heffernan, M., Seaman, J. & Knight, R. D. (1998) Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *Journal of clinical.oncology,* 16: 593-602.	Not specific to non-spinal bone disease. Extension of Berenson 1996.
13.	Diaz, C. (2004) Treatment of multiple myeloma with intravenous pamidronate. Pain prevention and suppresion of hypercalcemia risk. *Medicina,* 64: 289-294.	Paper not in English.
14.	Durr, H. R., Kuhne, J. H., Hagena, F. W., Moser, T. & Refior, H. J. (1997) Surgical treatment for myeloma of the bone. A retrospective analysis of 22 cases. *Archives of Orthopaedic & Trauma Surgery,* 116: 463-469.	Case series of 22 patients. After excluding spinal bone disease and chemotherapy 5 patients remain.
15.	Falkmer, U., Jarhult, J., Wersall, P. & Cavallin-Stahl, E. (2003) A systematic overview of radiation therapy effects in skeletal metastases. [Review] [65 refs]. *Acta Oncologica,* 42: 620-633.	Review. Not specific to myeloma.
16.	Heim, M. E., Clemens, M. R., Queisser, W., Pecherstorfer, M., Boewer, C., Herold, M., Franke, A., Herrmann, Z., Loose, R. & Edler, L. (1995) Prospective randomized trial of dichloromethylene bisphosphonate (clodronate) in patients with multiple myeloma requiring treatment. A multicenter study. *Onkologie.,* 18: 439-448.	Not specific to non-spinal bone disease.
17.	Imseis, R. E., Palmieri, G. M. A., Holbert, J. M., Leventhal, M. R. & Sebes, J. I. (1999) Effect of calcitriol and pamidronate in multiple myeloma. *American Journal of the Medical Sciences,* 318: 61-66.	Case reports of the effect of calcitriol and pamidronate in 2 patients with myeloma and bone disease, one with spinal disease.
18.	Karwicki, L., Kmieciak, M. & Kopka, M. (2003) Surgical treatment of metastasic tumors to long bones in the material of the Unit. *Ortopedia Traumatologia Rehabilitacja,* 5: 358-363.	Paper not in english
19.	Kivioja, A. H., Karaharju, E. O., Elomaa, I. & Bohling, T. O. (1992) Surgical-Treatment of Myeloma of Bone. *European*	Case series of 33 patients. Not specific to non-spinal bone disease.

Journal of Cancer, 28A: 1865-1869.	Spinal =13, non-spinal = 20. The factors analysed were age, sex, presenting symptom, the reason for operative treatment, site and extent of the disease, method of operative treatment and eventual outcome. Different outcomes to those listed in PICO.
20. Koeberle, D., Bacchus, L., Thuerlimann, B. & Senn, H. J. (1999) Pamidronate treatment in patients with malignant osteolytic bone disease and pain - A prospective randomized double-blind trial. *Supportive Care in Cancer,* 7: 21-27.	Not specific to myeloma
21. Kmetec, A. & Hajdinjak, T. (2013) Evaluation of safety and analgesic consumption in patients with advanced cancer treated with zoledronic acid. *Radiology and Oncology,* 47: 289-295.	Not specific to non-spinal bone disease.
22. Leigh, B. R., Kurtts, T. A., Mack, C. F., Matzner, M. B. & Shimm, D. S. (1993) Radiation therapy for the palliation of multiple myeloma. *International Journal of Radiation Oncology, Biology, Physics,* 25: 801-804.	Not specific to non-spinal bone disease. Also outcomes not relevant to PICO.
23. Mavrogenis, A. F., Angelini, A., Pala, E., Zinzani, P. & Ruggieri, P. (2012) The role of surgery for haematologic neoplasms of bone. *Acta Orthopaedica Belgica,* 78: 382-392.	Not specific to non-spinal bone disease.
24. McSweeney, E. N., Tobias, J. S., Blackman, G., Goldstone, A. H. & Richards, J. D. (1993) Double hemibody irradiation (DHBI) in the management of relapsed and primary chemoresistant multiple myeloma. *Clinical.oncology),* 5: 378-383.	Not specific to bone disease. Mix of patients with and without bone disease. For those with bone disease it is unclear how many spinal/non-spinal.
25. Parker, M. J. (2011) Survival after pathological fractures of the proximal femur. *HIP International,* 21: 526-530.	Small case series of 9 myeloma patients within larger cohort of other cancers. Study simply reports on survival in comparison to other cancers.
26. Ripamonti, C., Fulfaro, F., Ticozzi, C., Casuccio, A. & De, C. F. (1998) Role of pamidronate disodium in the treatment of metastatic bone disease. [Review] [132 refs]. *Tumori,* 84: 442-455.	Review (old – 1998) and any relevant myeloma papers will be assessed in the evidence review separately.
27. Rodriguez Merchan, E. C. (1994) A study of the surgical treatment of 52 pathological fractures of the proximal femur. *Journal of Orthopaedic Rheumatology,* 7: 199-202.	Small case series of 7 myeloma patients within larger cohort of other cancers. Descriptive study. No outcomes reported for myeloma.
28. Rudzianskiene, M., Inciura, A., Juozaityte, E., Gerbutavicius, R., Simoliuniene, R., Rudzianskas, V. et al. (2015). The impact of one fraction of 8 Gy radiotherapy in palliative treatment of multiple myeloma patients with painful bone destructions. Turkish Journal of Medical Sciences, 45, 364-371.	Does not report outcomes for spinal and non-spinal bone disease separately.
29. Stolting, T., Knauerhase, H., Klautke, G., Kundt, G. & Fietkau, R. (2008) Total and single doses influence the effectiveness of radiotherapy in palliative treatment of plasmacytoma. *Strahlentherapie und Onkologie,* 184: 465-472.	Plasmacytoma
30. Takei, T. (1996) Treatment of pathologic fracture and surgical value of prognostic factors in multiple myeloma. *International Surgery,* 81: 403-406.	58 myeloma patients, not all had bone disease. Analysis of lab data to find predictive factors for a surgical approach. Surgery performed in 7 patients.

	Includes case report of 39 year old male.
31. Terpos E., B. (2014) Management of bone disease in multiple myeloma. *Expert Review of Hematology,* 7: 113-125.	Expert review.
32. Thein, R., Herman, A., Chechik, A. & Liberman, B. (2012) Uncemented arthroplasty for metastatic disease of the hip: preliminary clinical experience. *Journal of Arthroplasty,* 27: 1658-1662.	Retrospective review of 57 consecutive patients (60 hips) who underwent uncemented hip arthroplasty 8 (13.3%) myeloma Outcomes for myeloma not relevant for PICO: Time to surgery 51 months (± 39) Mortality rate 1 (12.5%) Follow up time 16 (10-30)
33. Tripathy, D., Body, J. J. & Bergstrom, B. (2004) Review of ibandronate in the treatment of metastatic bone disease: Experience from phase III trials. *Clinical Therapeutics,* 26: 1947-1959.	Expert review.
34. Utzschneider S., S. (2011) Surgical therapy of skeletal complications in multiple myeloma. *International Orthopaedics,* 35: 1209-1213.	Retrospective study of 75 consecutive patients treated surgically for multiple myeloma. Not specific to non-spinal bone disease : 45 had spinal bone disease.
35. Yaneva, M. P., Goranova-Marinova, V. & Goranov, S. (2006) Palliative radiotherapy in patients with multiple myeloma. *Journal of B.U.On.,* 11: 43-48.	Not specific to non-spinal bone disease: 63 vertebral fractures 29 spinal cord compression 7 cauda equine syndrome 17 extramedullary soft tissue formations 11 non-vertebral fractures
36. Zeifang, F., Zahlten-Hinguranage, A., Goldschmidt, H., Cremer, F., Bernd, L. & Sabo, D. (2005) Long-term survival after surgical intervention for bone disease in multiple myeloma. *Annals of Oncology,* 16: 222-227.	Explorative study of 84 patients with myeloma who were consecutively surgically treated Not specific to non-spinal bone disease : 54 had spinal disease.

Managing spinal bone disease

Review question:

Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma, and in which circumstances and order should they be offered?

PICO Table			
Population	**Intervention**	**Comparator**	**Outcomes**
Myeloma patients with spinal bone disease grouped according to type of spinal disease: - Lytic lesions - Pathological fracture - Vertebral collapse with risk of spinal cord compression - Vertebral collapse leading to loss of height and deformity (kyphosis) - Spinal instability	• Vertebral cement augmentation • Vertebroplasty • Balloon kyphoplasty • Lordoplasty • Spinal surgery • Percutaneous fixation • External bracing • Radiotherapy • Bisphosphonates • Denosumab • Interventional pain management	• Each other • Conservative management	• Vertebral collapse • Spinal cord compression • Health related quality of life • Progression free survival • Overall survival • Performance status • Adverse events • Pain control • Activities of daily living/mobility • Dependency

	• Supportive care		

Additional comments on PICO

Look for whether rehabilitation is reported in studies (e.g., physiotherapy and OT)

Do any studies identify treatment algorithms which help clinicians decide the order of treatments, eg radiotherapy first or vertebroplasty first?

Make notes if any of the following are also reported to affect treatment decision:
Level of pain
Location of pain
Duration of pain
Time elapsed since the fracture occurred
Number of vertebrae affected
Previous treatments
Other conditions/co-morbidities

Table 8.10 GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (vertebroplasty versus kyphoplasty)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vertebroplasty	Kyphoplasty	Relative (95% CI)	Absolute	
Pain (from baseline up to 1 week post-procedure) (measured with: Visual Analogue Scale; Brief Pain Inventory; SF-36; Better indicated by lower values)											
11[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	For vertebroplasty and kyphoplasty: Mean pain reduction 4.8±0.56	⊕OOO VERY LOW
Pain (from baseline to >1yr post-procedure) (measured with: Visual Analogue Scale; Brief Pain Inventory; SF-36; Better indicated by lower values)											
14[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	For vertebroplasty and kyphoplasty: Mean pain reduction 4.4±0.48	⊕OOO VERY LOW
Activities of daily living (change from baseline up to 1 week post-procedure) (measured with: Owestry Disability Index; scale 0-100; Better indicated by lower values)											
3[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	Mean decrease 39.2 (16.3 to 75) P=0.37	⊕OOO VERY LOW
Activities of daily living (change from baseline to >1 year post-procedure) (measured with: Owestry Disability Index; scale 0-100; Better indicated by lower values)											
4[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	-	Mean decrease 46.5 (14.5 to 75) P=0.88	⊕OOO VERY LOW
Infection											
1[3]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/576 (0.2%)	0/367 (0%)	P=0.64	-	⊕OOO VERY LOW
Pulmonary embolism											
1[3]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/576 (0%)	1/367 (0.3%)	P=0.21		⊕OOO VERY LOW
Myocardial Infarction											
1[3]	observational studies	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/576 (0%)	1/367 (0.3%)	P=0.21		⊕OOO VERY LOW
Vertebral compression fracture at untreated levels											
1[3]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/576 (7.3%)	25/367 (6.8%)	P=0.78		⊕OOO VERY LOW
Neurologic symptoms requiring revision surgery											
1[3]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/576 (0%)	2/367 (0.5%)	P=0.08		⊕OOO VERY LOW
Transient perioperative pain											
1[3]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/576 (0.7%)	2/367 (0.5%)	P=0.78		⊕OOO VERY LOW
Spinal cord compression											
0	no evidence										

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vertebroplasty	Kyphoplasty	Relative (95% CI)	Absolute	
Progression-free survival											
0	no evidence										
Overall survival (Kaplan-Meier curve)											
1[4]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[5]	none	39	n/a		Median survival= 20 months (range 2-91)	⊕OOO VERY LOW
Performance status											
0	no evidence										
Dependency											
0	no evidence										
Health-related quality of life											
0	no evidence										
Pain (at 1 month) (follow-up 1 months; measured with: Visual Acuity Scale; range of scores: 0-10; Better indicated by lower values)											
1[6]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	351		-	Mean reduction 4.2 (4.0 to 4.5)[7]	⊕⊕OO LOW
Improvement in activity (Proportion of patients scoring 0-1 (no limitations); range of scores 0-6; Better indicated by lower values)											
1[6]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	354			28% at baseline vs 59% post-procedure	⊕⊕OO LOW

[1] As reported in systematic review by Khan et al. (2014)
[2] Prospective and retrospective case series. Studies differed in adjunctive therapy, disease stage and other factors. Small sample size in individual studies.
[3] As reported in systematic review by Khan et al. (2014). Number of participants not reported
[4] Chew et al. (2011)
[5] Small number of participants with Myeloma (n=39) limits precision of results
[6] Erdem et al. (2013a)
[7] Average reduction of pain from baseline to 1 month

Table 8.11: GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (balloon kyphoplasty for painful vertebral compression fractures)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Balloon kyphoplasty	Non-surgical management	Relative (95% CI)	Absolute	
Vertebral collapse											
0	no evidence										

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Balloon kyphoplasty	Non-surgical management	Relative (95% CI)	Absolute	
Spinal cord compression											
0	no evidence										
Health-related quality of life (follow-up 1 month; measured with: SF-36 Physical components scale; range of scores: 0-100; Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 8.4 higher (7.7 to 9.1 higher)[5]	⊕OOO VERY LOW
Progression-free survival											
0	no evidence										
Overall survival (mortality rate)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	29/108 (26.9%)[6]	6/26 (23.1%)	RR 1.16 (0.54 to 2.51)	37 more per 1000 (from 106 fewer to 348 more)	⊕OOO VERY LOW
Performance status (follow-up 1 month; measured with: Karnofsky performance status; range of scores: 0-100; Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 15.3 higher (13.5 to 17.1 higher)[5]	⊕OOO VERY LOW
Quality of life (follow-up 1 month; measured with: SF-36 mental components scale; range of scores: 0-100; Better indicated by higher values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 11.1 higher (10.7 to 11.5 higher)[5]	⊕OOO VERY LOW
Pain control (follow-up 7 days; measured with: Numerical rating scale; range of scores: 0-10; Better indicated by lower values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 3.5 lower (3.8 to 3.2 lower)[7]	⊕OOO VERY LOW
Pain control (follow-up 1 month; measured with: Numerical rating scale; range of scores: 0-10; Better indicated by lower values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 3.3 lower (3.6 to 3.0 lower)[7]	⊕OOO VERY LOW
Reduced activity days caused by back pain (follow-up 1 month; Better indicated by lower values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 6.3 lower (6.8 to 5.8 lower)[5]	⊕OOO VERY LOW
Back-specific physical functioning (follow-up 1 month; measured with: Roland-Morris Disability Questionnaire (RDQ); range of scores: 0-24; Better indicated by lower values)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	65	52	-	MD 8.4 lower (7.6 to 9.2 lower)[5]	⊕OOO VERY LOW
Dependency											
0	no evidence										
Adverse events (follow-up 1 month; Adverse events in first month)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	26/70 (37.1%)	19/64 (29.7%)	RR 1.25 (0.77 to 2.03)	74 more per 1000 (from 68 fewer to 306 more)	⊕OOO VERY LOW
Serious adverse events (serious AEs after 1 month until study end)											

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Balloon kyphoplasty	Non-surgical management	Relative (95% CI)	Absolute	
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	37/70 (52.9%)	8/26 (30.8%)	RR 1.72 (0.93 to 3.19)	222 more per 1000 (from 22 fewer to 674 more)	⊕OOO VERY LOW
Pain (follow-up 3 months; assessed with Visual Analogue Scale 0 to 10; better indicated by lower score)											
1[8]	observational study	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	69	n/a	-	Mean pain score decreased from 7.9 at baseline to 2.5 post-procedure	⊕OOO VERY LOW

[1] Berenson et al. (2011)
[2] Sponsors of the study (Medtronic Spine LLC) contributed to study design, data collection and analysis.
[3] 68% of kyphoplasty group and 56% of control group had cancer diagnosis other than myeloma which limits relevance of study to the review question
[4] Small sample size limits precision of results
[5] Mean change in intervention group. Statistically significant difference at one month in comparison with control group.
[6] Intervention group includes kyphoplasty + crossover patients
[7] Difference in change from baseline between control and kyphoplasty group
[8] Papanastassiou et al. (2014)
[9] Retrospective case series.
[10] Small sample size (n=69) limits precision of results

Table 8.12 GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (radiofrequency targeted vertebral augmentation)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Radiofrequency targeted vertebral augmentation	control	Relative (95% CI)	Absolute	
Vertebral collapse											
0	no evidence										
Spinal cord compression											
0	no evidence										
Health-related quality of life											
0	no evidence										
Progression-free survival											
0	no evidence										
Overall survival											

0	no evidence										
Performance status											
0	no evidence										
Pain control at 6 months versus baseline (assessed with Visual Analogue Scale, 0-10; better indicated by lower value)											
1[1]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	41	n/a	-	Mean decrease 5.6±2.8	⊕OOO VERY LOW
Pain control at 24h post-procedure versus baseline (assessed with Visual Analogue Scale, 0-10; better indicated by lower value)											
1[3]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	36	n/a	-	Mean score decrease from 9.1±0.9 to 3.4±1.2[4]	⊕OOO VERY LOW
Adverse events (Cement leakage)											
2[5]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	5/77 (6.5%)	n/a	-	-	⊕OOO VERY LOW
Patient activity (Proportion of patients with fully unassisted ambulation at baseline and 6-months)											
1[1]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	41	n/a	-	Increased from 31% to 63%	⊕OOO VERY LOW
Disability at 24h post-procedure versus baseline (measured with: Roland-Morris disability questionnaire; range of scores: 0-24; Better indicated by lower values)											
1[3]	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	36	n/a	-	Mean score decrease from 19.8 ±1.5 to 9.6 ±1.2[4]	⊕OOO VERY LOW
Dependency											
0	no evidence										

[1] Erdem et al. (2013b); [2] Small number of participants limits precision of results; [3] Orgera et al. (2014); [4] Mean score for RFA vertebroplasty (no difference between RFA and no-RFA vertebroplasty)
[5] Erdem et al. (2013b); Orgera et al. (2014)

Table 8.13: GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (surgery)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	spinal surgery	control	Relative (95% CI)	Absolute	
Vertebral collapse											
0	no evidence										
Spinal cord compression											
0	no evidence										
Health-related quality of life											
0	no evidence										
Progression-free survival											

0	no evidence										
Overall survival											
2[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	159	n/a	-	Median OS 3.9y and 4.7y across studies	⊕OOO VERY LOW
Performance status											
0	no evidence										
Adverse events											
2[1]	observational studies	serious[2]	no serious inconsistency	serious[5]	serious[4]	none	39/129 (30.2%)	n/a	-		⊕OOO VERY LOW
Pain control											
0	no evidence										
Activities of living/mobility											
0	no evidence										
Dependency											
0	no evidence										

[1] Zeifang et al. (2005); Utzschneider et al. (2011)
[2] Retrospective case series
[3] Survival not reported separately for spinal and non-spinal surgery. Cohort in Utzschneider (2011) dates back to 1980 which limits relevance to current UK practice
[4] Small sample size limits precision
[5] Complication not reported separately for spinal and non-spinal surgery patients in Utzschneider (2011)

Table 8.14: GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	radiotherapy	control	Relative (95% CI)	Absolute	Quality
Vertebral collapse											
0	no evidence										
Spinal cord compression											
0	no evidence										
Health-related quality of life											
0	no evidence										

Progression-free survival											
0	no evidence										
Overall survival											
2[1]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	319	n/a	-	Median OS 36 months and 32 months	⊕OOO VERY LOW
Performance status											
0	no evidence										
Adverse events (Grade 3-4)											
3[4]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	3/371 (0.8%)	n/a	-	-	⊕OOO VERY LOW
Pain relief (proportion of patients with good/complete relief of pain)											
3[4]	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	284/521 (54.5%)	n/a	-	-	⊕OOO VERY LOW
Activities of daily living/mobility (proportion of patients reporting improvement in motor function)											
1[5]	observational studies	serious[2]	no serious inconsistency	serious[3]	serious[6]	none	62/79 (78%)	n/a	-	-	⊕OOO VERY LOW
Dependency											
0	no evidence										

[1] Budak et al. (1991); Yaneva et al. (2006); [2] Non-comparative retrospective case series; [3] Outcomes not reported separately for spinal and non-spinal bone disease. Patients with spinal cord compression included in Budach et al. (1991); [4] Budach et al. (1991); Yaneva et al. (2006); Balducci et al. (2011); [5] Yaneva et al. (2006); [6] Small sample size limits precision

Table 8.15 GRADE profile: Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma (denosumab versus zoledronic acid in patients with myeloma and at least one osteolytic lesion)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	denosumab	zoledronic acid	Relative (95% CI)	Absolute	
time to first on-study SRE (Better indicated by higher values)											
1[1]	randomised trials	no serious limitations	no serious inconsistency	serious[2]	Serious[3]	none	93	87	HR of 1.03 95% CI, 0.68 to 1.5	Not reported	⊕⊕OO LOW
overall survival (Better indicated by lower values)											
1[1]	randomised trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	93	87	HR of 2.26 (95% CI, 1.13 to 4.50	Not reported	⊕⊕OO LOW

[1] Henry et al. (2011). [2] Included patients had ≥1 osteolytic lesion – it is not specified if these lesions were vertebral or non-vertebral; [3] no absolute data reported for myeloma. Small sample size and wide confidence intervals reduces precision.

Table 8.16 GRADE summary of findings table (benefits): Bisphosphonates for patients with multiple myeloma (from Mhaskar et al., 2012)

NB: not all studies included patients with lytic lesions or did not specify bone disease in inclusion criteria

Summary of findings			
No of patients	Effect		Quality
	Relative (95% CI)	Absolute	
Overall mortality			
2292 (12 studies)	HR 0.96 (0.82 to 1.13)	530 per 1000 with control, 504 per 1000 (449 to 561) with bisphosphonate	**low**[1,2,3]
Progression free survival			
364 (4 studies)	HR 0.70 (0.41 to 1.19)	350 per 1000 with control, 260 per 1000 (162 to 401) with bisphosphonate	**very low**[1,4]
Vertebral fractures			
1389 (6 studies)	RR 0.74 (0.62 to 0.89)	350 per 1000 with control, 259 per 1000 (217 to 311) with bisphosphonate	**moderate**[1,6]
Non vertebral fractures			
1389 (6 studies)	RR 1.03 (0.68 to 1.56)	140 per 1000 with control, 144 per 1000 (95 to 218)with bisphosphonate	**moderate**[1,7]
Skeletal-related events			
1497 (7 studies)	RR 0.80 (0.72 to 0.89)	303 per 1000 with control, 245 per 1000 (218 to 279) with bisphosphonate	**moderate**[1,8]
Pain			
1281 (8 studies	**RR 0.75** (0.6 to 0.95)	500 per 1000 with control, 375 per 1000 (300 to 475) with bisphosphonate	**very low**[9,10]
Hypercalcemia			
1934 (8 studies)	**RR 0.79** (0.56 to 1.11)	100 per 1000 with control, 87 per 1000 (61 to 124) with bisphosphonate	**moderate**[1]

[1] Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on allocation concealment and description of randomization method didn't change the estimates. Hence, the assessment of studies limitations may represent the poor quality of reporting rather than true biased estimates.

[2] I^2 = 55%. The pooled estimate is driven by studies by Aviles et al and Belch et al; when we removed these RCTs pooled estimates remained the same but heterogeneity disappeared.

[3] The overall mortality data were extractable from 11 of 16 studies. Also, note that overall mortality data denotes the mortality rates, i.e. the number of events refers to the number of deaths.

[4] The progression-free survival data could be extracted from only 4 of 16 studies.

[5] We have denoted only medium risks in controls for statistically nonsignificant outcomes while denoting low, medium and high risks in controls for statistically significant outcomes.

[6] Data related to patients with vertebral fractures were extractable from only 7 of 16 RCTs.

[7] Data related to patients with nonvertebral fractures were extractable from only 6 of 16 RCTs.

[8] Skeletal-related events data were extractable from only 7 of 16 RCTs.

[9] Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment.

[10] There was variation in the pain scales used to measure pain.

Table 8.17 GRADE summary of findings table (harms): Bisphosphonates for patients with multiple myeloma (from Mhaskar et al., 2012)

NB: not all studies included patients with lytic lesions or did not specify bone disease in inclusion criteria

Summary of findings				
No of patients	Effect		Quality	Comments
	Relative	Absolute		

	(95% CI)			
Gastrointestinal toxicity				
1689 (6 RCTs)	RR 1.23 (0.95 to 1.6)	86/836 (10.3%) with control, 110/853 (12.9%) with bisphosphonate	low	Limitations in design: serious [1] Serious imprecision [2]
Hypocalcemia				
1002 (3 RCTs)	RR 2.19 (0.49 to 9.74)	2/451 (0.4%) with control, 5/462 (1.1%) with bisphosphonate	Very low	Limitations in design: serious [1] Very serious imprecision [3] Reporting bias [4]
Osteonecrosis of jaw				
913 (3 RCTs)	RR 3.99 (0.44 to 35.84)	0/370 (0%) with control, 3/366 (0.8%) with bisphosphonate	Low	Limitations in design: serious [1] Reporting bias [4]
1400 (9 observational studies)	-	ONJ incidence range: 0% to 51%	Very low	reporting bias reduced effect for RR >> 1 or RR << 1 [5] dose response gradient [6]
Renal dysfunction				
414 (2RCTs)	-	Mean difference: −0.36 (−9.75 to 9.03)	Low	Limitations in design: serious [1] Reporting bias [7]

[1] *Only 37% (6/16) of trials had adequate allocation concealment. Only 18% (3/16) of trials reported methods of randomization. Similarly, 18% (3/16) of trials reported blinding procedures and personnel who were blinded to the intervention assignment. However, sensitivity analyses based on allocation concealment and description of randomization method didn't change the estimates. Hence, the assessment of studies' limitations may represent the poor quality of reporting rather than true biased estimates. Nonetheless, it should be noted that some authors would not downgrade evidence regarding treatment-related harms based on quality of randomization process.*

[2] *The pooled estimate has a wide confidence interval.*

[3] *All the RCTs have estimates with wide confidence intervals.*

[4] *Data related to patients with hypocalcemia and ONJ was extractable from only 3 of 16 RCTs.*

[5] *ONJ was observed in case control, case series and prospective observational studies and RCTs. Very few studies included consecutive prospective cohort with clear diagnostic criteria and blinded assessment of radiological findings. Therefore, while ONJ is considered a real adverse event, the exact incidence or risk is difficult to assess.*

[6] *While some studies indicate dose response, it could be that ONJ is related to the type of bisphosphonate. So far, no ONJ has been observed in the studies of clodronate.*

[7] *Data related to patients with renal dysfunction were extractable from only 2 of 16 RCTs.*

Figure 8.4. Bisphosphonates versus control; Outcome, overall survival (from Mhaskar et al., 2012)

Highlighted studies indicate where at least one bone lesion was specified in patient inclusion criteria

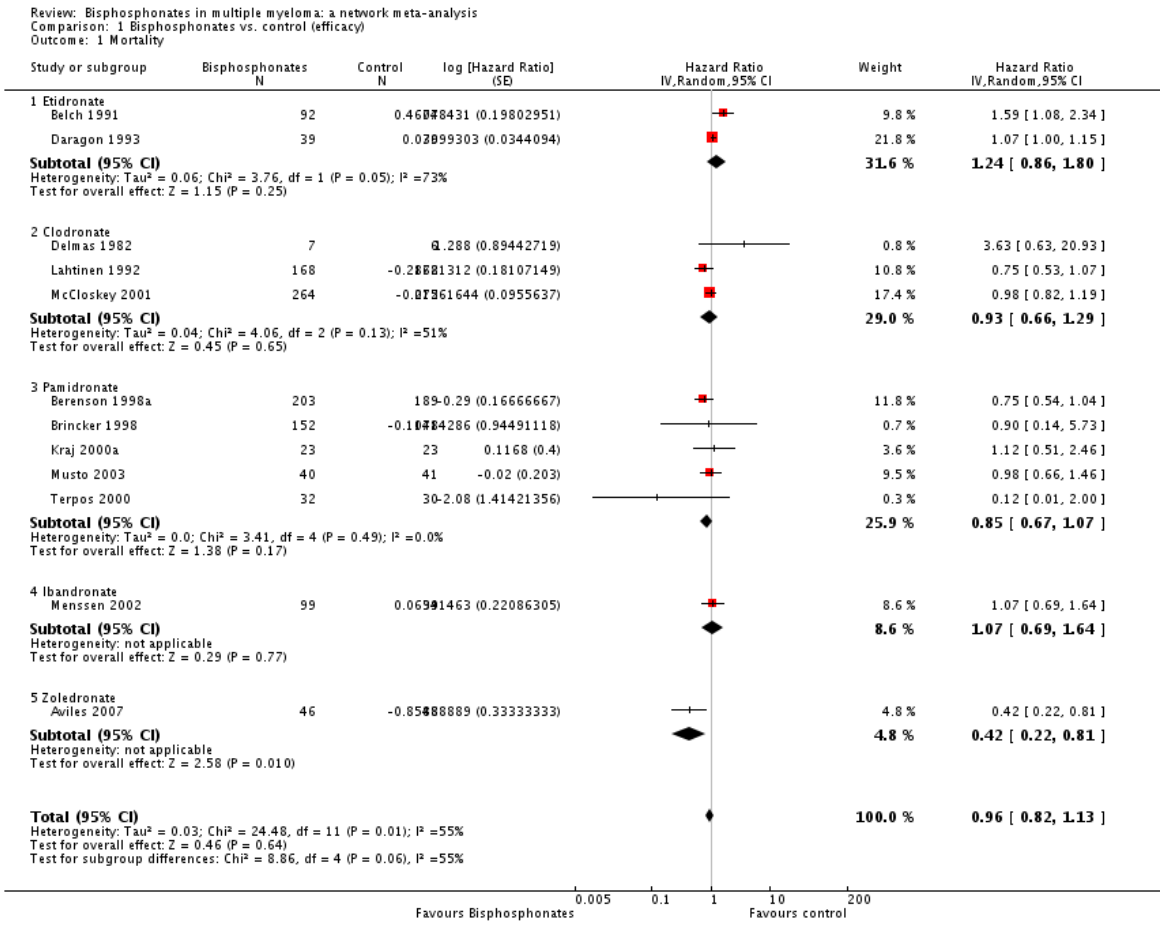


Figure 8.5. Bisphosphonates versus control; Outcome, progression-free survival (from Mhaskar et al., 2012)

Highlighted studies indicate where at least one bone lesion was specified in patient inclusion criteria

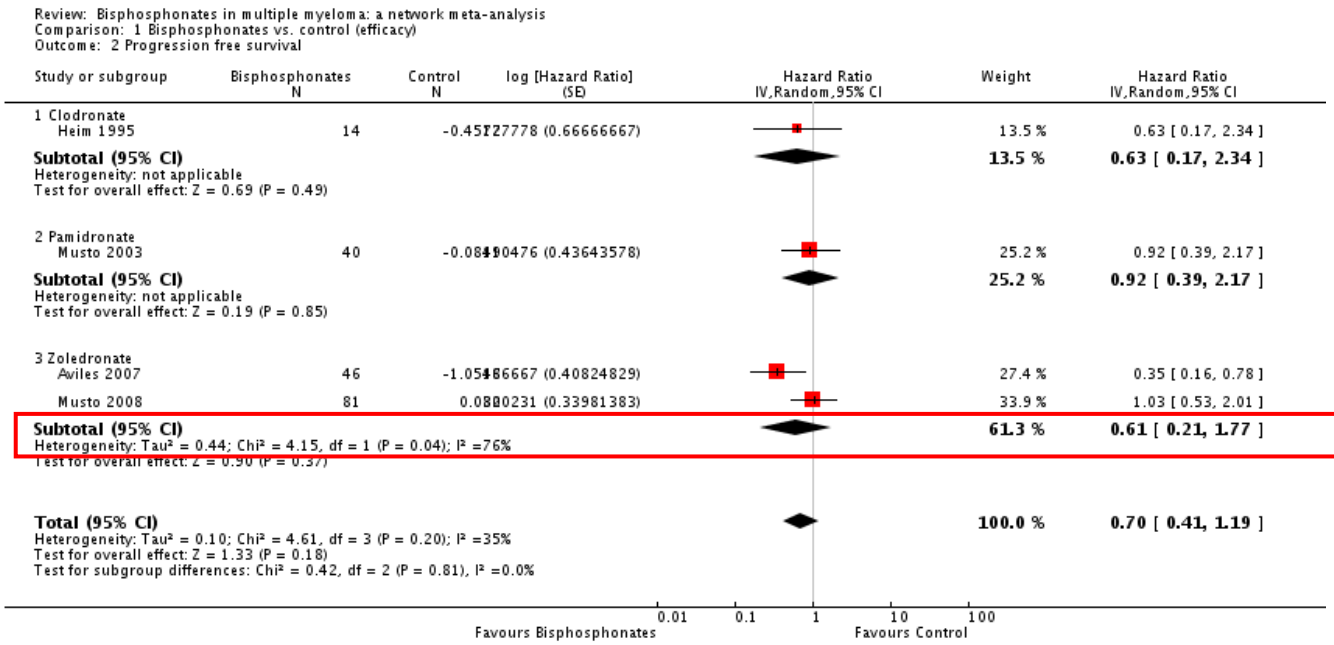
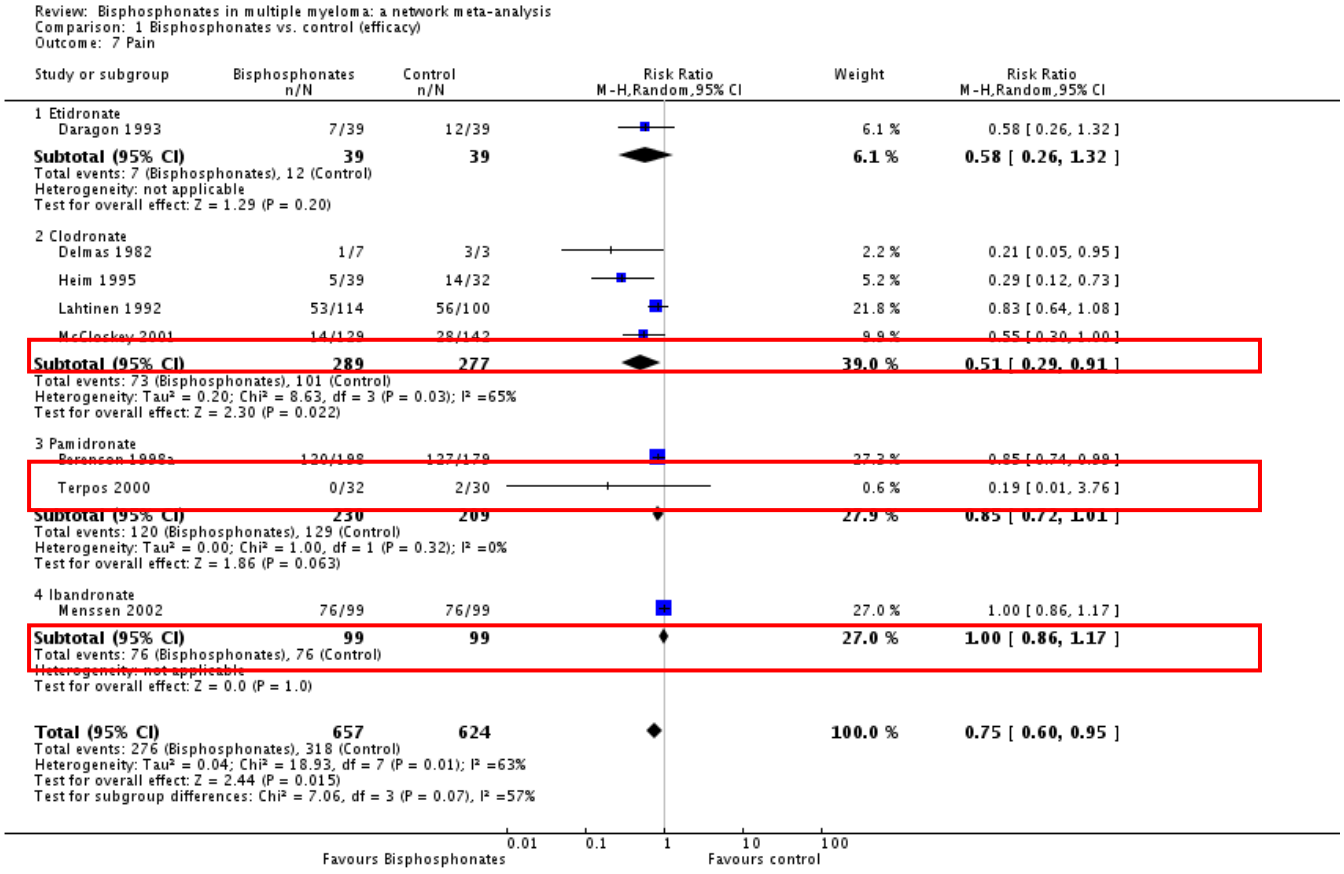


Figure 8.6. Bisphosphonates versus control; Outcome, pain (from Mhaskar et al., 2012)

Highlighted studies indicate where at least one bone lesion was specified in patient inclusion criteria



Evidence statements

Bisphosphonates

One systematic review and network meta-analysis of bisphosphonates for the prevention of skeletal-related events in myeloma (20 RCTs, 6692 patients) was identified (Mhaskar et al., 2012). In six trials it was specified that the inclusion criteria included the presence of at least one osteolytic lesion. However, it was not specified if the lesions were spinal or non-spinal, which limits relevance to the review question.

Pooled results showed no direct effect of bisphosphonates on overall survival compared with placebo or no treatment (HR 0.96, 95% CI 0.82 to 1.13; P = 0.64). However, there was a statistically significant heterogeneity among the included RCTs (I^2 = 55%, P = 0.01) for OS (Low quality).

Pooled analysis did not demonstrate a beneficial effect of bisphosphonates compared with placebo or no treatment in improving PFS (HR 0.70, 95% CI 0.41 to 1.19; P = 0.18) There was no heterogeneity among trials reporting PFS estimates (I^2 = 35%, P = 0.20) (Very low quality).

Pooled analysis demonstrated a beneficial effect of bisphosphonates compared with placebo or no treatment on prevention of pathological vertebral fractures (RR 0.74, 95% CI 0.62 to 0.89; I^2 = 7%) (moderate quality), skeletal-related events (SRE) (RR 0.80, 95% CI 0.72 to 0.89; I^2 = 2%) (moderate quality) and amelioration of pain (RR 0.75, 95% CI 0.60 to 0.95; I^2 = 63%) (very low quality).

The network meta-analysis did not show any difference in the incidence of osteonecrosis of the jaw (5 RCTs, 3198 patients) between bisphosphonates. Rates of osteonecrosis of the jaw in observational studies (9 studies, 1400 patients) ranged from 0% to 51% (very low quality). The pooled results (6 RCTs, 1689 patients) showed no statistically significant increase in frequency of gastrointestinal symptoms with the use of bisphosphonates compared with placebo or no treatment (RR 1.23, 95% CI 0.95 to 1.60; P = 0.11) (low quality).

The pooled results (3 RCTs, 1002 patients) showed no statistically significant increase in frequency of hypocalcemia with the use of bisphosphonates compared with placebo or no treatment (RR 2.19, 95% CI 0.49 to 9.74). The network meta-analysis did not show any differences in the incidence of hypocalcemia, renal dysfunction and gastrointestinal toxicity between the bisphosphonates used (low quality).

Denosumab

One randomised trial including 180 myeloma patients with at least 1 bone metastases or osteolytic lesion compared denosmab with zoledronic acid (Henry et al., 2011). The effect of denosumab on time to first on-study skeletal-related event (including fracture and spinal cord compression) relative to zoledronic acid resulted in a HR of 1.03 (95% CI: 0.68 to 1.57) (low quality).

An ad hoc analysis examining overall survival demonstrated an HR of 2.26 (95% CI: 1.13 to 4.50) (low quality).

Vertebral augmentation (kyphoplasty/vertebroplasty)

Very low quality evidence from one randomised trial of 134 patients (49 with multiple myeloma) compared balloon kyphoplasty with non-surgical management for painful vertebral body compression fractures (Berenson et al., 2011). Back-specific functional status (as measured by the

Roland-Morris disability questionnaire) at 1 month was reduced in the kyphoplasty group by 8.3 points (95% CI -6.4 to -10.2), and by 0.1 points (95% CI -0.8 to 1) in the control group. Patients in the kyphoplasty group also had significant improvements in quality of life, back pain and performance status, which were not seen in the control group. One patient in the kyphoplasty group had cement leakage and device-related vertebral compression fracture.

Very low quality evidence from one pooled analysis of case series of kyphoplasty (nine studies) and vertebroplasty (12 studies) or both (two studies) was identified, including a total of 923 patients (Khan et al., 2014). There was a decrease in pain from baseline across all time periods (≤1 week, 1 week to 1 year, >1 year). There were no differences between kyphoplasty and vertebroplasty studies in terms of mean pain reduction from baseline to the three time periods presented. There was no significant decrease in disability scores (as measured by the Owestry Disability Index) from baseline to any of the time periods. The most common complication was new vertebral fractures at untreated vertebral bodies. This occurred in 7.3% (42/576) of vertebroplasty patients and 6.8% (25/367) kyphoplasty patients (p=0.78).

Low quality evidence from three further case series (Erdem et al., 2013a; Simony et al, 2014; Ha et al, 2015) of vertebral augmentation in 424 myeloma patients reports typical reduction in pain from baseline to 1-month post-op of around 4 points (on a scale of 0-10) ($p<0.001$). One study (Erdem et al., 2013a) reports that no significant differences in pain improvements between the type of procedure performed (kyphoplasty versus vertebroplasty or kyphoplasty+vertebroplasty) for pain relief or improvement in activity .

One observational study including 39 patients with myeloma undergoing percutaneous vertebroplasty reported median overall survival of 20 months (range 2-91), with estimated 5-year survival of 40% (Chew et al., 2011) (very low quality).

Two observational studies (total 77 patients) of radio-frequency targeted vertebral augmentation in multiple myeloma both reported reductions in mean pain scores and improvements in disability post-procedure (Erdem et al., 2013b; Orgera et al., 2014). 5 patients (6.5%) had cement leakage (very low quality). One study reported that there were significant differences in pain reduction and complications between radiofrequency ablation and vertebroplasty compared with vertebroplasty alone (Orgera et al., 2014) (very low quality).

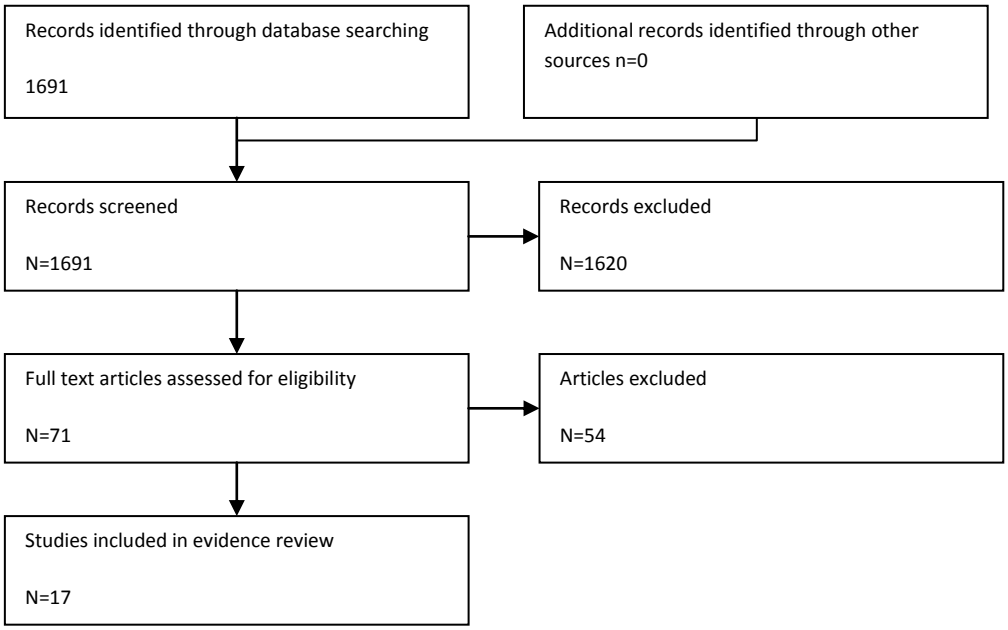
Surgery

Very low quality evidence from three observational studies of surgical intervention for myeloma bone disease (including both spinal and non-spinal disease) was identified (Zadnik et al., 2015; Zeifang et al., 2005; Utzschneider et al., 2011). Surgical interventions included posterior decompression-stabilisation, decompression alone, and endoprosthesis. Median survival was 3.9 years and 6.6 years. The most common adverse event related to wound complications.

Radiotherapy

Very low quality evidence from three observational studies of radiotherapy for skeletal lesions in multiple myeloma was identified (Budak et al., 1991; Yaneva et al., 2006; Balducci et al., 2011). Two studies reported median overall survival of 36 months and 32 months. Three studies reported that 55% (248/521) of patients reported good or complete relief of pain after treatment. One study reported that 78% (62/79) of patients reported improvements in motor function. Grade 3 or 4 adverse events were reported in 0.8% (3/371) patients.

Study flow diagram



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Reason: spinal and non-spinal bone destructions not reported separately

1 Evidence tables

Study: Berenson, J et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncology* 2011; 12(3): 225-235.

		Patient Characteristics	Intervention	Comparison	Outcomes	Results
Country	Multi-centre (Australia, Canada, Europe, USA)	*Inclusion criteria:* Aged at least 21 who had cancer and 1-3 painful VCFs (T5-L5) clinically diagnosed in conjunction with either plain radiographs or MRI. Pain numeric rating score (NRS) of at least 4 (on a scale of 0-10) and a Roland-Morris disability questionnaire (RDQ) score of at least 10. *Exclusion criteria:* Osteoblastic tumours, primary bone tumours, or a plasmacytoma at the index VCF, concurrent Phase I investigational anti-cancer treatment study, substantial clinical morbidities, VCF unsuitable for kyphoplasty, needed additional surgical treatment for index fracture, treatment with high dose steroids, intravenous pain medication, or nerve block to control chronic back pain unrelated to index VCFs *Demographics and baseline characteristics*	*Balloon kyphoplasty* With introducer tools, inflatable bone tamps, and polymethylmethacry-late bone cement and delivery devices (Medtronic Spine), by a percutaneous, bilateral, transpedicular or extrapedicular method. All patients could receive analgesics, bed rest, bracing, physiotherapy, rehabilitation programmes, walking aids, radiation treatment and other antitumour therapy at physician's discretion. Patients with concurrent osteoporosis or bone metastasis could also receive treatment with calcium, vitamin D supplements, and antiresorptive or anabolic agents. Most had general anaesthesia.	*Control group* Offered kyphoplasty after the 1-month assessment 38 crossed over. No patient had kyphoplasty before 1 month.	Safety data assessed during trial by independent committee. *Primary endpoint:* RDQ score at 1 month (scale 0-24, no disability to maximum disability) Minimally clinically important difference (MCID) = 2 to 3 points *Secondary endpoints at 1, 3, 6, & 12 mo:* RDQ, Karnofsky performance status (KPS) scale 0 (dead) to 100 (perfect health), SF-36, back pain NRS (0-10 points), use of analgesics for back pain, reduced activity days from back pain in last 2 wks, bed rest days in past 2 wks, subsequent radiographic VCFs, adverse events and serious adverse events. For patients who crossed over from control to have kyphoplasty, new baseline assessments were done before	*RDQ scores*
Design, period	Randomised controlled trial, May 2005-March 2008					
N	134 enrolled, 117 assessed at 1 month					
Follow-up	At 1, 3, 6, 12 months					
Funding source	Sponsored by Medtronic Spine LLC					

Demographics and baseline characteristics

	Kyphoplasty (n=68)	Control (n=61)
Mean (SD) age	64.8 (37.6-88)	63 (39.5-83.4)
Female	40 (59%)	35 (57%)
Median (IQR) estimated fracture age	3.4 (2-6.4)	3.5 (1.1-7.1)
Bisphosphonate use	30 (44%)	33 (54%)
Steroid use	20 (29%)	25 (41%)
Underlying cause		
-Multiple myeloma	22 (32%)	27 (44%)
-Breast cancer	16 (24%)	12 (20%)
-Lung cancer	7 (10%)	4 (7%)
-Prostate cancer	4 (6%)	4 (7%)
-Other cancer	19 (28%)	14 (23%)
No. of fractures		
1	24 (35%)	27 (44%)
2	18 (26%)	20 (33%)
3	26 (38%)	14 (23%)
Treatment for cancer		
Radiation (all sites)	39 (57%)	24 (39%)
Spine	16 (24%)	11 (18%)

RDQ scores

	Kyphoplasty	Control
Baseline	17.6	18.2
1 month	9.1	18
Mean change (95% CI)	-8.3 (-6.4 to -10.2) p<0.0001	0.1 (-0.8 to 1) p=0.83

Quality of life (SF-36, physical component summary, MCID=3.5 to 4.3 points)

	Kyphoplasty	Control
Mean change (95% CI) from baseline to 1mo	8.4 (7.7 to 9.1) p<0.0001*	P=0.26

* in comparison with control group

Quality of life (SF-36, mental component summary)

	Kyphoplasty	Control
Mean change (95% CI) from baseline to 1mo	11.1 (10.7 to 11.5) p<0.0002*	P=0.30

* in comparison with control group

KPS scores (MCID = 5 points)

	Kyphoplasty	Control
Mean change (95% CI) from baseline to 1mo	15.3 (5 to 17.1) p<0.0001*	p=0.71
KPS ≥70 at 1mo N (%)	47/63 (75%)	19/49 (39%)

* in comparison with control group

Reduced activity caused by back pain

	Kyphoplasty	Control
Mean change (95% CI) from baseline to 1mo	-6.3 (-6.8 to -5.8) p<0.0001*	p=0.10

* in comparison with control group

NRS scores (MCID=1 to 2.5 points)

	Kyphoplasty	Control
Baseline	7.3	7.3
7 days	3.5	7.0

Study: Berenson, J et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncology* 2011; 12(3): 225-235.

		Bone	7 (10%)	14 923%)		
		Surgery	34 (50%)	32 (52%)		
		Chemotherapy/hormonal	45 (66%)	41 (67%)		
		Steroids	20 (29%)	25 (41%)		
		Status of cancer at baseline				
		No evidence	10 (15%)	10 (16%)		
		Remission	4 (6%)	7 (11%)		
		Stable	27 (40%)	22 (36%)		
		Progressive	26 (38%)	21 (34%)		

crossover and follow-up at 7 days (NRS only), 1, 3, & 6 mo after surgery, final 12 mo visit from study entry also done.

Difference in change from baseline between control and kyphoplasty (95% CI)	
At 7 days	-3.5 (-3.8 to -3.2) p<0.0001
At 1 month	-3.3 (-3.6 to -3.0) p<0.0001

Fewer patients in kyphoplasty group used analgesics to manage pain relief than control group at 1 month (p=0.0018). At 1 month, fewer patients in kyphoplasty group were using walking aids (32% vs. 46%), back bracing (2% vs. 22%), bed rest (23% vs. 46%), or medication to treat index VCF (52% vs. 82%).

RDQ score between baseline and 6 months

	Kyphoplasty	Crossover	Control
Change (95% CI)	8.2 (6.5 to 9.9)	10.8 (8.6 to 12.9)	3.6 (-4.2 to 11.5)

Adverse events in first month
26/70 (37%) kyphoplasty including 1 myocardial infarction attributed to anaesthesia which resolved within 24h of procedure, 1 cement leakage and adjacent device related fracture one day after procedure, 1 wound infection, 1 asymptomatic balloon rupture, 1 asymptomatic extravasation to disc. 2 resulted in death
19/64 (30%) control including 3 cardiac disorders, 5 back pain, 3 symptomatic fracture, 1 lymphoedema. 1 resulted in death

Serious adverse events after 1 month until study end
37/70 (53%) kyphoplasty including 18 neoplasm, 9 symptomatic vertebral fractures, 5 cardiac disorders, none device related. 21 resulted in death
18/38 (47%) crossover including 1 airway complication caused by anaesthesia resolved within a few minutes, 1 possibly device-related VCF 13 days after kyphoplasty, 1 asymptomatic extravasation to disc. 6 resulted in death.
8/26 (31%) non-surgical management including 2 neoplasm, 1 pneumonia, 1 sepsis. 5 resulted in death.

No AEs related to death were device related.

Survival
Death rate in all those who had kyphoplasty was not different to surgical management group (p=0.13).

Study: Berenson, J et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncology* 2011; 12(3): 225-235.	
Comments	– Sponsors of the study contributed to study design, data monitoring, collection, analysis, and interpretation, and paid for core laboratory services, writing assistance and consultancy fees to the independent data safety monitoring committee. – Randomisation by computer generated algorithm by a secure central website to provide concealment of future assignments. – Investigators and patients non-blinded to treatment allocation – Intent-to-treat analysis performed for 1 month assessment – 65 patients in kyphoplasty group and 52 in the control group completed at 1 month. Reasons for withdrawal provided. No significant baseline differences between those who discontinued and those who completed the 1 month follow-up. – Not all myeloma patients – limits relevance to review question

1

Study: Khan, OA, Brinjikji, W, and Kallmes, DF. Vertebral augmentation in patients with multiple myeloma: a pooled analysis of published case series. *American Journal of Neuroradiology* 2014; 35(1): 207-210.

		Method	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	**n/a**	*Inclusion criteria:* PubMed search on 12th June 2012. Studies of vertebroplasty and/or kyphoplasty in English language were considered in patients with myeloma, with a minimum of 15 patients, and those that contained ≥1 of the following outcomes: numeric pain assessment scores for pre and post operative pain (Visual Analogue Scale, Brief Pain Inventory, SF-36), numeric Owestry Disability Index (ODI) assessment for pre and postoperative disability, rate of cement leakage (as detected on CT and plain film) and change in patient analgesic drug use. Included 23 studies (9 kyphoplasty, 12 vertebroplasty, 2 both). Mean age of total population=64.6 years (range 28-92)	*Kyphoplasty*	*Vertebroplasty*	Pre and post procedure pain (19 studies) Owestry Disability Index (ODI) (8 studies) Analgesic use (11 studies) Cement leakage (17 studies) Adverse events	*Pain scores in relation to time period (vertebroplasty and kyphoplasty combined)*
Design, period	Systematic review of case series					
N	23 studies of 923 patients					
Follow-up	Summarised into 3 time periods: baseline, ≤1 week, ≤ 1 year, >1 year					
Funding source	n/a					

Study Characteristics
VP=vertebroplasty, KP=kyphoplasty, R=retrospective, P=prospective

Study	Treatment	Design	N patients
Mendoza 2012	VP &/or KP	R	79
Chen 2012	VP	R	24
Yang 2012	VP	P	38
Trumm 2012	VP	R	39
Kasperk 2012	KP	R	35
Basile 2011	VP	P	24
Anselmetti 2012	VP	P	106
Masala 2011	VP	R	39
Astolfi 2009	KP	R	30
Masala 2008	VP	R	64
McDonald 2008	VP	R	67
Tran Thang 2008	VP	R	28

Pain scores in relation to time period (vertebroplasty and kyphoplasty combined)

	N studies	Mean difference ±SE	P value
Baseline vs. ≤1wk post-op	11	4.8 ± 0.56	<.001
Baseline vs. 1wk to 1yr post-op	14	4.6 ± 0.49	<.001
Baseline vs. > 1yr post-op	14	4.4 ± 0.48	<.001
≤1wk post-op vs. 1wk to 1yr post-op	9	0.077 ± 0.11	<.481
≤1wk post-op vs. >1yr post-op	7	0.49 ± 0.49	<.132
1wk to 1yr post-op vs. >1 yr post-op	10	0.33 ± 0.25	<.276

Mean ±SE pain reduction

	Vertebroplasty	Kyphoplasty	P value
≤1 week	2.8 ± 0.4	2.8 ± 0.4	0.9
1wk to 1yr post-op	2.5 ± 0.4	2.5 ± 05	1.00
> 1year	2.9 ± 0.6	2.7 ± 0.4	0.9

Change in ODI scores from baseline

	Mean decrease in ODI from baseline	P value
≤1 week	39.2 (16.3-75)	.37
1wk to 1yr post-op	40.7 (16.3-75)	.14

Study: Khan, OA, Brinjikji, W, and Kallmes, DF. Vertebral augmentation in patients with multiple myeloma: a pooled analysis of published case series. *American Journal of Neuroradiology* 2014; 35(1): 207-210.

		Kose 2006	KP	R	18		
		Kose 2006	VP	R	16		
		Khanna 2006	KP	P	56		
		Pflugmacher 2006	KP	R	20		
		Bosnjakovic 2009	VP	R	29		
		Huber 2009	KP	R	76		
		Zou 2010	KP	P	21		
		Julka 2012	KP	R	32		
		Lane 2004	KP	P	19		
		Garland 2011	VP	R	26		
		Lim 2009	VP	R	19		
		Dudeney 2002	KP	P	18		

> 1year	46.5 (14.5-75)	.88

Change in analgesic drug use from baseline

	Mean decrease in ODI from baseline	P value
≤1 week	81.9 (53.7-1.00)	.002
1wk to 1yr post-op	85 (46.1-1.00)	.003
> 1year	89.1 (57.7-1.00)	.08

Cement leakage

Plain film identified 11% (9/80) of patients as having leakage. CT identified 29% (22/77).

Reported symptomatic complications

Complication	Overall rate	VP rate	KP rate	p
Infection	1/943	1/576	0/367	.64
Pulmonary embolism	1/943	0/576	1/367	.21
Myocardial infarction	1/943	0/576	1/367	.21
VCF at untreated levels	67/943	42/576	25/367	.78
Neurologic symptoms requiring revision surgery	2/943	0/576	2/367	.08
Transient perioperative pain	6/943	4/576	2/367	.78

Comments

- Studies differed in adjunctive therapy, disease stage and other factors
- Combined use of prospective and retrospective case series
- Small sample size of individual studies

1

2

Study: Erdem, E et al. Vertebral augmentation in the treatment of pathologic compression fractures in 792 patients with multiple myeloma. *Leukemia* 2013a; 27(12): 2391-2393.

		Patient Characteristics	Intervention	Comparison	Outcome	Results
Country	USA	792 consecutive patients with myeloma-related symptomatic compression fractures who underwent 2693 vertebral augmentations (2223 vertebroplasty, 470 kyphoplasty)	Vertebral augmentation - vertebroplasty or kyphoplasty	Vertebroplasty versus kyphoplasty	Pain – Visual Acuity Scale (VAS) (0-10 scale)	*Pain (n=351 patients, 428 sessions)* Average reduction of 4.2 points (95% CI 4.0-4.5) from 6.9 at baseline to 2.7 at 1-month post-procedure

Study: Erdem, E et al. Vertebral augmentation in the treatment of pathologic compression fractures in 792 patients with multiple myeloma. *Leukemia* 2013a; 27(12): 2391-2393.

Design, period	Prospective case series 2001-2007	All of patients were on cancer therapy or about to receive therapy. *Patient characteristics (n=792)* Median (range) age: 63 (16-99) 1 augmentation: 75% 2 augmentations: 18% 3-6 augmentations: 7% Median (IQR) no. of repairs per session: 2 (1-3) Vertebroplasty T1-T10*: 37% Vertebroplasty T11-L2*: 39% Vertebroplasty L3-sarcum*: 24% *distribution across levels similar for kyphoplasty			Analgesic medication use Improvement in activity	*Analgesic medication use (n=355 patients, 437 sessions)* Across all sessions, 12% had patients reporting zero pain medications pre-procedure as compared with 34% post-procedure. Patients were taking narcotics for 70% of sessions pre-procedure compared to 48% post-procedure. Narcotics usage 65% lower: OR 0.35 (95% CI 0.21 to 0.58) at 1-month post-procedure compared with baseline (p<0.001) *Improvement in activity (n=354 patients, 430 sessions)* At baseline 28% of subjects scored 0-1 (no limitations) compared with 59% post-procedure. OR of good activity (score 0-1) was 4.2 (95% CI 3.1 to 5.8) times higher post-procedure compared to pre-procedure (p<0.001) No differences in improvements between vertebroplasty vs. Kyphoplasty or vertebroplasty + kyphoplasty for pain relief, decreased narcotics use or improvement in activity (p>0.05) after adjusting for age, gender, session, number of augmentations, and baseline scores or medication. (74% session vertebroplasty only, 13% kyphoplasty only, 13% both procedures) 2 patients required antibiotics for local infections and no neurological deficits were observed.
N	792 361 provided outcome data					
Follow-up	1 month					
Funding source	n/a					
Comments	– Patients participating in study were more likely to be younger, male and from out of the state than non-participants. Number of levels repaired did not differ significantly for non-participants and participants. – Scores not reported separately for vertebroplasty and kyphoplasty					

1

2

Study: Erdem, E et al. Radiofrequency-targeted vertebral augmentation for the treatment of vertebral compression fractures as a result of multiple myeloma. *Spine* 2013b; 38(15): 1275-1281.

		Patient Characteristics	Intervention	Comparison	Outcome	Results
Country	USA	66 consecutive patients with vertebral compression fractures (VCF) secondary to multiple myeloma (MM) who underwent radiofrequency targeted vertebral augmentation (RFTVA). All patients managed by MDT including neuroradiologists and hematologists/oncologists. Requirements for RFTVA included presence of VCF, intractable pain at level of VCF unresponsive	Radiofrequency targeted vertebral augmentation: Performed under biplane fluoroscopy guidance. General anaesthesia to patients with more than 5 levels of treatment in 1 session. Otherwise conscious sedation. RFTVA using StabiliT Vertebral	n/a	Back pain: 10-point VAS (0=no pain, 10=worst pain) Pain medication use: 0=no med, 1=over-the-counter meds,	*Pain (VAS)* Mean baseline score = 8.1±1.7, at 6-months = 2.5±2.4. Average change of 5.6±2.8 (p<0.001) *Pain medication* At baseline 42 (88%) reported use of narcotics for pain relief, at 6-months 22 patients reported narcotics (p<0.001) *Patient activity*
Design, period	Prospective case series 2008-2009					

Study: Erdem, E et al. Radiofrequency-targeted vertebral augmentation for the treatment of vertebral compression fractures as a result of multiple myeloma. *Spine* 2013b; 38(15): 1275-1281.						
N	66 cases, 41 included in analysis	to conservative treatment, bone marrow edema on short tau inversion recovery MRI pulse sequence, and confirmed MM, with or without point tenderness over the fractured vertebra. Patients excluded if they presented with preoperative VAS pain score of less than 4 (n=18) or self-assessment data was incomplete (n=4). 48 procedures in 41 patients. Mean age 56.9 ±14.2 y. 20 males, 21 females. Overall 139 levels treated (average 2.9±1.4 levels per procedure). 88 (63%) thoracic, 49 (35%) lumbar, 2 (2%) sacral. 94 (68%) occurred between T8 and L3.	Augmetation System. Polymethylmethacry-late (PMMA) applied through activation element.		2=physician prescribed non-narcotic med, 3= physician prescribed narcotics Patient activity: 0=no limitation, 6= flat in bed.	At baseline most patients required ambulatory aid or were limited to chair or bed. Patients with fully unassisted ambulation increased from 31% to 63% at 6 months. Patients in category 4-6 unable to ambulate prior to surgery (42%) decreased to 12% at 6-months. *Complications* At 6 months there was no evidence of neurological or clinical complications related to RFTVA. 1 patient had PMMA leakage into intervertebral disc space.
Follow-up	6 months					
Funding source	No funds were received					
Comments	– Non-comparative case series – Short follow-up					

1

Study: Orgera, G et al. Percutaneous vertebroplasty for pain management in patients with multiple myeloma: Is radiofrequency ablation necessary? *Cardiovascular and Interventional Radiology* 2014; 37(1): 203-210.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Italy	*Inclusion criteria:* Consistent vertebral involvement of multiple myeloma in 1-3 vertebral bodies of the thoracic and lumbar spine; at least 3 month history of pain refractory to conservative analgesic treatment, either alone or in combination with chemotherapy and/or radiotherapy; Karnofsky score >30; and absence of neurological symptoms indicating radiculopathy or myelopathy. *Exclusion criteria:* vertebral involvement in more than 3 levels, involvement of cervical spine, younger than 18 y and older than 85y. Contraindications were: symptomatic improvement with analgesic therapy, myelopathy in patients with spinal canal compromise due to retropulsion of bone fragments or tumour involvement, infection, non-correctable coagulopathy, allergy to bone cement or contrast agents. 36 patients were randomly divided into two groups: Group A (n=18, 14 females, mean age 63.1) where	*RFA vertebroplasty:* RFA system (Cool-tip). Ablation process lasted 8-10mins at 55-85°C, then slow injection of 2-4ml PMMA. n=18 patients, 22 procedures. 8 thoracic, 14 lumbar spine.	*Vertebroplasty:* Injection of PMMA performed without previous RFA. N=18 patients, 28 procedures. 11 thoracic, 17 lumbar spine. For both groups: All but two cases performed under conscious sedation. All received prophylactic dose of antibiotics	*Pain:* Visual Analogue Scale (VAS) scale 0 (no pain) to 10 (worst pain imagined). Assessed 24h pre-procedure and at 6 wks after treatment. *Pain-related disability:* Roland-Morris Questionnaire (RMQ) scale 0 (no disability) to 24 (severe disability) *Analgesic*	*Pain (VAS)*- no significant differences between groups VAS scores before and after procedure *Pain-related disability:* Medication use decreased significantly at all time points for both group, without significant differences between the two groups. Mean (SD) score RFA vertebroplasty = 2.7 (0.4) and for vertebroplasty
Design, period	Prospective randomised trial 2008-2012					
N	36					
Follow-up	6 weeks post-procedure					

Mean (SD) VAS score	*RFA vertebroplasty*	*Vertebroplasty*
Before procedure	9.1 (0.9)	9.3 (0.6)
24h post-procedure	3.4 (1.2)	3.0 (0.9)
6wk post-procedure	2.0 (0.9)	2.3 (0.9)

Mean (SD) RMQ score	*RFA vertebroplasty*	*Vertebroplasty*
Before procedure	19.8 (1.5)	19.9 (1.6)
24h post-procedure	9.6 (1.2)	9.5 (1.0)
6wk post-procedure	8.2 (1.0)	8.7 (0.8)

<table>
<tr><td colspan="8">Study: Orgera, G et al. Percutaneous vertebroplasty for pain management in patients with multiple myeloma: Is radiofrequency ablation necessary? Cardiovascular and Interventional Radiology 2014; 37(1): 203-210.</td></tr>
<tr><td>Funding source</td><td>Not reported</td><td>radiofrequency ablation (RFA) was performed before vertebroplasty and Group B (n=18, 12 females, mean age 65.3) where vertebroplasty only was performed.</td><td></td><td>before procedure. All procedures performed under CT-fluoroscopic guidance.</td><td>consumption: 3-point scale (1=increased; 2=same; 3=decreased) assessed before and after (24h and 6wks) procedure</td><td colspan="2">alone = 2.7 (0.4).

Complications<table><tr><th>Event</th><th>RFA vertebroplasty</th><th>Vertebroplasty</th></tr><tr><td>Asymptomatic extra osseus cement leakage</td><td>N=2 (9%)</td><td>N=2 (7%)</td></tr><tr><td>Death within 30 days post-procedure</td><td>1 renal failure</td><td>1 myeloma progression</td></tr></table></td></tr>
<tr><td>Comments</td><td colspan="7">– Randomisation performed by use of a sealed envelope that was opened at the time that access to vertebral body was obtained.
– Significance (p values) of pre- and post-procedure pain and disability not reported
– Short follow-up (6 wks)</td></tr>
</table>

1

Study: Papanastassiou, ID et al. Comparison of Unilateral versus Bilateral Kyphoplasty in Multiple Myeloma Patients and the Importance of Preoperative Planning. *Asian Spine Journal* 2014; 8(3): 244-252.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	USA	*Inclusion criteria:* Patients were candidates for cement augmentation if they had VCF with at least 20% loss of anterior or middle vertebral body height and persistent pain not related to other causes; the pain level should be at least 4/10 and not responsive for at least 2 weeks to conventional medical therapy, including narcotic analgesics, bracing, physical therapy and bed rest. Acute or subacute fracture (fracture age up to 3 months); satisfactory visualization of the end plates; minimal follow-up of 3 months; index level fracture with collapse and edema in MRI. 57% males, mean age 61.6 years (range 44-79). In 36/69 patients both approaches (unilateral and bilateral) were used.	Balloon kyphoplasty (bilateral) 51 bilateral (24 thoracic, 27 lumbar fractures)	Balloon kyphoplasty (unilateral) 54 unilateral procedures (28 thoracic, 26 lumbar fractures). Unilateral approach favoured in the thoracic spine and in lumbar spine if safe and feasible.	*Pain:* numeric pain scale (0=no pain, 10 = worst pain) assessed pre- and 3 mo post-procedure	*Pain:* Mean pre-procedure pain score = 7.9 Mean post-procedure pain score = 2.5 (p<0.0005) – more than 30% improvement from baseline. No difference in improvement between unilateral and bilateral groups *Complications:* No serious complications. 13.3% of levels, cement extravasation was reported in the disk space and in 4.8% in the spinal canal. None were symptomatic.
Design, period	Retrospective case series, 2007-2010					
N	69 patients, 101 levels					
Follow-up	3 months					

Study: Papanastassiou, ID et al. Comparison of Unilateral versus Bilateral Kyphoplasty in Multiple Myeloma Patients and the Importance of Preoperative Planning. *Asian Spine Journal* 2014; 8(3): 244-252.						
Funding source	None					
Comments	– Retrospective case series – No details about patient characteristics, cancer stage/grade, cancer treatment received, comorbidities etc					

1

Study: Chew, C et al. A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases. *Clinical Radiology* 2011; 66(12): 1193-1196.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	UK	Indications for vertebroplasty include intractable pain from metastases and vertebral collapse unresponsive to oral analgesia, as well as an adjunct to planned radiotherapy. Uncontrolled coagulopathy, infection, spinal cord compression and complete vertebral collapse were contraindications. Total n patients: 128 Male: 68 Female: 60 Mean age (range): 60 (31-88) Myeloma: 41 Metastasis (e.g. breast, lung, renal): 87 Total number vertebrae treated: 264 Total number procedures: 158	*Vertebroplasty:* Vertebra infiltrated with local anaesthetic. Opacified PMMA is injected under continuous fluoroscopic screening. Most procedures under conscious sedation. No more than 4 vertebrae were injected at a single procedure, volume of cement <5ml per injected vertebra.	n/a	*Survival:* calculated using Kaplan-Meier method	39 myeloma patients had long-term follow-up. *Survival:* Median survival was 20 months (range 2-91 months). Kaplan-Meier estimate of 5-yr survival from the date of vertebroplasty was 40%.
Design, period	Prospective case series, 2001-2010					
N	41 treated, 39 in survival analysis					
Follow-up	Median 3yr (range 1-9)					
Funding source						
Comments	– Also included non-myeloma cancer patients with survival reported separately for myeloma and non-myeloma patients.					

Study: Chew, C et al. A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases. *Clinical Radiology* 2011; 66(12): 1193-1196.	
	– Pain data not extracted as not reported separately for myeloma and non-myeloma groups although pain and disability were improved after vertebroplasty. – Small sample size

1

Study: Zeifang, F et al. Long-term survival after surgical intervention for bone disease in multiple myeloma. *Annals of Oncology* 2005; 16(2): 222-227.

		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Germany	84 consecutively surgically treated multiple myeloma patients. Median age 61.5 % male 60.7 Salmon-Durie stage I 9.5 Stage II 9.5 Stage IIIA/B 81 Median follow-up (y) 2.63 Adjuvant treatment Previous conventional chemo 45 Previous high-dose chemo (HDT) +peripheral blood stem cell transplant (PBSCT) 36 Previous radiotherapy 32 Additional systemic therapy given as either single conventional chemotherapy dose in 38 patients with median 6 cycles, or as HDT with PBSCT in 30 patients. No chemo in 16 patients. All received supportive care measures with bisphosphonates. Most patients were mobile and ECOG performance status of 1 or 2. 4/84 (5%)were capable of only limited self-care and confined to bed or chair for >50% of waking hours. 1 patient was completely disabled. 11 heart disease, 3 pulmonary disease, 5 diabetes, 11 hypertension.	Spinal surgery (n=54): Indicated for progressive neurological deficiency (18 thoracic, 5 lumbar vertebrae) or impending instability (6 cervical, 11 thoracic, 9 lumbar vertebrae). 15 patients with single thoracic of lumbar lesions treated with combined anterior resection and posterior instrumentation. When contiguous vertebral bodies were involved or the patients general health status was reduced, a single one-stage posterior decompression-stabilisation procedure was performed (n=18). Tumour surgery in the cervical vertebrae was only by ventral decompression and stabilisation (n=6) decompressive laminectomy alone was not indicated due to risk of vertebral instability.	n/a	*Complications* *Recurrence* *Survival*	*Complications* 3/54 had complication including 1 major implant failure requiring re-osteosynthesis; 1 major delayed wound healing requiring secondary wound closure; and 1 local recurrence requiring dorsal spondylodesis. *Recurrence* Local recurrence in 4 patients following surgery of vertebral column. 48/84 patients developed additional skeletal lesions during course of disease. Majority of these were locally irradiated, 14 needed surgical intervention *Survival* Survival estimates at 1, 3, 5, and 10 years = 86.8%, 68%, 50%, 30.1% Median overall survival since surgery = 47 months (±17 months)
Design, period	Retrospective case series, 1990-2002					
N	57 spinal surgery (84 total)					
Follow-up	Survival follow-up median 46 mo					
Funding source						
Comments	– Survival not reported separately for spinal surgery vs. surgery to extremities. – Small sample size – Non-comparative study					

2

1

Study: Utzschneider S., S. Surgical therapy of skeletal complications in multiple myeloma. *International Orthopaedics* 2011; 35(8): 1209-1213.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Germany	75 patients treated surgically because of skeletal manifestations. Indications for surgery were pathological or impending fracture, or neurological impairment due to spinal lesion. Mean age 60 years (range 31-85). 42 male, 33 female. Spinal bone lesions: 8 cervical, 16 thoracic, 21 lumbar. Mean duration of symptoms 7.5 months (range 0-122; median 3 months). Pain present in all patients, 64% pathological fracture, 31% neurological impairment. Salmon Durie stage IA (n=11), stage IB (n=1), stage IIA (n=30), stage IIB (n=11), stage IIIA (n=15), stage IIIB (n=6), unknown (n=12). 83 operations performed (14 incisional biopsy only).	Spinal surgery: 4 decompression only, 27 decompression including instrumentation, 6 vertebroplasty/kyphoplasty. In 9 patients an endoprosthesis was implanted, Of total patients (including non-spinal surgery): 66 received radiotherapy, 9 before surgery, 8 before and after. 58 had chemotherapy, 11 before surgery, 14 pre and post operatively.	n/a	*Survival* *Complications*	*Survival:* Median 4.7 years. 5-yr survival 37%. Predicting factors for improved survival: single bone lesion vs multiplpe (p=0.04), negative vs positive bone marrow biopsy (p=0.0007), post-operative vs preoperative radiation (p=0.02), Salmon-Durie stage I vs stage II and III (p=0.04), without vs with paraproteinaemia in serum (p=0.03). *Complications* Deep vein thrombosis (n=1), respiratory insufficiency (n=4), cardiovascular insufficiency (n=2), septicaemia (n=2), revision due to deep wound infection (n=2), transient bowel atonia (n=1), pleural effusion (n=1), haemothorax from post-op bleeding (n=1), severe bleeding during surgery (n=5), severe post-op bleeding (n=3), vascular injuries at surgery (n=2), progressive neurological impairment with paraplegia (n=5) including atonia of the bladder and rectum in 2 cases, prolonged wound healing (n=5).
Design, period	Retrospective case series, 1980-2005					
N	45 spine (75 total)					
Follow-up	Mean 5.4 years (range 1-25)					
Funding source	None reported					
Comments	– Cohort treated between 1980-2005 – relevance to current practice? – Outcomes not reported separately for spinal and non-spinal surgery patients although location of bone lesion did not influence prognosis – Small sample size – Retrospective study					

2

Study: Budach, V. Multiple myeloma: Results of radiotherapy in skeletal lesions. A review of 163 patients. *Tumor Diagnostik und Therapie* 1991; 12(6): 238-243.						
Country	Germany	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Study: Budach, V. Multiple myeloma: Results of radiotherapy in skeletal lesions. A review of 163 patients. *Tumor Diagnostik und Therapie* 1991; 12(6): 238-243.						
		Multiple myeloma patients. 86 male, 71 female. Median 61.5 years (range 36-82). 64% received radiotherapy in more than one site. Severe localised pain was reason for radiation in 94% of sites. 74% pain caused by osteolytic lesions, 22% from pathological fractures, 3.3% accompanied by neurological symptoms. A soft tissue tumour or diffuse pain showing some peak localisation required irradiation in 9% (n=35) of all lesions. Cervical spine sites (n=10), thoracic (n=96), lumbar (n=89) Neurosurgical intervention necessary prior to radiotherapy in 26 cases of spinal involvement with symptomatic spinal cord compression in 10 cases (5.1%)	Radiotherapy: Linear accelerator. Doses range 5.4Gy to 54 Gy, with daily fraction of 1.8 to 3Gy	n/a	Pain relief: Assessed by staff and patients by decreased analgesic use and increased mobility. Good to complete pain relief = group 1, partial pain relief=group 2, no pain relief = group 3. Survival Side effects	Pain relief: 222/389 (57.1%) showed good/complete pain relief (group 1). 122/389 (31.3%) partial pain relief (group 2) 45/389 (11.6%) no response (group 3) Group 1 mean dose 28.6Gy (range 10-50) average 20 days Group 2 mean dose 26.9Gy (range 10.3-44) average 18 days Group 3 mean dose 20.4 Gy (range 5.4-54 Gy) average 12 days Survival: Median survival 36 months (range 1-192) No difference in survival according to response groups. Side effects: Usually mild and consisted of acute skin reactions (WHO grade I-II). One severe complication in a patient with disseminated MM who had radiation to pelvis stopped due to severe diarrhoea.
Design, period	Retrospective case series 1972-1990					
N	157 patients, 389 sites (50% spine)					
Follow-up	Not reported					
Funding source	Not reported					
Comments	– Non-comparative retrospective study – Outcomes not reported separately for spinal and non-spinal bone disease groups – limits relevance to review question – Includes patients with spinal cord compression (total number not reported) – limits relevance to review question – No details about stage of myeloma or other treatment received – Cohort treated between 1972 and 1990 – limited relevance to current practice?					

1

2

Study: Yaneva, MP, Goranova-Marinova, V, and Goranov, S. Palliative radiotherapy in patients with multiple myeloma. *Journal of Balkan Union of Oncology* 2006; 11(1): 43-48.						
Country	Bulgaria	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Study: Yaneva, MP, Goranova-Marinova, V, and Goranov, S. Palliative radiotherapy in patients with multiple myeloma. *Journal of Balkan Union of Oncology* 2006; 11(1): 43-48.						
		162 patients with myeloma – 87 underwent radiotherapy. 63 vertebral fractures – 58 irradiated (mostly thoracic and lumbar spine) Mean age of total patients 60.8 y (range 38-81). Salmon-Durie satge I (n=4), stage II (n=25), stage III (n=58)	Radiotherapy: 2 basic treatment regimens 2 fractions 8.5 Gy interval 72 hours; 5 fractions 4Gy each consecutive day on the involved sites targeting the involved vertebra and parts of the neighbouring not involved vertebrae.		Pain relief: patients assessment and analgesic use Motor activity Toxicity Survival	78/87 (90%) bone pain palliation achieved and in 21/87 (27%) pain completely resolved for median 3.5 months (range 1.5-16). Improvement of motor function in 62/79 (78%); the range of movements increased and ability of walking without help (median duration 4.5 months, range 1-16). 11.5% bone pain relapsed at treated site. Toxicity Hematological toxicity: Grade 1 (n=24) Grade 2 (n=11) Grade 3-4 leucopenia (n=1) Non-haematological toxicity (nausea, vomiting, fatigue): Grade 1 (n=51) Grade 2 (n=31) Grade 3 nausea (n=1) Survival: Irradiated patients median 32 months (range 25-50) Non-irradiated patients median 33 months (range 28-36) (p>0.05) 5x4 Gy median 34 months (range 25-50) 2x8 Gy median 32 months (range 27-37) (p>0.05)
Design, period	Retrospective case series 1994-2004					
N	162					
Follow-up	Mean 21 months (range 2-41)					
Funding source	None reported					
Comments	– Retrospective non-comparative study – Outcomes not reported separately for spinal and non-spinal bone disease – limits relevance to review question – No details about other treatment					

1

Study: Balducci, M et al. Impact of radiotherapy on pain relief and recalcification in plasma cell neoplasms: long-term experience. *Strahlentherapie und Onkologie* 2011; 187(2): 114-119.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Italy	52 patients with osteolytic lesions and diagnosed plasma cell neoplasms. Female: N (%) 19 (37)	Radiotherapy: Megavoltage radiotherapy, using linear accelerator.	n/a	*Pain*: Numerical rating scale (NRS) score ≤4 mild pain, 5-7 moderate,	*Pain relief (n=45 (9 solitary plasmacytoma)):* 2 months after RT no patient reported increase of pain. Pain relief reported in 41/45 patients (91%), including all patients with severe pain at baseline.

Study: Balducci, M et al. Impact of radiotherapy on pain relief and recalcification in plasma cell neoplasms: long-term experience. *Strahlentherapie und Onkologie* 2011; 187(2): 114-119.

Design, period	Retrospective case series 1996-2007	Male: 33 (63) Mean age: 66 Range: 22-71 Solitary plasmacytoma: 10 (19) Multiple myeloma: 42 (81) Treatment Radiotherapy (all plasmacytoma): 8 (15) RT prior to chemotherapy: 13 (25) RT after chemotherapy: 31 (60) Surgery No: 29 (56) Yes: 23 (44) Irradiated sites Spinal cord: 35 (68) Pelvic bone: 6 (12) Extremities: 5 (9) Skull: 4 (7) Ribs: 2 (4)	Surgery always performed before RT for spinal cord compression or bone fractures. RT delivered before chemotherapy in 13 patients because of pain or risk of fractures. In spinal lesions, the target volume was represented by the involved vertebrae plus upper and lower vertebrae. Planning target volume was obtained by adding 1cm margin to CTV. Median total dose was 38 Gy (range 16-50), median daily fraction 2 Gy (range 2-4Gy)tailored to PS, degree of pain, site of lesion, and palliation guidelines. Bisphosphonates (zoledronic acid) monthly for median 4 months.		≥8 severe. Assessed at baseline and 30-45 days after RT. Classified as complete response, partial response and no change. *Toxicity*: RTOG score	7/21 (33%) with complete response obtained drug reduction or suspension. Patients with mild pain reported a median NRS of 3 (range 1-4) before radiotherapy Patients with moderate pain reported a median NRS of 5 (range 5-7) before radiotherapy Patients with severe pain reported NRS of 8 (range 8-10) before radiotherapy. After radiotherapy the median NRS was 1 (range 0-7) for the whole group. *Toxicity:* No RTOG Grade 3-4 toxicity. Grade 1-2 observed in 22 (44%) patients, haematological toxicity in 11 (48%), gastroenteric toxicity in 6 (26%), pharyngeal toxicity in 2 (9%), and cutaneous toxicity in 4 (17%). *Progression:* 6 patients had disease progression (1 with skull, 4 with spine, 1 pelvic bone lesions) With median follow-up of 61 months (range 21-210)5-yr local was 81%. 76% in multiple myeloma, 90% in solitary plasmacytoma.
N	42 myeloma (52 total)					
Follow-up	Median 57 months (range 21-210)					
Funding source	None reported					
Comments	– Non-comparative retrospective study – Outcomes not reported separately for spinal and non-spinal bone disease groups – limits relevance to review question – Includes patients with spinal cord compression (total number not reported) – limits relevance to review question – No details about stage of myeloma					

1

Study: Mhaskar, R., et al. (2012) Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database of Systematic Reviews,* 5: CD003188.

		Method	Intervention	Comparison	Outcome	Results
Country	**n/a**	Included RCTs in which interventions consisted of bisphosphonates against placebo or no treatment or other bisphosphonates in MM	Bisphosphonates	• Placebo • No treatment • Different	• OS • PFS • skeletal-related	Pooled results showed no direct effect of bisphosphonates on OS compared with placebo or no treatment (HR 0.96, 95% CI 0.82 to 1.13; P = 0.64). However, there was a statistically significant

Study: Mhaskar, R., et al. (2012) Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database of Systematic Reviews,* 5: CD003188.						
Design, period	Systematic review of randomised trials	patients. All studies required biopsy-proven myeloma as the diagnostic criterion and bone involvement that met criteria for administration of bisphosphonates according to the studies' investigators. 6 RCTs included the presence of at least one osteolytic lesion for patient inclusion in trial.		bisphosphonate	events • pain • quality of life • incidence of hypercalcemia • adverse events - gastrointestinal toxicities - osteonecrosis of jaw - hypocalcemia - renal dysfunction	heterogeneity among the included RCTs (I^2 = 55%, P = 0.01) for OS. Results from network meta-analyses showed superior OS with zoledronate compared with etidronate (HR 0.43, 95% CI 0.16 to 0.86) and placebo (HR 0.61, 95% CI 0.28 to 0.98). However, there was no difference between zoledronate and other bisphosphonates. Pooled analysis did not demonstrate a beneficial effect of bisphosphonates compared with placebo or no treatment in improving PFS (HR 0.70, 95% CI 0.41 to 1.19; P = 0.18) There was no heterogeneity among trials reporting PFS estimates (I^2 = 35%, P = 0.20). Pooled analysis demonstrated a beneficial effect of bisphosphonates compared with placebo or no treatment on prevention of pathological vertebral fractures (RR 0.74, 95% CI 0.62 to 0.89; I^2 = 7%), skeletal-related events (SRE) (RR 0.80, 95% CI 0.72 to 0.89; I^2 = 2%) and amelioration of pain (RR 0.75, 95% CI 0.60 to 0.95; I^2 = 63%). The network meta-analysis did not show any difference in the incidence of osteonecrosis of the jaw (5 RCTs, 3198 patients) between bisphosphonates. Rates of osteonecrosis of the jaw in observational studies (9 studies, 1400 patients) ranged from 0% to 51%. The pooled results (6 RCTs, 1689 patients) showed no statistically significant increase in frequency of gastrointestinal symptoms with the use of bisphosphonates compared with placebo or no treatment (RR 1.23, 95% CI 0.95 to 1.60; P = 0.11). The pooled results (3 RCTs, 1002 patients) showed no statistically significant increase in frequency of hypocalcemia with the use of bisphosphonates compared with placebo or no treatment (RR 2.19, 95% CI 0.49 to 9.74). The network meta-analysis did not show any differences in the incidence of hypocalcemia, renal dysfunction and gastrointestinal toxicity between the bisphosphonates used.
N	20 RCTs, 6692 patients					
Follow-up	Varied across studies					
Funding source	n/a					
Comments	– Also included in evidence review for Topic L1 – 6 studies specified presence of at least one osteolytic lesion for patient inclusion in trial – it is not specified if lesions were spinal or non-spinal, which limits the relevance of the review to this topic. – Overall methodological quality of reporting was moderate. Thirty per cent (6/20) of trials reported the method of generating the randomization sequence. Forty per cent (8/20) of trials had adequate allocation concealment. Withdrawals and dropouts were described in 60% (12/20) of trials.					

1

Study: Henry, D. H., et al. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of clinical oncology,* 29: 1125-1132.						
Country	USA	**Patient Characteristics**	**Intervention**	**Comparison**	**Outcome**	**Results**

Study: Henry, D. H., et al. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of clinical oncology,* 29: 1125-1132.						
		Myeloma patients with at least 1 bone metastases or osteolytic lesion. Excluded patients with prior bisphosphonate treatment, planned radiation or surgery to bone and unhealed dental/oral surgery. Most patients had prior systemic anti-cancer therapy.	Denosumab	Zoledronic acid	Time to first on-study SRE (fracture, spinal cord compression, or radiation/surgery to bone) Overall survival	The effect of denosumab on time to first on-study SRE relative to zoledronic acid resulted in an HR of 1.03 (95% CI: 0.68 to 1.57). An ad hoc analysis examining overall survival demonstrated an HR of 2.26 (95% CI: 1.13 to 4.50).
Design, period	Randomised trial, 2006-2008					
N	180 myeloma patients					
Follow-up	2 years					
Funding source	Amgen					
Comments	– Also included patients with solid tumours (except breast and prostate). SRE reported separately by disease type. – Not specified whether spinal or non-spinal bone lesions – limits relevance to review question. – Independent randomisation					

1

2

Study: Zadnik PL, Goodwin CR, Karami KJ, Mehta AI, Amin AG, Groves ML et al. (2015). Outcomes following surgical intervention for impending and gross instability caused by multiple myeloma in the spinal column. Journal of Neurosurgery Spine, 22, 301-309.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcomes**	**Results**
Country	USA	Histologically confirmed multiple myeloma (N=25) or solitary plasmacytoma of the spine (N=6). All had indeterminate or gross spinal column instability. 74% were ambulatory at presentation Median age 58.5 yrs, 71% male	Surgical intervention. Approach was posterior in 48%, staged in 29% and anterior in 23% of cases. Reconstruction: allograft with cage (48%), none (39%), PMMA/cement (9%) and allograft only (3%).	None	Functional and pain outcomes, Overall survival, complications of spinal instrumentation postoperative medical and surgical complications	**Functional and pain** 88% of ambulatory patients remained so at 1 year post-op. At one year post op 45% of patients were taking narcotics for pain control (compared to 63% at baseline). **Overall survival** 5 patients died within 1 year of surgery. Median OS was 78.9 months (6.6 years). **Complications of spinal instrumentation** 4/31 patients experienced complications of spinal instrumentation – rod fracture, loosening of screws and loss of correction. **post-op complications** 14/31 patients experienced post-op complications: 2 had pulmonary embolus, 2 deep vein thrombosis, 2 wound dehiscence, 3 reoperations, and there were single cases of pressure sore, pnemothorax, pneumonia, M.I. and wound infection.
Design, period	Retrospective case series 2002-2012					
N	31					
Follow-up	Median 12.5 months					
Funding source	Not reported					
Comments	–					

1

Study: Simony, A. (2014). Pain reduction after percutaneous vertebroplasty for myeloma-associated vertebral fractures. Danish Medical Journal, 61, A4945.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Denmark	Patients with myeloma-associated vertebral body fractures and severe pain. Mean age 62.5 years, 59% male	Percutaneous vertebroplasty	None	Pain (on VAS scale) Cement leakage	**Pain** Pain decreased from 7.7 preoperatively to 3.4 postoperatively ($p<0.005$)

Study: Simony, A. (2014). Pain reduction after percutaneous vertebroplasty for myeloma-associated vertebral fractures. Danish Medical Journal, 61, A4945.						
Design, period	Retrospective case series 2004-2010					**Cement leakage** 8 leakages occurred in the 64 levels treated. Three leaks were to the spinal canal – but none lead to neurological complications.
N	17					
Follow-up	3 months					
Funding source	Not reported					
Comments	–					
	–					

1

2

Study: Ha KY, Min CK, Seo JY, Kim YH, Ahn JH, Hyun NM et al. (2015). Bone cement augmentation procedures for spinal pathologic fractures by multiple myeloma. Journal of Korean Medical Science, 30, 88-94.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	Korea	Patients with myeloma and pathological spine fractures.0	Cement augmentation (vertebroplasty or kyphoplasty)	No surgery (conservative management – pain control, external brace)	Pain (VAS) Oswestry disability index (ODI)	
Design, period	retrospective case series 2009-2011					

	Cement Augmentation	**No surgery**	**P**
Pain (VAS) 1 month post-op	3.2 (±0.8)	6.1 (±0.9)	<0.05
ODI	54.9% (±9.8%)	72.8% (±6.8%)	<0.01
Bone cement leakage*	10/49 vertebrae	-	-

Study: Ha KY, Min CK, Seo JY, Kim YH, Ahn JH, Hyun NM et al. (2015). Bone cement augmentation procedures for spinal pathologic fractures by multiple myeloma. Journal of Korean Medical Science, 30, 88-94.						
N	56					*did not lead to clinical symptoms
Follow-up	Mean 16.8 months (6-33)					
Funding source	No funding received					
Comments	–					

1

Study: Julka, A., Tolhurst, S. R., Srinivasan, R. C., & Graziano, G. P. (2014). Functional Outcomes and Height Restoration for Patients With Multiple Myeloma-related Osteolytic Vertebral Compression Fractures Treated With Kyphoplasty. Journal of Spinal Disorders & Techniques, 27, 342-346.						
		Patient Characteristics	**Intervention**	**Comparison**	**Outcome**	**Results**
Country	USA	Patients with myeloma and vertebral compression fractures. Mean age: 64.3 years, 56% male	Kyphoplasty	None	Oswestry disability index (ODI) Length of stay Surgical complications Post-op complications	**Oswestry disability index (ODI):** available for 27 patients – at a mean of 24 months post-op the mean score was 29% (excluding 2 who had died and 3 who were lost to follow-up). **Length of stay:** mean 1.34 days **Surgical complications**: 12/32 (37.5%) –cement leakage **Post-op complications**: none observed
Design, period	Retrospective case series					
N	32					

Study: Julka, A., Tolhurst, S. R., Srinivasan, R. C., & Graziano, G. P. (2014). Functional Outcomes and Height Restoration for Patients With Multiple Myeloma-related Osteolytic Vertebral Compression Fractures Treated With Kyphoplasty. Journal of Spinal Disorders & Techniques, 27, 342-346.						
Follow-up	Mean 24 months					
Funding source	Not reported					
Comments	–					

1

2

Chapter 9: Preventing and managing complications

Preventing infection

Recview question:
What is the most effective prophylactic strategy for infection in patients with myeloma (including immunoglobulin, antibiotics, growth factors and vaccinations)?

Questin in PICO format

Population	Intervention	Comparator	Outcomes
• Newly diagnosed myeloma patients • relapsed myeloma patients • Patients on active therapy or maintenance therapy • myeloma patients currently off treatment • post autologous transplant myeloma patients	• Antibiotics (including anti-mycobacterial prophylaxis) • Anti-virals • Anti-fungals • Pneumocystis prophylaxis • Immunoglobulins • Growth factors • Vaccination	• placebo • no treatment • each other (within treatment type group)	• sepsis • recorded infections • death related to infection • hospital admissions • adverse events (e.g. growth factor related bone pain) • response to vaccination • patient adherence and acceptability

Evidence Statements

Newly Diagnosed Myeloma patients

Low quality evidence from one randomised trial including 212 patients with newly diagnosed myeloma (Vesole et al, 2012) suggests uncertainty about the effectiveness of prophylactic antibiotics (quinolone/ofloxacin or trimethoprim-sulfamethoxazole) compared to observation alone. The rate of severe bacterial infection was 9.3% with antibiotics versus 15.9% with observation (RR=0.59; 95% C.I. 0.28 to 1.28) ***Patients on active therapy or maintenance therapy***

Growth Factors

Moderate evidence from one randomised trial including 281 patients undergoing chemotherapy in a high dose Melphalan (HDM) transplant setting (Blijlevens et al, 2013) suggests uncertainty about the effectiveness of prophylactic palifermin compared to placebo for the prevention of oral mucositis. The rate of severe oral mucositis was 38% with palifermin versus 37% with placebo (RR 1.04; 95% C.I. 0.69 to 1.57). *Immunoglobulins*

Low quality evidence came from a single randomised trial including 81 patients with myeloma comparing polyvalent intravenous immunoglobulins (IVIG) with placebo, identified in the Raanani et al (2009) systematic review. Low quality evidence suggests uncertainty about the effect of polyvalent IVIG versus placebo in terms on all cause mortality during study follow-up (19% versus 7% respectively; RR 2.67; 95% CI 0.76 to 9.35). Low quality evidence suggests that polyvalent IVIG is effective compared to placebo in preventing major infections (5% versus 24% respectively; RR 0.20; 95% CI 0.05 to 0.86) and clinically documented infections (42% versus 93% respectively; RR 0.45; 95% CI 0.31 to 0.65). *Antibiotics*

Low quality evidence came from one randomised trial including 54 patients (Oken et al, 1996) comparing 2 months of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis with no prophylaxis in patients with myeloma. Low quality evidence suggests that TMP-SMZ prophylaxis is effective compared to no prophylaxis in reducing the rate of infection (18% versus 46% respectively; RR 0.39; 95% CI 0.16 to 0.95).

Post autologous transplant myeloma patients

Growth factors

Low quality evidence from one randomised trial including 47 patients (31 with myeloma; Ozkan et al, 2013) suggests uncertainty about whether G-CSF daily versus every other day is the more effective in terms of time to neutrophil engraftment (median was 10 days in both groups; P=0.31); Very low quality evidence from one retrospective study including 117 patients (Cox et al, 2014) reported significantly longer time to neutrophil engraftment in patients receiving delayed G-CSF administration compared with conventional administration (15 days versus 12 days respectively; P<0.0001).

Low quality evidence from one randomised trial including 47 patients (Ozkan et al, 2013) suggests uncertainty about the relative effectiveness of daily G-CSF daily versus every other day for the prevention of blood stream infection (rates were 14% versus 19% respectively; RR 0.74; 95% CI 0.20 to 2.76).

Immunoglobulins

Moderate quality evidence from one systematic review and meta-analysis including a total of 4223 patients (Raanani et al, 2009) reported no significant difference in all cause mortality for patients treated with polyvalent IVIG versus no treatment (1418 patients in 8 trials; 0.99 (0.88 to 1.12) p=0.92). Infection related death did not differ significantly between the groups (275 patients in 3 trials; Risk Ratio 0.64 (0.28 to 1.49) P=0.3).

Moderate quality evidence from one systematic review and meta-analysis including a total of 4223 patients (Raanani et al, 2009) reported significantly more adverse events for patients treated with polyvalent IVIG compared with placebo/no treatment (728 patients in 5 trials; Risk Ratio 8.12 (3.15 to 20.97) P=0.000015).

Anti-fungals

Very low quality evidence from a retrospective study of 104 patients (Orvain et al., 2015) suggests uncertainty about the effectiveness miconazole mucoadhesive buccal tablets compared with oral amphotericin B suspension in reducing hospital stay after stem cell re-infusion (mean 15.3 days versus 16.4 days respectively; p=0.09).

Viral Vaccinations

Varicella zoster vaccine (VZV)

Low quality evidence from two randomised trials including 139 patients with haematological malignancies (Cheuk et al, 2011) suggests uncertainty about the benefit of VZV compared to no vaccine on all cause mortality (Risk Ratio 0.96; 95% CI0.54 to 1.69:P=0.89). Low quality evidence suggests that both systemtic and local adverse events (at the injection site) are more likely with VZV than with no vaccination. Systemic adverse events occurred at a rate of 5% with VZV and local adverse events at a rate of 21%, no adverse events were reported in the no vaccination group.

Influenza Vaccine

Low quality evidence from 2 trials (Cheuk et al, 2011) comparing influenza vaccine to no vaccine in patients with haematological malignancies suggests uncertainty about its effectiveness in preventing infection related mortality (Risk Ratio 0.2 [0.01-3.97] p=0.29). In this analysisLower respiratory tract infections were more likely in the no vaccine group (Risk ratio 0.39; 95% CI[0.19-0.78] p=0.0082). Rates of hospitalisation (Risk ratio 0.17 [0.09-0.31] p<0.00001) were significantly higher in the no vaccine group while the frequency of adverse events (Risk Ratio 35 [4.9-249.8] p=0.00039) were significantly higher in the vaccine group.

Relapsed Myeloma Patients and Myeloma patients currently off treatment

No evidence relating to prophylactic infection strategies for relapsed myeloma patients or those currently off treatment was identified.

Table 9.**1**: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (antibiotics compared to observation for patients with newly diagnosed myeloma)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Observation	Relative (95% CI)	Absolute	
Severe Bacterial Infection at 2 months (follow-up 2 months)											
1[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/138 (9.4%)	10/63 (15.9%)	RR 0.59 (0.28 to 1.28)	65 fewer per 1000 (from 114 fewer to 44 more)	⊕⊕OO LOW
Any infection during the first 2 months											
1[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/138 (21.7%)	14/63 (22.2%)	RR 0.98 (0.56 to 1.71)	4 fewer per 1000 (from 98 fewer to 158 more)	⊕⊕OO LOW
Severe infection during the 1st month											
1[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/138 (2.9%)	3/63 (4.8%)	RR 0.61 (0.14 to 2.64)	19 fewer per 1000 (from 41 fewer to 78 more)	⊕⊕OO LOW

[1] No details provided on randomisation method or blinding
[2] Small sample size,
[3] Vesole et al, 2012

Table 9.2: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (palifermin compared to placebo for patients undergoing conditioning chemotherapy)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Growth Factors	Placebo	Relative (95% CI)	Absolute	
Incidence of ulcerative oral mucositis (follow-up 14 days)											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	79/115 (68.7%)	33/57 (57.9%)	RR 1.19 (0.92 to 1.53)	110 more per 1000 (from 46 fewer to 307 more)	⊕⊕⊕O MODERATE
Incidence of severe oral mucositis (follow-up 14 days)											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	44/115 (38.3%)	21/57 (36.8%)	RR 1.04 (0.69 to 1.57)	15 more per 1000 (from 114 fewer to 210 more)	⊕⊕⊕O MODERATE

Serious adverse events											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/109 (16.5%)	3/57 (5.3%)	RR 3.14 (0.96 to 10.21)	113 more per 1000 (from 2 fewer to 485 more)	⊕⊕⊕O MODERATE

[1] Small sample size, [2] Blijlevens et al, 2013

Table 9.3: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (immunoglobulins compared to placebo/no treatment for patients with lymphoproliferative disorders)?

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Immunoglobulins**	**Placebo/No treatment**	**Relative (95% CI)**	**Absolute**	
All cause mortality (follow-up 1 years1)											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	8/41 (19.5%)	3/41 (7.3%)	RR 2.67 (0.76 to 9.35)	122 more per 1000 (from 18 fewer to 611 more)	⊕⊕OO LOW
Major Infections											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/41 (4.9%)	10/41 (24.4%)	RR 0.20 (0.05 to 0.86)	195 fewer per 1000 (from 34 fewer to 232 fewer)	⊕⊕OO LOW
Clinically documented infection											
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	17/41 (41.5%)	38/41 (92.7%)	RR 0.45 (0.31 to 0.65)	510 fewer per 1000 (from 324 fewer to 640 fewer)	⊕⊕OO LOW

[1] All cause mortality was assessed at 1 year in the two trials for which this outcome was reported
[2] Raanani (2009) systematic review - single MM trial Chapel (1994)
[3] Small sample size

Table 9.4: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (trimethoprim-sulfamethoxazole versus no treatment for patients with a confirmed melanoma diagnosis (Oken et al, 1996))?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Trimethoprim-sulfamethoxazole**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Infection Incidence												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	5/28 (17.9%)	12/26 (46.2%)	RR 0.39 (0.16 to 0.95)	282 fewer per 1000 (from 23 fewer to 388 fewer)	⊕⊕OO	

											LOW	
Death from infection												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	1/28 (3.6%)	4/26 (15.4%)	RR 0.23 (0.03 to 1.94)	118 fewer per 1000 (from 149 fewer to 145 more)	⊕⊕OO LOW	

[1] Oken et al (1996)
[2] No details on randomisation method or blinding
[3] Small sample size

Table 9.5: GRADE Profile: What is the most effective prophylactic strategy for infection in patients with myeloma (G-CSF (conventional dosing) versus delayed or reduced dose for patients undergoing autologous stem cell transplant)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G-CSF (conventional dosing)	Delayed or reduced dose	Relative (95% CI)	Absolute	
Neutrophil engraftment (randomised trials) (Better indicated by lower values)											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	21	26	-	Median 18 days in both groups	⊕⊕OO LOW
Neutrophil engraftment (observational studies)											
1	observational studies[4]	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	65	-	Mean 12 days with conventional versus 15 days with delayed dose	⊕OOO VERY LOW
Blood stream infections											
1[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency	serious[2]	Serious[3]	none	3/21 (14.3%)	5/26 (19.2%)	RR 0.74 (0.20 to 2.76)	50 fewer per 1000 (from 154 fewer to 338 more)	⊕⊕OO LOW
Hospitalisation (Better indicated by lower values)											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	Serious[3]	none	21	26	-	MD 1.1 days shorter with conventional dose	⊕⊕OO LOW

[1] Ozkan (2013); [2] Mixed haematological malignancies including myeloma; [3] Small sample size; [4] Cox (2014); [5] Unbalanced baseline characteristics between groups

Table 9.6: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (immunoglobulins versus placebo or no treatment/different preparation, schedule or dose in patients undergoing hematopoietic stem cell transplantation)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunoglobulins	Placebo/no treatment/different preparation, schedule or dose	Relative (95% CI)	Absolute	
All cause mortality											
8	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	300/756 (39.7%)	273/662 (41.2%)	RR 0.99 (0.88 to 1.12)[3]	4 fewer per 1000 (from 49 fewer to 49 more)	⊕⊕⊕O MODERATE
Infection related death											
3	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	8/137 (5.8%)	12/138 (8.7%)	RR 0.64 (0.28 to 1.49)[4]	31 fewer per 1000 (from 63 fewer to 43 more)	⊕⊕⊕O MODERATE
Clinically documented infections											
5	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	267/388 (68.8%)	181/300 (60.3%)	RR 1.00 (0.9 to 1.1)[5]	0 fewer per 1000 (from 60 fewer to 60 more)	⊕⊕⊕O MODERATE
Adverse Events											
5	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	49/415 (11.8%)	2/313 (0.64%)	RR 8.12 (3.15 to 20.97)[6]	45 more per 1000 (from 14 more to 128 more)	⊕⊕⊕O MODERATE

[1] Raanani et al (2009)
[2] Not all included patients were Myeloma patients

Table 9.7: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (miconazole mucoadhesive buccal tablets versus oral amphotericin-B suspension in patients receiving high dose melphalan and autologous stem cell transplant for haematological malignancy)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Miconazole mucoadhesive buccal tablets	Oral amphotericin-B suspension	Relative (95% CI)	Absolute	
Duration of hospital stay (Better indicated by lower values)											
1	observational studies[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	60	44	-	MD 1.1 lower with MBT	⊕OOO VERY LOW

[1] Orvain (2015); [2] Not a randomised trial (prospective cohort compared with a historical cohort); [3] All haematological malignancies; 51/104 patients with myeloma; [4] Small sample size

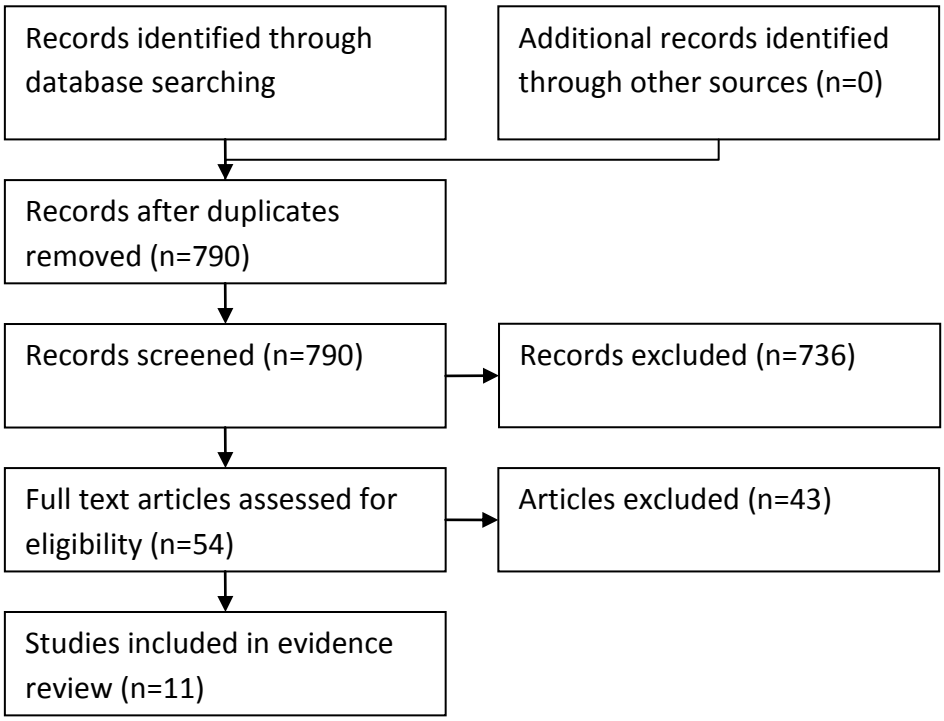
Table 9.8: GRADE profile: What is the most effective prophylactic strategy for infection in patients with myeloma (viral vaccines versus placebo, no vaccines, alternative dosing regimens or schedules in patients with haematological malignancies)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Viral vaccines	Placebo, no vaccines, alternative dosing regimens or schedules	Relative (95% CI)	Absolute	
All cause mortality (Varicella zoster vaccine)											
2	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	17/67 (25.4%)	19/72 (26.4%)	RR 0.96 (0.54 to 1.69)	11 fewer per 1000 (from 121 fewer to 182 more)	⊕⊕OO LOW
Local adverse events (Varicella zoster vaccine)											
2	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	20/97 (20.6%)	0/97 (0%)	RR 20.94 (2.88 to 152.36)	-	⊕⊕OO LOW
Systemic adverse events (Varicella zoster vaccine)											
2	randomised trials[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	5/97 (5.2%)	0/97 (0%)	RR 5.94 (0.73 to 48.55)	-	⊕⊕OO LOW

[1] Cheuk (2011)
[2] All haematological malignancies
[3] Low sample size

Search Results

Figure 9.1. Study flow diagram



Study characteristics and quality

Four systematic reviews, 5 randomised trials and 2 non randomised comparative studies (1 prospective and 1 retrospective) which met the inclusion criteria were indentified. The design of each study is summarised in Table 9.9

Due to the nature of the topic, inclusion of studies was not limited to those with exclusively a myeloma population and as such some of the studies included patients with other haematological malignancies, such as lymphoma or leukaemia.

Studies in which neutropenia was the primary outcome of interest were excluded as the prophylactic treatment of neutropenia is covered by current NICE guidance on neutropenic sepsis Much of the available evidence concentrated on prophylaxis in patients undergoing stem cell transplants with little evidence available relating to patients on active maintenance, relapsed myeloma or myeloma patients off treatment. No studies investigating the effect of prophylactic treatment on hepatitis in patients with myeloma were identified.

1 **Table 9.9: Characteristics of included studies**

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
Blijlevens et al (2013)	RCT	Patients with multiple myeloma treated with autologous hematopoietic stem cell transplant	281	Palifermin pre and post HDM treatment Palifermin pre (placebo post) HDM treatment	Placebo	• Severity of oral mucositis • Incidence of severe oral mucositis • Mean duration of severe oral mucositis
Cheuk et al (2011)	SR/MA	Patients with haematological malignancies	593	All forms of viral vaccine including influenza, varicella, hep A, hep B measles, mumps, rubella and poliomyelitis	Placebo vaccine No Vaccine Alternative dosing regimens or schedules	• Incidence of viral infection • Mortality due to viral infection • All cause mortality • Incidence of severe viral infection • Rate of hospitalisation due to viral infection • In vitro immune response to vaccine • Frequency of systemic and local adverse effects
Cox et al (2014)	Retrospective comparative study	Patients with multiple myeloma treated with autologous hematopoietic stem cell transplant	117	Deferred G-CSF	Routine G-CSF	• Neutrophil engraftment • Duration of severe neutropenia • Time to platelet recovery to 20,000/µl and to 50,000/µl • Episodes of febrile neutropenia • Regimen related toxicity

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
						• Duration of hospitalisation • Cost analysis
Lockhart et al (2005)	RCT	Patients planned for ABSCT	36 (n=9 myeloma)	Pilocarpine	Placebo	• Incidence of oral mucositis • Severity of oral mucositis • Duration of oral mucositis
Oken et al (1996)	RCT	Patients with a confirmed myeloma diagnosis	57	Trimethoprim-sulfamethoxazole	No prophylaxis	• Infection incidence • Infection Rate • Infection Type • Toxicity
Orvain et al (2015)	Non randomised comparative study	Patients receiving HDT/ASCT for treatment of haematological malignancies	104 (n=51 myeloma)	Miconazole mucoadhesive buccal tablets	Oral amphotericin B suspension	• Opioid and non opioid analgesic use • Total parenteral nutrition • Antibiotic and systemic antifungal use • Infectious complications • Hospitalisation
Ozkan et al (2013)	RCT	Patients with non-myeloid haematological malignancies undergoing APSCT transplant	47 (n=31 myeloma)	G-CSF every other day	Daily G-CSF	• Neutrophil engraftment • Infectious complications and hospitalisation
Raanani et al (2009)/Raanani et al (2008)	SR/MA	Patients undergoing haematopoietic stem cell transplantation	4223	Intravenous or intramuscular polyvalent immunoglobulin or hyperimmune cytomegalovirus-IVIG	Placebo No treatment Another immunoglobulin preparation A different administration schedule A different dose	• All Cause Mortality • Clinically documented infections • Microbiologically documented bacterial infections • CMV infection • Interstitial pneumonitis • Acute graft versus host

STUDY ID	DESIGN	PATIENT CHARACTERISTICS	N	INTERVENTION	COMPARISON	OUTCOMES MEASURED
						disease (GVHD) • Veno-occlusive disease (VOD) • Adverse events
Raanani et al (2009b)	SR/MA	Patients with lymphoproliferative disorders and plasma cell dyscrasias	408 (some data missing)	IVIG	Placebo No treatment A different dose	• All cause mortality • Major infection • Clinically and microbiologically documented bacterial infection • Adverse events
Vesole et al (2012)	RCT	Patients with symptomatic and untreated myeloma receiving myelosuppressive and/or immunosuppressive chemotherapy	212	Daily quinolone Trimethoprim-sulfamethoxazole	Observation	• Severe bacterial infection • Any infection • Severe infection during first month following prophylaxis

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1

2

1 Evidence Tables

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Cox et al (2014) USA

Study type, study period

Retrospective comparative study (January 2005-September 2012)

Aim

To determine whether delayed G-CSF dosage could result in equivalent ANC recovery and thereby improve cost-effectiveness

Number of patients

N=117

Patient characteristics

Patients with multiple myeloma treated with autologous hematopoietic stem cell transplant (ASCT)

	CGD (52)	**DGD (65)**	**p**
Age	35-75	37-79	0.501
Male	58%	55%	0.803
No. of prior chemotherapy courses			
0-1	22 (42%)	45 (69%)	0.003
2+	30 (58%)	20 (31%)	
Method of stem cell collection			
G-CSF alone	26 (50%)	27 (42%)	<0.0001
G-CSF plus chemotherapy	20 (38%)	2 (3%)	
G-CSF plus Mozobil	6 (12%)	36 (55%)	
CD-34 dose ($x10^6$)	3.79 (2.61-9.42)	4.49 (2.49-10.2)	0.021
Conditioning Regimen			
Melphalan 200	39 (75%)	44 (68%)	0.387
Melphalan 140	13 (25%)	21 (32%)	

Intervention

Deferred G-CSF

G-CSF was optionally administered to accelerate neutrophil recovery once this had begun (>200µ/ml) and if subsequent increases to levels required for discharge (>500µ/ml) did not follow within 48 hours

Comparison

Routine G-CSF

Length of follow-up

No details

Outcome measures and effect

Neutrophil engraftment
Duration of severe neutropenia
Time to platelet recovery to 20,000/µl and to 50,000/µl
Episodes of febrile neutropenia
Regimen related toxicity
Duration of hospitalisation
Cost analysis

	CGD	**DGD**		**Comment**
No. of Doses (median)	5	0	P<0.0001	55% of DGD group received no G-CSF Median post transplant day when G-CSF administration started in the DGD group was 14 days (range: 9-18)
Neutrophil and platelet recovery				
Time to neutrophil engraftment (days)	15	12	P<0.0001	
Duration of severe neutropenia (days)	6 (4-9)	8 (4-10)	P<0.0001	
Duration of neutropenia	7 (5-9)	10 (6-16)	P<0.0001	
Days to platelets 20,000µl	17 (10-25)	17 (9-35)	0.472	
Days to platelets 50,000µl	18 (12-25)	17 (11-35)	0.476	
Infection risk and antimicrobial utilisation				

Incidence of febrile neutropenia	60%	63%	0.702	
Duration of febrile neutropenia			0.759	
No. of antimicrobial drugs			0.597	
Incidence of positive cultures			0.338	
Duration of iv antibiotic treatment (days)	5	7	0.016	
Toxicity and supportive care utilisation				
Toxic Deaths (by day 100)	0	0		
Incidence/Duration of toxicity	No significant difference in the incidence or duration of mucositis, weight gain, rash or bone pain			
Duration of hospital stay	17	19	<0.0001	

Source of funding/Conflict of interest

None declared

Risks of bias

Selection bias: High risk. Not a randomised trial/A change in treatment policy led to the deferred G-CSF treatment from 2010 so effectively comparing with a historical cohort
Performance bias: Unclear/Unknown risk. Lack of blinding is not likely to affect any of the reported outcomes. From the study, changes in treatment policy were made, in part, due to improvements in cell collection techniques and in post-transplant supportive care both of which could be confounding factors.
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

1

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Ozkan et al (2013) Turkey

Study type, study period

Randomised Trial (June 2011-November 2011)

Aim

To compare effectiveness of daily administration of G-CSF to every other day administration of G-CSF following APSCT transplant in adult patients with non-myeloid haematological malignancies

Number of patients

N=47

N=31 myeloma

Patient characteristics

	G-CSF administration		
	Daily (n=21)	**Every other day (n=26)**	**p**
Age	54 (19-66)	53 (23-69)	0.97
Male	62%	65%	0.81
Diagnosis			
Myeloma	14 (67%)	17 (65%)	0.93
Lymphoma	7 (33%)	9 (35%)	
No. of prior chemotherapy regimens			
1	7	9	0.93
2	11	12	
3	3	5	
Conditioning regimens			
Melphalan	14	17	0.93
BEAM	7	9	
Prior Radiotherapy			
Yes	2	8	0.15
N	19	18	
Stem call dose	6 (4.24-34.5)	5.95 (3.67-17.6)	0.97

(X10^6 CD34 cells/kg)			

Intervention

G-CSF every other day

Comparison

Daily G-CSF

Length of follow-up

No details

Outcome measures and effect

Neutrophil engraftment
Infectious complications and hospitalisations

	G-CSF administration		
	Daily (n=21)	**Every other day (n=26)**	**p**
G-CSF duration to neutrophil engraftments (median)	9 (7.1-10)	5 (4-6.65)	<0.001
Days to neutrophil engraftment (median)	10 (8.1-11)	10 (9-12)	0.31
Days to platelet engraftment (median)	12 (9.1-14.9)	11 (9.35-14.65)	0.059
Number of febrile days	4 (±2.9)	3.2 (±2.1)	0.43
Duration of non-prophylactic antibiotics (mean)	14.5 (±4.7)	11.9 (±2.9)	0.085
Duration of hospitalisation	18 (14-27.9)	18 (13.35-40.2)	0.81
Blood stream infections	3 (14.3%)	5 (19.2%)	0.72
No. of RBC transfusions (median)	2 (0-7.8)	2 (0-6)	0.25
No. of plts transfusions	1 (0-3.9)	1 (0-2)	0.64

Source of funding

No details

Risks of bias

Selection bias: Unclear risk. No details on randomisation method/no power calculations provided/
Performance bias: Unclear/Unknown risk. Lack of blinding is not likely to affect any of the reported outcomes.
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

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Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Blijlevens et al (2013) Multi-centre European study

Study type, study period

Multicentre randomised controlled trial (December 2006-February 2009)

Aim

To evaluate the efficacy of palifermin in a chemotherapy only, high-dose Melphalan (HDM) transplant setting, to reduce oral mucositis and its sequelae

Number of patients

281

Patient characteristics

Inclusions:
Aged 18-70 years
Creatinine clearance (CC) ≥30ml/min or 140 mg/m^2 if CC <30 ml/min
ECOG PS≤2 (or 3 if the reason for status 3 was due to multiple myeloma)
≥2.0x10^6 CD34+ cells per kg collected
Corrected carbon monoxide diffusing capacity ≥50% of predicted
ANC≥1.5x10^9/l and platelets ≥100x10^9/l
Total bilirubin ≤2mg/dl
Aspartate amino transferase and/or alanine amino transferase ≤4.0x institutional upper limit of normal

	Placebo	Pre/Post HDM	Pre HDM
Female	42%	45%	46%
Caucasian	95%	96%	95%
Median Age (range)	58 years (41-68)	58 years (40-68)	55 years (32-69)
Myeloma Stage			
Stage I	15.8%	15.7%	20.2%
Stage II	26.3%	23.5%	23.9%
Stage III	56.1%	60%	56%
Missing	1.8%	0.9%	0
International prognostic index codes			
Group 1	59.6%	54.8%	51.4%
Group 2	28.1%	18.3%	24.8%
Group 3	8.8%	16.5%	17.4%
Missing	3.5%	10.4%	6.4%
ECOG performance status			
0	43.9%	46.1%	47.7%
1	45.6%	40.9%	47.7%
2	5.3%	8.7%	4.6%
3	1.8%	1.7%	0
Missing	3.5%	2.6%	0

Intervention

Palifermin pre and post HDM treatment

Palifermin pre (placebo post) HDM treatment

Comparison

Placebo

Length of follow-up

No details

Outcome measures and effect

Severity of oral mucositis
Incidence of severe oral mucositis
Mean duration of severe oral mucositis

Maximum severity of oral mucositis	**Placebo**	**Pre/Post HDM**	**Pre HDM**
Grade 0	25%	19%	28%
Grade 1	18%	10%	17%
Grade 2	21%	30%	28%
Grade 3	19%	20%	13%
Grade 4	18%	18%	11%
Placebo versus pre/post HDM: OR=0.7 [95% CI, 0.4-1.3] Placebo versus pre-HDM: OR=1.2 [95% CI, 0.6-2.4)			

Incidence of severe OM	37%	24%	38%	Pre/post HDM vs. Placebo: 4.2 (-13.5 to 21.9)	0.66
				Pre HDM vs. Placebo: -9.9 (-27.5 to 7.7)	0.81
Duration of severe OM (mean; SD)	2.4 (3.7)	2.7 (4.0)	1.9 (3.4)	Pre/post HDM vs. Placebo: 0.3 (-1.1 to 1.6)	0.66
				Pre HDM vs. Placebo: -0.6 (-1.9 to 0.8)	0.81
Incidence of ulcerative OM	58%	51%	69%		
Duration of ulcerative OM (mean; SD)	5.0 (6.0)	7.4 (6.8)	4.8 (6.1)		
AUC for patient reported MTS	25	40	30		

	Palifermin (60µg/kg/day)					
	Pre/post HDM (n=115)	**Pre HDM (n=109)**	**Placebo (n=57)**			**p**
Incidence of febrile neutropenia	34%	25%	26%	Pre/post HDM vs placebo	11.1 (-5.6 to 27.9)	0.16
				Pre HDM vs placebo	1.8 (-15 to 18.6)	0.81
Incidence of significant infections	51%	39%	26%	Pre/post HDM vs placebo	24.1 (7 to 41.2)	**0.003**
				Pre HDM vs placebo	11.9 (-5.4 to 29.2)	0.13
Incidence of anti-infective drug use	77%	73%	75%	Pre/post HDM vs placebo	1.4 (-13.9 to 16.7)	0.84
				Pre HDM vs placebo	-4.3 (-20.4 to 11.7)	0.55
Duration of anti-infective drug use	18 (SD: 15)	20 (SD:17)	21 (SD: 16)	Pre/post HDM vs placebo	-2.4 (-8.3 to 3.6)	0.3
				Pre HDM vs placebo	-0.8 (-6.8 to 5.2)	0.79
Incidence of opioid analgesic use	67%	64%	77%	Pre/post HDM vs placebo	-1.0 (-25.5 to 5.6)	0.18
				Pre HDM vs placebo	-14.5 (-30.6 to 1.6)	0.06
Duration of opioid analgesic use(mean days)	11 (SD: 14)	11 (SD: 14)	12 (SD: 13)	Pre/post HDM vs placebo	-0.7 (-5.6 to 4.2)	0.3
				Pre HDM vs placebo	-0.5 (-5.5 to 4.4)	0.3
Incidence of TPN	61%	49%	40%	Pre/post HDM vs placebo	20.6 (2.7 to 38.4)	**0.012**
				Pre HDM vs placebo	7.6 (-10.9-26)	0.360
Duration of TPN	8 (SD: 8.6)	5.8 (AD: 8.5)	4.2 (SD: 6.2)	Pre/post HDM vs placebo	3.9 (0.9 to 6.8)	**0.004**
				Pre HDM vs placebo	7.6 (-1.4 to 4.7)	0.3
Incidence of blood product use	77%	77%	67%	Pre/post HDM vs placebo	12.5 (-3.5 to 28.6)	0.07
				Pre HDM vs placebo	10 (-6.5 to 26.6)	0.16
Hospitalisation days	23 (SD: 6.6)	23 (SD: 7)	23 (SD: 5.3)	Pre/post HDM vs placebo	0.4 (-2.0 to 2.8)	0.6
				Pre HDM vs placebo	0.5 (-1.9 to 2.9)	0.48

	Placebo (n=57)	Palifermin (60µg/kg/day)			All subjects
		Pre/post HDM (n=109)	Pre HDM (n=111)	All (n=220)	
All adverse events (AE)	56 (98.2%)	109 (100%)	110 (99.1%)	219 (99.5%)	275 (99.3%)
Serious adverse events	3 (5.3%)	18 (16.5%)	13 (11.7%)	31 (14.1%)	34 (12.3%)
Severe adverse events	26 (45.6%)	65 (59.6)	56 (50.5%)	121 (55%)	147 (53.1%)
Treatment related AE	17 (29.8%)	78 (71.6%)	63 (56.8%)	141 (64.1%)	158 (57%)
Serious Adverse Events	0	2 (1.8%)	2 (1.8%)	4 (1.8%)	4 (1.4%)
Severe adverse events	0	15 (13.8%)	8 (7.2%)	23 (10.5%)	23 (8.3%)
AE leading to study withdrawal	1 (1.8 %)	1 (0.9%)	7 (6.3%)	8 (3.6%)	9 (3.2%)
AE leading to IP discontinuation	1 (1.8%)	8 (7.3%)	9 (8.1%)	17 (7.7%)	18 (6.5%)
Fatal adverse events	0	1 (0.9%)	0	1 (0.5%)	1 (0.4%)

Source of funding

Risks of bias

Selection bias: Low risk. Randomisation in a 1:2:2 ratio and performed using an interactive voice response system before planned admission and stratified by renal function and BMI.
Performance bias: Low Risk – trial was double blinded
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

1

2

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Vesole et al (2012) USA

Study type, study period

Randomised Trial (July 1998-January 2008)

Aim

To evaluate the impact of prophylactic antibiotics on the incidence of serious bacterial infections during the first 2 months of treatment

Number of patients

N=212

Patient characteristics

Patients with symptomatic and untreated multiple myeloma receiving myelosuppressive and/or immunosuppressive chemotherapy

No active infection/antibiotics during the 7 days prior to initiation of chemotherapy
Serum creatinine level ≤5mg/dl

Exclusions
Patients with documented hypersensitivity to quinolones or sulfa based agents

No significant differences between the three groups in relation to gender, race, type of induction chemotherapy, performance status or age.

Intervention

Daily quinolone 500mg every 12 hours or Ofloxacin 400mg every 12 hours (C, n=69)

Trimethoprim-sulfamethoxazole (160mg trimethoprim/800mg sulfamethoxazole every 12 hours) (T, n=76)

Comparison

Observation (O, n=67)

Length of follow-up

3 months

Outcome measures and effect

Outcomes
Severe bacterial infection (SBI) defined as being ≥grade 3 ECOG toxicity criteria and/or hospitalisation
Any infection
Severe infection during first month after prophylaxis

Infection incidence during study period					
Outcome	**Treatment Arm**	**N at risk**	**N**	**% [95% CI]**	**p**

Severe Bacterial infections during the first 2 months	C	64	8	12.5% [5.6-23.2]	0.218
	T	74	5	6.8% [2.2-15.1]	
	O	63	10	15.9% [7.9-27.3]	
Any infection during the first 2 months	C	64	13	20.3% [11.3-32.2]	0.954
	T	74	17	23% [14-34.2]	
	O	63	14	22.2% [12.7-34.5]	
Severe infection during the first month	C	64	2	3.1% [0-7.4]	0.799
	T	74	2	2.7% [0-6.4]	
	O	63	3	4.8% [0-10]	
Incidence of non-bacterial infection	C	N/R	N/R	N/R	1.00
	T	N/R	N/R	N/R	
	O	N/R	N/R	N/R	
Incidence of severe bacterial infection in month 3 with the absence of prophylaxis	C	3.1%	N/R	N/R	0.799
	T	2.7%	N/R	N/R	
	O	4.82%	N/R	N/R	
Initial response to therapy	C	N/R	N/R	N/R	0.858
	T	N/R	N/R	N/R	
	O	N/R	N/R	N/R	
Overall Survival	C	N/R	N/R	N/R	0.863
	T	N/R	N/R	N/R	
	O	N/R	N/R	N/R	

C, quinolone or ofloxacin
T, Trimethoprim-sulfamethoxazole
O, observation
N/R, not reported

Source of funding

Risks of bias

Selection bias: Unclear risk. Randomisation in a 1:1:1 ratio but no details on randomisation method
Performance bias: Unclear Risk – no details on blinding though unlikely to impact the outcomes
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

1

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Oken M et al; 1996 (USA)

Study type, study period

Randomised Trial

Aim

To determine whether the morbidity and mortality of early infection can be prevented by prophylactic administration of trimethoprim-sulfamethoxazole.

Number of patients

N=57

Patient characteristics

Confirmed multiple myeloma diagnosis
Bone marrow plasmacytosis with ≥10% abnormal plasma cells or multiple biopsy proven plasmacytomas

Exclusion
Active infection in the 7 days prior to treatment
Radiotherapy in the 10 days prior to treatment
Prior chemotherapy other than corticosteroids

Intervention

Trimethoprim-sulfamethoxazole (TMP-SMX) for 2 months

Comparison

No prophylaxis

Length of follow-up

3 months

Outcome measures and effect

Infection incidence
Infection Rate
Infection Type
Toxicity

	Control (n=26)	TMP-SMZ (n=28)	P
Patients with infection			
During 3 month period	12	5	0.04
Months 1-2	10	3	0.026
Month 3	5	2	0.243
Patients with bacterial infection			
During 3 month period	11	2	0.004
Months 1-2	9	1	0.004
Month 3	5	1	0.095
Number of Infections			
Months 1-2	11	3	0.026
Month 3	5	2	0.226
Number of bacterial infections			
Months 1-2	10	1	0.006
Month 3	5	1	0.093
Deaths due to infection			
During 3 month period	4	1	0.184

	Control (n=26)	TMP-SMZ (n=28)	P
Infections per patient-year	2.59	0.72	0.01
Months 1-2	2.59	0.64	0.024
Month 3	2.59	0.89	0.195
Bacterial infection per patient year	2.43	0.29	0.001
Months 1-2	2.36	0.21	0.006
Month 3	2.61	0.44	0.083
Infections per patients year (months 1-3)			
Patients with prior infection (n=11)	5.45	1.2	0.1
Patients without prior infection (n=43)	1.9	0.00	0.002

Toxicity
21% (n=6) of patients on TMP-SMZ developed skin rash resulting in discontinuation of prophylaxis.

Source of funding

No details

Risks of bias

Selection bias: Unclear risk. No details on randomisation method but patients were stratified according to age, stage and chemotherapy
Performance bias: Unclear Risk – no details on blinding though unlikely to be blinded as no placebo mentioned for the control group. A lack of blinding is unlikely to bias results.
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

1

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Lockhart et al; 2005 (USA)

Study type, study period

Randomised trial

Aim

To determine the efficacy of oral pilocarpine hydrochloride in the moderation of oral mucositis when administered during autologous blood stem cell transplant (ABSCT)

Number of patients

N=36

N=9 myeloma patients

Patient characteristics

Inclusion
Patients between age 18-65 years planned for ABSCT at a single institute

Exclusions

Allergy to pilocarpine
Salivary gland disease
Medications that interfere with the safety and efficacy of pilocarpine
Clinically significant asthma
Pregnancy
Acute iritis and/or narrow angle glaucoma
Any condition considered by investigators to contraindicate participation

No significant difference in baseline characteristics (age, weight, gender, ethnicity, primary diagnosis, treatment protocol, oral health)

Intervention

Placebo (n=16)

Comparison

Pilocarpine (n=20)

Length of follow-up

Patients were followed up until study exit though no details on when that was

Outcome measures and effect

Incidence, severity and duration of oral mucositis focusing on the gingival, oral and oropharyngeal mucosa.

Two subjects in each arm received total body irradiation (TBI)
Compliance was similar for both groups

Outcome measure	Pilocarpine	Placebo	P
Overall Mucositis (Incidence)	80% (16)		
Oral mucositis (duration)	5.2±3.6	4.9±4.3	NS
Gingival mucositis (duration)	0.81±1.2	1.7±2.1	NS
Oropharyngeal mucositis (duration)	3.6±3.6	2.9±3.2	NS
Nutrition problems (incidence)	50% (10)	56% (9)	NS
Nutrition problems (duration)	2.3±3.1	2.2±2.9	NS
Oral hygiene problems (incidence)	35% (7)	31% (5)	NS
Oral hygiene problems (duration)	1.4±2.0	1.0±2.3	NS
Eating Problems (highest grade)	1.8±1.1	2.2±1.1	NS
Eating problems (duration)	7.8±4.2	6.9±6.2	NS
Speaking problems (duration)	5.4±5.5	4.8±5.4	NS
Sleeping problems (duration)	1.04±5.4	7.1±6.7	NS
pain at rest (duration)	1.2±0.4	1.4±1.0	NS
Pain with swallowing (duration)	1.1±0.2	1.3±0.5	NS
Xerostomia (average, all days)	63±25.1	75.3±25.1	NS
Xerostomia (duration)	1.2±0.4	1.2±0.6	NS
Missed doses of study drug	4.5±4.6	5.3±6.3	NS
WBC nadir day	4.0±1.3	4.3±1.8	NS
WBC engraftment	7.4±4.7	6.4±1.9	NS
Systemic narcotic use (incidence)	35% (7)	25% (4)	NS
Systemic narcotic use (duration)	1.9±3.4	1.7±3.6	NS

There was a statistically significant increase (p=0.03) in sleeping problems in the pilocarpine group during the broad time periods (4-10 days)

Source of funding

Risks of bias

Selection bias: Low risk. Randomisation was by computer generated numbering scheme patients were stratified according to according to initial diagnosis.
Performance bias: Low Risk study was double bind
Attrition bias: Low risk.
Detection bias: Low risk

Additional comments

Investigators were unable to find a validated tool for assessment of mucositis and so developed data entry forms to capture relevant subjective and objective data including toxicity criteria (a modified version of the southwest oncology group toxicity scale).

1

2

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Orvain et al, 2015 (France)

Study type, study period

Non randomised comparison (prospective cohort (November 2008-August 2011) compared with a historical cohort (January 2006-November 2008))

Aim

To evaluate the impact of miconazole MBT in comparison to oral amphotericin B suspension in relation to oral mucositis-related complications in patients receiving HDT/ASCT for treatment of haematological malignancies.

Number of patients

N=104

N=51 myeloma patients

Patient characteristics

Baseline characteristics of the patients were similar in the two groups (age, sex, haematological disease, total CD34+ cells, neutropenia, leucopenia)

Intervention

Miconazole mucoadhesive buccal tablets (MBT) (50mg tablet placed on the upper gum once daily in the morning which stayed in the oral cavity until erosion or detachment)

Comparison

Oral amphotericin-B suspension (500mg, 3 times a day with one gargled dose and one swallowed dose)

Length of follow-up

No details

Outcome measures and effect

Opioid and non opioid analgesic use
Total parenteral nutrition
Antibiotic and systemic antifungal use
Infectious complications
Hospitalisation

	Oral amphotericin (n=44)	Miconazole (n=60)	p
Hospital stay (days)	16.4	15.3	0.09
Nefopam use (days)	5.7	5.4	0.37
Morphine use	70%	50%	0.04
Length of morphine use (days)	4.9	3.9	0.12
Parenteral nutrition use (days)	10	9	0.15
Analgesic drug use	18%	7%	0.09
Antibiotic use (days)	12.3	7.8	0.0001
Intravenous antifungal use (days)	3.6	1.4	0.02

	Lymphoma	Myeloma	p
Time to engraftment (days with neutrophil count <500/mm^3)	10.3	4.5	<0.0001
Units of platelets transfused	5.8	1.9	<0.001
Unit of packed red blood cells	3.7	1	<0.0001
Previous treatment	2.1 lines	1.4 lines	0.02
Morphine use (days)	6.8	1.8	0.001
Parenteral nutrition	11	7.7	0.008
Intravenous antibiotics	12.6	4.3	<0.0001
Intravenous antifungals	2.7	0.9	0.019

Source of funding

No details

Risks of bias

Selection bias: High risk. Not randomised, comparison with a historical cohort
Performance bias: Unclear Risk study was not blinded
Attrition bias: Low risk.
Detection bias: Unclear risk

Additional comments

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Cheuk et al; 2011 (various)

Study type, study period

Systematic review and meta-analysis (Cochrane Review)

Aim

To determine the effectiveness and safety of viral vaccines in patients with haematological malignancies

- Whether viral vaccines are effective in preventing viral infections in patients with haematological malignancies
- Whether viral vaccines are effective in preventing complications or mortality associated with viral infections, or reduction in severity of viral infections
- Whether a particular type of vaccine /dosing schedule is more effective
- Whether viral vaccines administered to patients with haematological malignancies are associated with adverse events

Number of patients

N=593 patients (8 trials included)

Patient characteristics

Included trials
N=8
N=2 evaluating heat-inactivated varicella zoster virus vaccine
N=5 evaluating influenza vaccines
N=1 evaluating inactivated polio vaccine

N=7 trials had a high risk of bias and n=1 trial had a moderate risk of bias

Intervention

All forms of viral vaccine including influenza, varicella, hepatitis A, hepatitis B, measles, mumps, rubella and poliomyelitis

Comparison

Placebo vaccine, no vaccine or alternative dosing regimens or schedules

Length of follow-up

Outcome measures and effect

Outcomes
Incidence of viral infection
Mortality due to viral infection
All cause mortality
Incidence of severe viral infection
Rate of hospitalisation due to viral infection
In vitro immune response to vaccine
Frequency of systemic and local adverse effects

Patients of all ages with haematological malignancies were included

Inactivated Poliovirus vaccine
There was one trial (Parkkali et al, 1997) comparing two different dosing schedules (early versus late) of IPV vaccine for patients aged 16 and above with haematological malignancies who had received a matched sibling stem cell transplant (SCT)

No data was reported on the incidence of poliomyelitis

	1st dose	2nd dose	3rd dose
Antibody Type 1	RR=0.45 [0.2-1.01]	RR=0.59 [0.34-1.05]	RR=0.71 [0.45-1.13]
Antibody Type 2	RR=0.34 [0.15-0.8]*	RR=0.59 [0.34-1.05]	RR=0.69 [0.41-1.16]
Antibody Type 3	RR=0.57 [0.34-0.96]*	RR=0.70 [0.48-1.01]	RR=0.81 [0.61-1.09]
Notes	RR=Risk Ratio *favours the late schedule		

Varicella zoster vaccine (VZV)
There were two trials comparing VZV vaccine versus no vaccine (Hata et al, 2002; Redman et al, 1997)

	Vaccine	**No Vaccine**	**Risk Ratio**	**p**
All cause mortality	17/67	19/72	0.96 [0.54-1.69]	0.89
4 fold rise in VZV antibody titre	3/62	3/61	0.96 [0.2-4.52]	0.96

Lymphocyte stimulation index	**Mean Difference**	**p**
Month 1 (mean)	0.00 [-0.79-0.79]	1.00
Month 3 (mean)	7.63 [6.6-8.66]	<0.00001
Month 4 (mean)	10.92 [2.13-19.71]	0.01
Month 5-6 (mean)	9.72 [-3.05-22.5]	0.14

Month 12 (mean)	29.45 [8.51-50.39]	0.006		

Frequency of systemic adverse events			**Risk Ratio**	**p**
All systemic adverse events	5/97	0/97	5.94 [0.73-48.55]	0.1
Headache	3/97	0/97	3.97 [0.45-34.93]	0.21
Arthralgia or myalgia	2/38	0/37	4.87 [0.24-98.18]	0.3
Frequency of local adverse events	20/97	0/97	20.94 [2.88-152.36]	0.003

Influenza Vaccines
There were 5 trials in total looking at different influenza vaccine comparisons:
Vaccine versus No Vaccine - Esposito et al, 2010 and Musto et al, 1997
2 doses versus single dose ~ Ljungman et al, 2005
Recombinant vaccine versus standard vaccine ~ Safdar et al, 2006
Comparison of vaccine schedules ~ Hseih et al, 2002

	Vaccine	**No Vaccine**	**Risk Ratio**	**p**
Mortality due to infection (pneumonia)*	0/25	2/25	0.2 [0..01-3.97]	0.29
Frequency of at least on lover respiratory infection	9/116	24/116	0.39 [0.19-0.78]	0.0082
Frequency of at least one infection other than influenza type illness*	27/91	33/91	0.82 [0.54-1.24]	0.35
Rate of hospitalisation	10/116	60/116	0.17 [0.09-0.31]	<0.00001
Frequency of at least one adverse effect	34/116	0/116	35 [4.9-249.8]	0.00039
Frequency of systemic adverse effects*				
Fever	7/91	0/91	15 [0.87-258.82]	0.062
Irritability	9/91	0/91	19 [1.12-321.67	0.041
Decreased appetite	6/91	0/91	13 [0.74-227.43]	0.079
Rhinitis	44/91	0/91	9 [0.49-164.78	0.14
Cough	7/91	0/91	15 [0.87-258.82]	0.062
Vomiting	2/91	0/91	5 [0.24-102.72]	0.3
Frequency of local adverse effects				
At least one adverse event	21/116	0/116	22 [3.05-158.51]	0.0022
Redness*	3/91	0/91	7 [0.37-133.62]	0.2
Swelling or induration*	3/91	0/91	7 [0.37-133.62]	0.2
Frequency of at least one upper respiratory infection	47/116	84/116	0.56 [0.44-0.72]	<0.00001
*Results from a single study				

	Mean Difference	**p**		
Number of upper respiratory tract infection*	-1.23 [-1.52 to -0.94]	<0.00001		
Number of lower respiratory tract infections*	-0.3 [-0.44 to -0.16]	0.000015		
Number of infections other than influenza like illness*	-0.1 [-0.35 to 0.15]	0.43		
Number of days with fever*	-1.7 (-2.25 to -1.15]	<0.00001		
Number of antibiotics course*	-1.85 [-2.3 to -1.4]	<0.00001		
Number of days lost from school*	-4.94 [-5.65 to -4.23]	<0.00001		
*Results from a single study				

	Two doses	**Single dose**	**Risk Ratio**	**p**
Four fold rise in antibody titre*				
Influenza A/H3	9/34	5/36	1.91 [0.71-5.12]	0.2
Influenza A/H1	6/34	8/36	0.79 [0.31-2.05]	0.63
Influenza B	9/34	8/36	1.19 [0.52-2.73]	0.68
Antibody titre above 1:40*				
Influenza A/H3	7/34	8/36	0.93 [0.38-2.28]	0.87
Influenza A/H1	9/34	9/36	1.06 [0.48-2.35]	0.89
Influenza B	5/34	6/36	0.88 [0.3-2.63]	0.82
*Results from a single study				

	Recombinant influenza vaccine 15µg	Standard influenza vaccine	Risk Ratio	p
Four fold rise in antibody titre haemoagglutination inhibiting*				
Influenza A/H3	3/9	2/6	1.00 [0.23-4.31]	1.0
Influenza A/H1	0/9	1/6	0.23 [0.01-4.93]	0.35
Influenza B	1/9	2/6	0.33 [0.04-2.91]	0.32
Four fold rise in influenza neutralising antibody titre*				
Influenza A/H3	4/9	1/6	2.67 [0.39-18.42]	0.32
Influenza A/H1	1/9	2/6	0.33 [0.04-2.91]	0.32
Influenza B	1/9	2/6	0.33 [0.04-2.91]	0.32
Four fold rise in influenza inhibiting or neutralising antibody titre*				
Influenza A/H3	4/9	2/6	1.33 [0.35-5.13]	0.68
Influenza A/H1	1/9	2/6	0.33 [0.04-2.91]	0.32
Influenza B	1/9	2/6	0.33 [0.04-2.91]	0.32
*Results from a single study				

	Recombinant influenza vaccine 45µg	Standard influenza vaccine	Risk Ratio	p
4 fold rise in influenza haemoagglutination inhibiting antibody titre*				
Influenza A/H3	1/6	2/6	0.5 [0.06-4.15]	0.52
Influenza A/H1	1/6	1/6	1.00 [0.08-12.56]	1.0
Influenza B	0/6	2/6	0.2 [0.01-3.46]	0.27
4 fold rise in influenza neutralising antibody titre*				
Influenza A/H3	6/6	1/6	4.33 [1.03-18.17]	0.045
Influenza A/H1	3/6	2/6	1.5 [0.38-6.0]	0.57
Influenza B	0/6	2/6	0.2 [0.01-3.46]	0.27
4 fold rise in influenza haemoagglutination inhibiting or neutralising antibody titre*				
Influenza A/H3	3/6	2/6	1.5 [0.38-6]	0.57
Influenza A/H1	3/6	2/6	1.5 [0.38-6.00]	0.57
Influenza B	0/6	2/6	0.2 [0.01-3.46]	0.27
*Results from a single study				

	Recombinant influenza vaccine 135µg	Standard influenza vaccine	Risk Ratio	p
4 fold rise in influenza haemoagglutination inhibiting antibody titre*				
Influenza A/H3	3/6	2/6	1.5 [0.38-6.0]	0.57
Influenza A/H1	1/6	1/6	1.00 [0.08-12.56]	1.0
Influenza B	2/6	2/6	1.00 [0.2-4.95]	1.0
4 fold rise in influenza neutralising antibody titre*				
Influenza A/H3	3/6	1/6	3.00 [0.42-21.3]	0.27
Influenza A/H1	2/6	2/6	1.00 [0.2-4.95]	1.0
Influenza B	2/6	2/6	1.00 [0.2-4.95]	1.0
4 fold rise in influenza haemoagglutination inhibiting or neutralising antibody titre*				
Influenza A/H3	3/6	2/6	1.5 [0.38-6.00]	0.57
influenza A/H1	2/6	2/6	1.00 [0.2-4.95]	1.0
Influenza B	2/6	2/6	1.00 [0.2-4.95]	1.0
*Results from a single study				

	First Dose with reinduction	Second dose with re-induction	Risk Ratio	p
Four fold rise in neutralising antibody titre after 1st vaccine dose*				
Influenza A/H3	7/14	8/11	0.69 [0.36-1.30]	0.25
Influenza A/H1	4/14	0/11	7.20 [0.43-120.96]	0.17
Influenza B	6/14	5/11	0.94 [0.39-2.29]	0.9
Four fold rise in neutralising antibody titre after second vaccine dose*				
Influenza A/H3	8/14	7/11	0.9 [0.48-1.7]	0.74
Influenza A/H1	5/14	1/11	3.93 [0.53-28.93]	0.18
Influenza B	6/14	5/11	0.94 [0.39-2.29]	0.9
Seroconversion after 1st vaccine dose (increase of antibody titre from <40-≥40)				
Influenza A/H3				
Influenza A/H1				
Influenza B				
Seroconversion after 2st vaccine dose (increase of antibody titre from <40-≥40)				
Influenza A/H3	6/7	5/6	1.03 [0.64-1.64]	0.91

Influenza A/H1	2/7	0/3	2.5 [0.15-40.67]	0.52
Influenza B	5/9	3/5	0.93 [0.37-2.33]	0.87
*Results from a single study				

Source of funding

No details

Risks of bias

Seven of the eight included trials had high risk of bias

Selection bias: Unclear Risk - None of the trials reported on random sequence generation or allocation concealment
Performance bias: Unclear Risk Four studies blinded treating physicians but only one trial blinded patients as well. Outcome assessor blinding was unknown in five trials and not used in the remaining three trials
Attrition bias: Unclear risk. Most of the individual trials reported their drop-out rates and reasons for drop out. The amount of missing data was variable for individual outcomes and in some studies no drop outs were reported and there were insufficient data to assess the amount of missing data.
Detection bias: Unclear risk None of the included trials reported the use of intention to treat analysis; baseline characteristics were not completely comparable in 4 trials and in 3 trials baseline comparisons could not be made due to insufficient data.

Additional comments

Included Studies

Trials on Varicella zoster vaccine

- Hata et al (2002) use of inactivated varicella vaccine in recipients of hematopoietic cell transplants *New England Journal of Medicine* 347;26-34
- Redman et al (1997) Early reconstitution of immunity and decreased severity of herpes zoster in bone marrow transplant recipients immunised with inactivated varicella vaccine *Journal of Infectious Diseases* 176;3:578-585

Trials on influenza vaccine

- Esposito et al (2010) Impact of influenza like illness and effectiveness of influenza vaccination in oncohaematological children who have completed cancer therapy *Vaccine* 28;1558-65
- Musto et al (1997) Vaccination against influenza in multiple myeloma *British Journal of Haematology* 97;2:505-506
- Ljungman et al (2005) Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study *British Journal of Haematology* 130;96-98
- Safdar et al (2006) Dose related safety and immunogenicity of Baculovirus expressed trivalent influenza vaccine. A double blind, controlled trial in adult patients with non-Hodgkin B cell lymphoma *Journal of Infectious Disease* 194;1394-1397
- Hseih et al (2002)

Trial on inactivated poliovirus vaccine

- Parkkali et al (1997) Randomised comparison of early and late vaccination with inactivated poliovirus vaccine after allogenic BMT *Bone Marrow Transplantation* 20:663-668

1

Guideline

Myeloma – topic N (prophylaxis for infection)

Study, country

Raanani et al (2009)

Also Cochrane review Raanani et al (2008) but data taken from the more recent, 2009 publication.

Study type, study period

Systematic review and Meta-analysis (January 1996-December 2007)

Aim

To evaluate the role of immunoglobulins (IVIG) prophylaxis in patients undergoing hematopoietic stem cell transplantation (HSCT) in terms of survival and infection

Number of patients

N=30 trials included reporting on patients receiving IVIG after bone marrow transplant (26 trials) or peripheral blood stem cell transplant (2 trials) or both (2 trials)

N=4223 patients

Patient characteristics

Prophylaxis was initiated during conditioning in 26 trials and immediately after transplant in 4 trials.
Prophylaxis was administered weekly in 16 trials, bi-weekly in 8 trials or by using a different schedule in 6 trials
In most trials, prophylaxis was given for 3 months with a maximum period of administration of 1 year.

Intervention

Intravenous of intramuscular polyvalent immunoglobulins (polyvalent IVIG) or hyperimmune cytomegalovirus-IVIG (CMV-IVIG)

Comparison

Placebo
No treatment
Another immunoglobulin preparation
A different administration schedule

A different dose

Length of follow-up

Outcome measures and effect

All Cause Mortality
Clinically documented infections
Microbiologically documented bacterial infections
CMV infection
Interstitial pneumonitis
Acute graft versus host disease (GVHD)
Veno-occlusive disease (VOD)
Adverse events

All cause mortality	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (8 trials) Placebo or no intervention (8 trials)	300/756 273/662	0.99 [0.88-1.12]	0.92
Hyperimmune CMV-IVIG (4 trials) Placebo (4 trials)	45/143 54/145	0.086 [0.63-1.16]	0.31
Polyvalent IVIG & Hyperimmune CMV-IVIG (12 trials) Placebo or no intervention (12 trials)	345/899 327/807	0.97 [0.87-1.09]	0.61
IVIG + antifungal prophylaxis (2 trials) Placebo or no treatment with antifungal prophylaxis (2 trials)	60/177 27/74	1.07 [0.74-1.53]	0.73
IVIG without anti fungal prophylaxis (3 trials) Placebo/no treatment without antifungal prophylaxis (3 trials)	137/251 159/256	0.88 [0.76-1.02]	0.078
Polyvalent IVIG (3 trials) CMV-IVIG (3 trials)	31/105 22/107	1.46 [0.92-2.32]	0.11

Infection related death	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (3 trials) Placebo or no intervention (3 trials)	8/137 12/138	0.64 [0.28-1.49]	0.3
Hyperimmune CMV-IVIG (3 trials) Placebo (3 trials)	12/117 18/117	0.67 [0.34-1.32]	0.24
Polyvalent IVIG & Hyperimmune CMV-IVIG (6 trials) Placebo or no intervention (6 trials)	12/117 18/117	0.66 [0.39-1.12]	0.12

Clinically documented infections	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (5 trials) Placebo or no intervention (5 trials)	267/388 181/300	1.00 [0.9-1.10]	0.96

CMV infections	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (6 trials) Placebo or no intervention (6 trials)	115/543 96/443	0.84 [0.66-1.07]	0.15
Polyvalent IVIG (3 trials) CMV-IVIG (3 trials)	54/105 38/107	1.42 [1.07-1.89]	0.014

Interstitial pneumonitis	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (7 trials) Placebo or no intervention (7 trials)	54/543 72/447	0.64 [0.45-0.89]	0.008
Polyvalent IVIG (2 trials) CMV-IVIG (2 trials)	11/82 13/81	0.83 [0.4-1.75]	0.63

VOD	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (4 trials) Placebo or no intervention (4 trials)	28/268 4/179	2.73 [1.11-6.71]	0.03

Adverse Events	**No. of events**	**Risk ratio**	**p**
Polyvalent IVIG (5 trials) Placebo or no intervention (5 trials)	49/415 2/313	8.12 [3.15-20.97]	0.000015

Source of funding
No details
Risks of bias
Additional comments

1

Guideline
Myeloma – topic N (prophylaxis for infection)
Study, country
Raanani et al (2009) Immunoglobulin prophylaxis in chronic lymphocytic leukaemia and multiple myeloma: systematic review and meta-analysis *Leukaemia and Lymphoma* 50;5:764-772
Study type, study period
Systematic Review and Meta-analysis (January 1996-December 2008)
Aim
To evaluate whether prophylactic administration of IVIG reduces mortality and major infections as well as other patient related outcomes including the rate of clinically and microbiologically documented bacterial infections and adverse events in patients with lymphoproliferative disorders and plasma cell dyscrasias.
Number of patients
Nine trials of relevance were identified (8 trials reported on patients with either chronic lymphocytic leukaemia (CLL) or multiple myeloma (MM) and one trial reported on both MM and low grade lymphoma Seven trials compared polyvalent IVIG with control and two trials compared different doses Five trials had useable data for meta-analysis
Patient characteristics
• N=116 patients with multiple myeloma • Stage of myeloma ranged from stage I-stage III (salmon-durie) • 5 trials included patients with multiple myeloma though only 3 trials included myeloma patients exclusively • 1 trial which included myeloma patients reported sufficient data for inclusion in meta-analysis (Chapel et al, 1994) for any of the outcomes of interest
Intervention
IVIG
Comparison
Placebo/No treatment A different dose
Length of follow-up
All cause mortality was assessed at 1 year in the two trials which reported this outcome
Outcome measures and effect
All Cause Mortality Major Infections Clinically and microbiologically documented bacterial infections Adverse Events *Intravenous immunoglobulins compared with placebo/no treatment*

Outcome	Polyvalent IVIG	Placebo/No treatment	Risk Ratio	p
All cause mortality at 1 year (2 trials)	11/82	8/81	1.36 [0.58-3.19]	0.47
Major infections (3 trials)	17/106	34/99	0.45 [0.27-0.75]	0.002
Clinically documented infection (3 trials)	45/106	88/99	0.49 [0.39-0.61]	<0.00001

Different doses of intravenous immunoglobulin Two trials compared different doses of IVIG of which one included myeloma patients (n=10). The trial which included myeloma patients did not report all cause mortality or adverse events separately for the two arms. The second trial reported 2 deaths and 6 clinically documented infections in the 500mg/kg arm (total n=16) and 2 deaths and 11 clinically documented infections in the 250mg/kg arm (total n=18)
Source of funding
No details
Risks of bias
Selection bias: Low Risk ~ adequate allocation concealment and generation Performance bias: Low Risk Trials included in the meta-analysis were double blinded Attrition bias: Unclear risk. Not reported Detection bias: Unclear risk Not all of the trials included sufficient data for inclusion in a meta-analysis /Outcomes were reported heterogeneously/Reporting was a mix of intent to treat and per protocol.
Additional comments

Managing peripheral neuropathy

Review Question

What is the most effective way to manage neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain?

Question in PICO Format

Population	Intervention	Comparator	Outcomes
Patients with myeloma who have neuropathy resulting from myeloma treatment	• Graded dose reduction • Anti-myeloma drug withdrawal • Use of nutritional supplements, including vitamins • Complementary therapies (e.g. reflexology, acupuncture) • TENS (trans-cutaneous nerve stimulation) • active monitoring	• each other • standard care / best supportive care	• Improvement or resolution of symptoms • Quantitative sensory testing • Overall survival • HRQOL • Physical and social functioning • Adverse events • Reduction or early discontinuation of myeloma treatment

Evidence Statements

Myeloma treatment modifications

In one cohort study (Richardson et al, 2009), 72/91 patients had chemotherapy dose modification per guidelines and 49/72 (68%) experienced improvement or resolution of peripheral neuropathy in a median of 110 days (range: 4-376) [Very low quality evidence].

41 patients had dose modifications but did not discontinue bortezomib; 71% (n=29) had resolution of peripheral neuropathy in a median of 78 days (range 9-376) and in the patients who discontinued treatment, 65% (n=20) experienced improvement (n=8) or resolution (n=12) in a median of 122 days (range 4-296) [Very low quality evidence].

From one cohort study (Richardson et al, 2009), the occurrence of peripheral neuropathy did not adversely affect response rate, median time to progression or median overall survival and no effect of dose reductions or modification was observed for response rate, median time to progression or median overall survival [Very low quality evidence].

From one study which evaluated the impact of dose-modification on treatment compliance (Cho et al, 2014) patients who received dose modifications according to guidelines were more likely to complete bortezomib treatment (OR=1.4, 95% CI, 0.31-6.32, p=0.66) though the difference was not statistically significant [Very low quality evidence].

Acupuncture/Electroacupuncture

From two studies (Boa et al, 2014; Garcia et al, 2014) no significant adverse events (no excessive bruising, local persistent pain or evidence of excessive bleeding at point of needle placement) associated with acupuncture treatment were reported in a total of 46 patients [Very low quality evidence].

From two studies (Boa et al, 2014; Garcia et al, 2014), mean scores, as assessed using FACT/GOG-NTx were significantly improved from baseline indicating a benefit of acupuncture [Very low quality evidence]

Nutritional supplements

One prospective case series study (n=30) evaluated the therapeutic potential of palmitoylethanolamide (PEA) on pain and nerve function (Truni et al, 2011) and reported a reduction in mean pain scores following 2 months of treatment (4.5±2.4 versus 3.4±1.0, p<0.002) [Very Low quality evidence].

Other Interventions

Mack et al (2010) conducted a single arm, cohort study including 20 patients of whom 16 were myeloma patients evaluating Viv-Arte training program including whole body vibration with Galileo training device (SKMT) for chemotherapy induced peripheral neuropathy and found that treatment was well tolerated in all patients [Very Low].

A large difference was observed with regard to locomotoric and sensoric multi dimensional tests pre and post treatment with pre-treatment paraesthesiae of the feet measured on a scale of 1-10 showing the greatest change from pre-treatment to post treatment (median 8 (range: 1-10) versus median 2 (range: 0-7))

Study Quality

The evidence base consisted of one non-randomised, comparative study (Cho et al, 2014) and five single arm, non-comparative studies all of very low quality (Bao et al, 2014; Garcia et al, 2014; Mack et al, 2010; Richardson et al, 2009; Truni et al, 2011) as assessed by GRADE and NICE checklists. Evidence was not available for all interventions or outcomes of interest, with no evidence found to report on use of nutritional supplements, active monitoring or TENS. None of the inlcuded studies reported overall survival as an outcome, primarily because follow-up in the studies was restricted to only a short period of time following treatment. In reporting and assessing the effect of interventions on neuropathy, all studies relied on self reporting of outcomes by included patients through the use of standard questionnaires, leaving them at high risk of bias.

All inlcuded studies had very small sample sizes, while one study included participents other than those with myeloma . Given these considerations therefore, the evidence presented should be considered with caution.

	Appropriate length of follow-up	Precise definition of an outcome	Valid method of measuring outcomes	Investigators blind to participants exposure to intervention?	Investigators blind to potential confounders and prognostic factors?	Quality
Bao et al (2014)	Unclear	Yes	Yes	No	No	Very Low
Cho et al (2014)	Unclear	Yes	Yes	No	No	Very Low
Garcia et al (2014)	Unclear	Yes	Yes	No	No	Very Low
Mack et al (2010)	Unclear	Yes	Yes	No	No	Very Low
Richardson et al (2009)	No	Yes	Yes	No	No	Very Low
Truni et al (2011)	Unclear	Yes	Yes	No	No	Very Low

Table 9.10 GRADE profile: What is the most effective way to manage neuropathy in patients with myeloma (graded dose reduction/anti-myeloma drug withdrawal/use of nutritional supplements/complementary therapies/TENS/active monitoring versus each other/standard care)?

Quality assessment							Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
Resolution or improvement of symptoms							
6	observational studies	very serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none[3]	VERY LOW
Adverse Events							
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Reduction/discontinuation of myeloma treatment							
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none[3]	VERY LOW
Overall Survival							
1	observational studies	very serious[1,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Physical and Social Functioning							
5	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW

[1] All studies were single arm, no comparative studies with small sample sizes

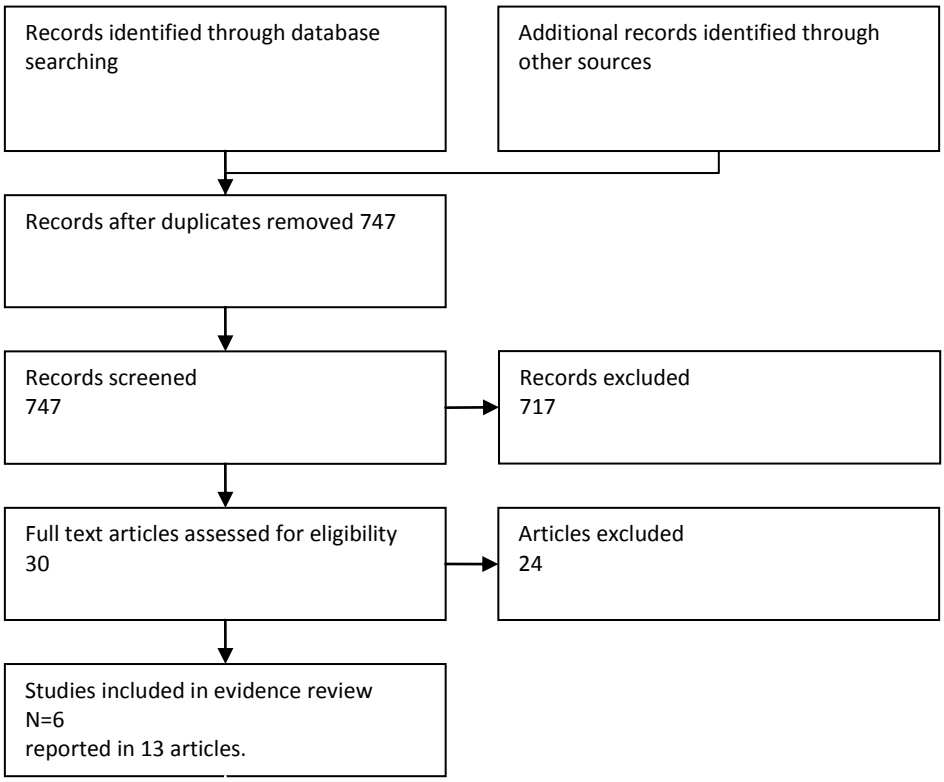
[2] One study included non-myeloma patients however it was 4/20 patients who were not myeloma patients.

[3] Dose-response is an outcome that is relevant to this topic however the sample sizes in the individual studies were too small to accurately assess the size of the effect.

[4] Follow-up time does not appear to be long enough to make accurate assessments of overall survival

Screening Results

Figure 9.2: Screening results



1 **Table 9.11: Characteristics of included studies**

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
Bao et al (2014)	Single Arm Prospective Study	To assess the safety, feasibility and efficacy of acupuncture in reducing Bortezomib induced peripheral neuropathy (BINP)	N=27	10 Acupuncture treatment sessions: twice weekly for 2 weeks, weekly for 4 weeks and then biweekly for 4 weeks.	N/A	Safety Assessment (excessive bruising, local persistent pain, evidence of bleeding beyond approx on drop of blood at needle placement point) Peripheral Neuropathy Assessments both objective and self reported. Biomarker Collection and Testing Nerve Conduction Studies
Cho et al (2014)	Retrospective cohort study	To assess the patterns of bortezomib induced peripheral neuropathy (BiPN) and evaluate the effectiveness of dose modification on symptom management and treatment compliance in myeloma patients	N=55 N=32 in the intervention group	Dose modification or reduction Duration Adjustment Dose reduction and duration adjustment	No treatment modification /reductions	Changes in neuropathy symptoms Treatment continuation/completion
Garcia et al (2014)	Single arm prospective study	To evaluate the feasibility, safety and initial efficacy of	N=27 patients with grade ≥2 neuropathy N=19 analysed for primary	20 acupuncture treatments over 9 weeks	N/A	Adverse Events Efficacy

		electroacupuncture for thalidomide/bortezomib induced peripheral neuropathy	outcomes			
Mack et al (2010)	Single Arm Pilot Study (Abstract)	The evaluate Viv-Arte training program including whole body vibration with Galileo training device (SKMT) in patients with chemotherapy induced peripheral neuropathy	N=20 (n=16 myeloma)	Viv-Arte training program including whole body vibration with Galileo training device (SKMT) SKMT was composed of 4 parts: • Manual therapy including passive mobilisation, massage and active 3-D complex movements • Whole body vibration training • Gymnastics • Training of specific individualised tasks	N/A	Efficacy
Richardson et al (2009)	Retrospective analysis of a single arm of a Randomised Trial	To assess the impact of a dose-modification guideline on the incidence and reversibility of bortezomib associated	N=331 patients with relapsed multiple myeloma randomised to bortezomib and had received at least one dose of bortezomib.	Protocol specified dose modification guideline	N/A This analysis only analysed a a single arm of an earlier trial	Incidence and severity of peripheral neuropathy Reversibility of peripheral neuropathy (impact of dose modification guideline) Effect of dose modification for

		peripheral neuropathy				peripheral neuropathy on outcome
Truni et al (2011)	Prospective Case Series Study Single centre (Italy)	To investigate the therapeutic potential of prolonged treatment with Palmitoylethanolamide (PEA) on pain and nerve function	N=30 consecutive patients with multiple myeloma and painful neuropathy (score of at least 4 on Bouhassira's DN4 screening tool for neuropathic pain). 10 patients excluded due to insufficient DN4 score or because other sources of neuropathy could not be ruled out.	Palmitoylethanolamide (PEA)	N/A	Efficacy

References

Included studies

1. Bao, T., Goloubeva, O., Pelser, C., Porter, N., Primrose, J., Hester, L. et al. (2014). A Pilot Study of Acupuncture in Treating Bortezomib-Induced Peripheral Neuropathy in Patients With Multiple Myeloma. Integrative cancer therapies, 2014/05/29.
2. Cho, J., Kang, D., Lee, J. Y., Kim, K., & Kim, S. J. (2014). Impact of dose modification on intravenous Bortezomib-induced peripheral neuropathy in multiple myeloma patients. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2014/04/29.
3. Garcia, M. K., Cohen, L., Guo, Y., Zhou, Y., You, B., Chiang, J. et al. (2014). Electroacupuncture for thalidomide/bortezomib-induced peripheral neuropathy in multiple myeloma: a feasibility study. Journal of hematology & oncology, 7, 41.
4. Mack, S., Kirchner, E., Stocker, F., Bauder Misbach, H., Eisenschink, A. M., Breitbart, A. et al. (2010). The Viv-Arte training program supplemented by whole-body vibration training in the treatment of chemotherapy-induced sensorimotor polyneuropathy. Onkologie, 33 (6), 75.
5. Richardson, P. G., Sonneveld, P., Schuster, M. W., Stadtmauer, E. A., Facon, T., Harousseau, J. L. et al. (2009). Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. British Journal of Haematology, 144, 895-903.
6. Truini, A., Biasiotta, A., Di Stefano, G., La Cesa, S., Leone, C., Cartoni, C. et al. (2011). Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. CNS & Neurological Disorders Drug Targets, 10, 916-920.

Excluded studies

1. Argyriou, A. A., Cavaletti, G., Bruna, J., Kyritsis, A. P., & Kalofonos, H. P. (2014). Bortezomib-induced peripheral neurotoxicity: an update. Archives of Toxicology, 88, 1669-1679.

   Reason: expert review

2. Bao, T., et al (2012) A pilot study of acupuncture in treating bortezomib-induced peripheral neuropathy (BIPN) in multiple myeloma (MM) patients. *Blood* 120;21

   Reason: Abstract
3. Brioli, A., Zannetti, B. A., Zamagni, E., Tacchetti, P., Pantani, L., Mancuso, K. et al. (2014). Peripheral neuropathy induced by subcutaneous bortezomib-based induction therapy for newly diagnosed multiple myeloma. Haematologica, 99.

   Reason: not treatment for P.N.

4. Cachia, E., et al (2010) An exploratory study of the late effects of pain, peripheral neuropathy and psychosocial issues in intensively treated advanced multiple myeloma patients. *Supportive Care in Cancer* 18;S191.

   Reason: Not relevant to PICO
5. Cai, Z., et al (2013) Acupuncture combined with methylcobalamin for chemotherapy-induced peripheral neuropathy of patients with myeloma. *Clinical Lymphoma, Myeloma and Leukemia* 13;S226.

   Reason: No data
6. Callander, N. (2014). Acetyl-L-carnitine (ALCAR) for the prevention of chemotherapy-induced peripheral neuropathy in patients with relapsed or refractory multiple myeloma treated with bortezomib, doxorubicin and low-dose dexamethasone: a study from the Wisconsin Oncology Network. Cancer Chemotherapy & Pharmacology, 74, 875-882.

   Reason: prevention of P.N.

7. Chaudhry, V., et al (2008). Characteristics of bortezomib- and thalidomide-induced peripheral neuropathy: Research report. *Journal of the Peripheral Nervous System* 13;275-282.

Reason: No neuropathy data

8. Clarke, H. and Gillibrand, R. (2010) A randomised controlled trial of an educational booklet for multiple myeloma patients with peripheral neuropathy. Haematologica.Conference: 15th Congress of the European Hematology Association (var.pagings) 95;588-589.

Reason: No data

9. Du, H. (2014). Research progress of bortezomib-induced peripheral neuropathy. Cancer Research and Clinic, 26, 638-640.

Reason: Chinese language

10. Faiman, B., et al (2013) Placebo controlled study to estimate the effect size of glutamine to prevent peripheral neuropathy in myeloma. *Clinical Lymphoma, Myeloma and Leukemia* 13;S200-S201.

Reason: Abstract

11. Franconi, G., et al (2013) A systematic review of experimental and clinical acupuncture in chemotherapy-induced peripheral neuropathy. *Evidence-based Complementary and Alternative Medicine*

Reason: Population not relevant to PICO

12. Genuardi, M., et al (2009) Peripheral neuropathy in bortezomib, melphalan, prednisone and thalidomide (VMPT) versus bortezomib, melphalan and prednisone (VMP): Impact of low-dose thalidomide and weekly infusion of bortezomib. *Haematologica* 94;84.

Reason: Comparison not relevant to PICO

13. Giometto, B et al (2012) Treatment for paraneoplastic neuropathies. Cochrane Database of Systematic Reviews . 2012. John Wiley & Sons, Ltd.

Reason: Population not relevant to PICO

14. Hadden R. et al, (2006) European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *European Journal of Neurology* 13;809-818.

Reason: Outcomes not relevant to PICO

15. Jung, Joo Young, et al (2014) The positive effects of one-hour intravenous administration of bortezomib on peripheral neuropathy in multiple myeloma patients. *BioMed Research International*

Reason: Not relevant to PICO

16. Koeppen, S. (2015). Peripheral neurotoxicity. Preventive dosage modification. Onkologe, 21, 311-+.

Reason: expert review

17. Koh, Y. (2014). Bortezomib-associated peripheral neuropathy requiring medical treatment is decreased by administering the medication by subcutaneous injection in Korean multiple myeloma patients. Cancer Chemotherapy & Pharmacology, 74, 653-657.

Reason: does not compare treatment for P.N.

18. Minarik, J. (2015). Subcutaneous bortezomib in multiple myeloma patients induces similar therapeutic response rates as intravenous application but it does not reduce the incidence of peripheral neuropathy. PLoS ONE [Electronic Resource], 10, e0123866.

Reason: does not compare treatment for P.N.

19. Offidani, M et al (2004) Common and rare side-effects of low-dose thalidomide in multiple myeloma: focus on the dose-minimizing peripheral neuropathy. *European Journal of Haematology* 72;403-409.

Reason: Not relevant to PICO

20. Reece, D. Et al (2006) Hematology Disease Site Groupof Cancer Care Ontarios Program, and Evidence-based, Care. Bortezomib in multiple myeloma and lymphoma: a systematic review and clinical practice guideline. *Current oncology* 13;160-172

Reason: Not relevant to PICO

21. Richardson, Paul G., et al (2006) Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *Journal of Clinical Oncology* 24;3113-3120.

Reason: No relevant outcome data

22. Stork, A. C. J., Lunn, M. P. T., Nobile-Orazio, E., & Notermans, N. C. (2015). Treatment for IgG and IgA paraproteinaemic neuropathy. Cochrane Database of Systematic Reviews.

Reason: MGUS only

23. Thomas, S. K., Mendoza, T. R., Dougherty, P. M., Williams, L. A., Wang, X. S., Prasad, S. et al. (2014). A phase 2 trial of minocycline versus placebo to prevent neuropathy in patients (pts) with multiple myeloma (MM). Journal of Clinical Oncology, 32.

Reason: abstract, prevention of P.N.

24. Tacchetti, P. (2014). Bortezomib- and thalidomide-induced peripheral neuropathy in multiple myeloma: clinical and molecular analyses of a phase 3 study. American Journal of Hematology, 89, 1085-1091.

Reason: does not compare treatment for P.N.

1 **Evidence Tables**

2

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
Bao et al (2014)	Single Arm Prospective Study Single Institute (University Hospital) USA Patients recruited between May 2011 and February 2012	To assess the safety, feasibility and efficacy of acupuncture in reducing Bortezomib induced peripheral neuropathy (BINP)	N=27 <u>*Inclusions*</u> Patients with multiple myeloma who have been treated with bortezomib in the past with persistent BIPN (grade ≥2) <u>*Exclusions*</u> Patients who had undergone acupuncture treatment in the month prior to study inclusion 1 patient withdrew consent after 3 ear needles were placed due to fear of pain. 1 patient discontinued the study after 1 acupunture treatment due to transportation issues. 25 patients completed 4 acupuncture sessions. 20 patients completed all 10 sessions 22 patients maintained	10 Acupuncture treatment sessions: twice weekly for 2 weeks, weekly for 4 weeks and then biweekly for 4 weeks. Patients continued with prescribed peripheral neuropathy medications and were encouraged not to change dose/type of treatment during the study.	N/A	Assessment 4 weeks after treatment completion	Safety Assessment (excessive bruising, local persistent pain, evidence of bleeding beyond approx on drop of blood at needle placement point) Peripheral Neuropathy Assessments both objective and self reported. Biomarker Collection and Testing Nerve Conduction Studies All patients had persistent peripheral neuropathy after discontinuation of Bortezomib for a median of 19 months (range 1-83 months) No significant adverse events were associated with acupuncture treatment. No excessive bruising, local persistent pain or evidence of excessive bleeding at point of needle placement was reported. Mean FACT/GOG-Ntx scores

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
			the same dose of pain medications throughout the study. 3 patients increased pain medication 2 patients decreased pain medication				decreased from 20.1 (SD=6.5) at baseline to 13.2 (SD=8.2) at week 10 (p<0.0001) At week 14 FACT/GOG-Ntx scores remained low (mean 13.3 (SD=13.3) (p<0.001). Mean NPS scores decreased from 41 (SD=25) to 29 (SD=21) following first acupuncture treatment and to 16 (SD=18) after 10 weeks of treatment (p<0.0001) A significant reduction in mean NPS score was observed at week 14 (mean score=18, SD=17; p<0.0001). Among 19 patients enrolled 6 or more months after bortezomib discontinuation, FACT/GOG-Ntx scores were significantly reduced from 19.9 (SD=6.6) at baseline to 14.3 (SD=8.9) at week 10 (p=0.03) and remained low at week 14 (mean=13.7, SD=8.9, p=0.001). NPS scores were significantly reduced from 40 (SD=26) at baseline to 20 (SD=20) at week 10 (p=0.003) and remained low at week 14 (mean=20, SD=19, p=0.001).

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							In the 25 patients who completing at least 4 acupuncture treatments, 14 (56%) reported improved daily functions (e.g. walking and coordination); 10 (40%) reported a greater than 50% decrease in average NPS and 7 (28%) reported a greater than 50% reduction in FACT/GOG-Ntx scores. Improvements in the FACT/GOG-NTx scores during the study were reported in walking, hand function (buttoning buttons, trouble feeling objects) and ear functions (ears ringing or buzzing, trouble hearing). Overall function (joint pain/muscle cramps/weakness) did not improve. Improvements of multiple components of neuropathic pain were reported during the study and patients also reported reductions in unpleasant hot/cold sensations. 15 patients had nerve conduction studies before and after acupuncture treatments of whom 5 (33%) showed a greater than 10% increase in motor nerve

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							amplitude, 8 (53%) showed no significant difference and 2 (13%) showed a greater than 10% decrease in motor nerve amplitude. At baseline, 87% of patients had severe sensory nerve deficits with no measureable sural nerve sensory responses. 13% of patients (n=2) had a greater 10% increase in sensory nerve amplitude, 80% (n=12) showed no significant changes and 7% (n=1) showed a greater than 10% decrease in sensory nerve amplitude. No significant correlation was observed between symptoms/functional improvements and results of nerve conduction studies. No significant changes were observed in any of the 12 cytokines at any of the time points investigated. No association was found between the severity of BIPN measured by NPS, FACT/GOG-Ntx or BIPN grade with serum MIP-1α level. 69% (18/26) patients had at least

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							a 30% reduction in NPS scores from baseline to the end of acupuncture treatments. Factors including race, age, body mass index, diabetes status, grade of BIPN, duration of BIPN or the presence of painful PN were not predictors of response to acupuncture treatment. NPS score improvement after the first acupuncture treatment was positively associated with continued improvement of the NPS score at week 10 (r=0.82, p<0.0001).
Cho et al (2014)	Retrospective cohort study	To assess the patterns of bortezomib induced peripheral neuropathy (BiPN) and evaluate the effectiveness of dose modification on symptom management and treatment compliance in myeloma patients	N=55 N=32 in the intervention group	Dose modification or reduction Duration Adjustment Dose reduction and duration adjustment	No treatment modification /reductions	No details	Changes in neuropathy symptoms Treatment continuation/completion A total of 18 patients discontinued bortezomib voluntarily or due to disease progression or relapse and were excluded from the analysis. 16/37 patients discontinued chemotherapy due to peripheral neuropathy despite disease responding to Bortezomib.

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							The intervention group had 14 (SD=8.6) bortezomib administrations versus 8.9 (SD=6.8) administrations in the non-intervention group. Patients with intervention had on average 5.2 (95% CI, 3.79-6.59) more bortezomib administrations than the non-intervention group (p<0.001, adjusted for age, stage at diagnosis and regimen). In the intervention group, 58.3% of patients completed 8 treatment cycles. In the non-intervention group, 53.9% of patients finished treatment. Patients who received intervention were 1.4 time more likely to complete treatment (OR=1.4, 95% CI, 0.31-6.32, p=0.66).
Garcia et al (2014)	Single arm prospective study	To evaluate the feasibility, safety and initial efficacy of electroacupuncture for thalidomide/bortezomib induced peripheral	N=27 patients with grade ≥2 neuropathy N=19 analysed for primary outcomes All patients had sensory neuropathy and one patient had combined	20 acupuncture treatments over 9 weeks	N/A	No details	Adverse Events Efficacy No serious adverse events related to acupuncture were recorded. One patient recorded worsening of symptoms through the course of the study.

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
		neuropathy	sensory and motor symptoms.				*FACT/GOG-Ntx* Mean scores improved significantly between baseline and all subsequent time points (p<0.0001). • Baseline (N=19): Mean 20.8, SD=9.6 • Week 4 (N=18): Mean 16.7, SD=9.4, p=0.0263 • Week 9 (N=15): Mean 9.9, SD=5.6, p<0.0001 • Week 13 (N=15):Mean 13.2, SD=8.5, p<0.0001 A moderate effect size was found by week 4 (Cohen's d=0.4) with the largest effect size occurring between baseline and week 9 (Cohen's d=1.4). At one month follow-up the effect size remained (Cohen's d=0.9) *Brief Pain Inventory-Short Form* Mean scores showed significant improvements in pain severity and interference and worst pain in 24 hours at all time points (p<0.0001). Pain severity: • Baseline (N=18): Mean 25.4, SD=18.5 • Week 4 (N=18): Mean 18.2,

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							SD=16.4, p=0.0056 • Week 9 (N=16): Mean 15.1, SD=14.5, p<0.0001 • Week 13 (N=16): Mean 17.6, SD=16.6, p<0.0001 Cohen's d effect size estimates: week 4=0.7; week 9=1.1; week 13=0.9 Pain Interference • Baseline (N=18): Mean 25.4, SD=18.5 • Week 4 (N=18): Mean 18.2, SD=16.4, p=0.0056 • Week 9 (N=16): Mean 15.1, SD=14.5, p<0.0001 • Week 13 (N=16): Mean 17.6, SD=16.6, p<0.0001 Cohen's d effect size estimates were moderate (week 4=0.4; week 9=0.6; week 13=0.5) Worst pain in last 24 hours • Baseline (N=18): Mean 6.2, SD=3.5 • Week 4 (N=18): Mean 3.8, SD=2.7, p=0.0004 • Week 9 (N=16): Mean 2.9, SD=2.1, p<0.0001 • Week 13 (N=15): Mean 3.6, SD=2.5, p<0.0001

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							Cohen's d effect size estimates: week 4=0.8; week 9=1.2; week 13=0.9 <u>*Fact-G*</u> Physical Well being • Baseline (n=18): Mean 9.2, SD=6.1 • 4 weeks (n=18): Mean 7.2, SD=5.6, p=0.3 • 9 weeks (n=14): Mean 5.0, SD=3.8, p=0.002 • 13 weeks (n=16): Mean 5.5, SD=4.3, p=0.0004 Social/family well-being • Baseline (n=19): Mean 20.5, SD=6.3 • 4 weeks (n=16): Mean 19.7, SD=6.3, p=0.4 • 9 weeks (n=14): Mean 19.4, SD=8.5, p=0.1 • 13 weeks (n=15); Mean19.6, SD=7.0, p=0.3 Emotional well being • Baseline (n=19): Mean 5.3, SD=5.5 • 4 weeks (n=18): Mean 4.4, SD=4.0, p=0.5 • 9 weeks (n=16): Mean 3.8, SD=4.3, p=0.2 • 1 month (n=16): Mean 4.1, SD=3.9, p=0.2

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							Functional well being • Baseline (n=19): Mean 20.8, SD=6.7 • 4 weeks (n=17): Mean 19.7, SD=8.4, p<0.05 • 9 weeks (n=14): Mean 19.6, SD=7.0, p=0.1 • 1 month (n=15): Mean 20.4, SD=8.9, p=0.3
Mack et al (2010)	Single Arm Pilot Study (Abstract)	The evaluate Viv-Arte training program including whole body vibration with Galileo training device (SKMT) in patients with chemotherapy induced peripheral neuropathy	N=20 (n=16 myeloma)	Viv-Arte training program including whole body vibration with Galileo training device (SKMT) SKMT was composed of 4 parts: • Manual therapy including passive mobilisation, massage and active 3-D complex movements • Whole body vibration training • Gymnastics • Training of specific individualised tasks	N/A	No details	Treatment was well tolerated in all patients. Al large difference was observed with regard to locomotoric and sensoric multi dimensional tests pre and post treatment. Pre-treatment paresthesia of the feet measured on a scale of 1-10 showed the greatest change: • Pre-treatment median 8 (range: 1-10) versus post treatment median 2 (range: 0-7) Impairment of climbing stairs measured on a scale of 1-6: • Pre treatment median 4 (range: 3-6) versus post-treatment median 1 (range: 1-4) Plane walking distancemeasured

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							as steps per day: • Pre treatment median <1,000 (range <1,000-7,000) versus post-treatment median 5250 (range 2,000-7,000) Physical fitness measured with chair rising test, improved slightly from pre-treatment to post treatment. • Pre treatment median 17 seconds (range 13-21 seconds) versus post treatment median <10 seconds (range <10-18 seconds).
Richardson et al (2009)	Retrospective analysis of a single arm of a Randomised Trial	To assess the impact of a dose-modification guideline on the incidence and reversibility of bortezomib associated peripheral neuropathy	N=331 patients with relapsed multiple myeloma randomised to bortezomib and had received at least one dose of bortezomib. *Exclusions* Patients with neuropathy ≥2 peripheral neuropathy at baseline Patients were assessed every 3 weeks for 39 weeks and then every 6 weeks until disease progression after which	Protocol specified dose modification guideline	N/A This analysis only analysed a a single arm of an earlier trial	22 months (median)	Incidence and severity of peripheral neuropathy Reversibility of peripheral neuropathy (impact of dose modification guideline) Effect of dose modification for peripheral neuropathy on outcome *Incidence and severity of peripheral neuropathy* 37% (124/331) patients had treatment emergent peripheral neuropathy: • Grade ≥2=27% (n=91) • Grade ≥3=9% (n=30) • Grade 4=<1% (n=2)

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
			they were followed every 3 months.				Neuropathy was predominantly sensory with only 5 patients experiencing peripheral motor neuropathy. Onset of neuropathy generally occurred by cycle 5, corresponding to a cumulative dose of approximately 26mg/m^2. Actuarial overall incidence and incidence of grade ≥3 peripheral neuropathy reached a plateau by cycle 8 at a cumulative dose of approximately 42 mg/m^2 with an increase in risk of grade ≥3 peripheral neuropathy of approx. 4% compared with cycle 5. At baseline, 67% (n=221) reported peripheral neuropathy symptoms according to their responses to questions 4, 8 and 9 of he FACT/GOG-Ntx questionnaire and overall incidence of treatment-emergent peripheral neuropathy in these patients was 39% including 11% grade ≥3 compared with 38% and 5% in patients without baseline symptoms. There were statistically significant increases in total scores between basaeline and end of study in all

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							patients and in patients who did or did not experience treatment emergent peripheral neuropathy (p<0.001 for all differences). The difference in total score between patients who did or did not have peripheral neuropathy was not statistically significant at baseline (p=0.453) but reached significance by the end of the study (p=0.016) indicating a statistically significant greater increase in patients experiencing treatment emergent peripheral neuropathy (p<0.001). *Reversibility of peripheral neuropathy (impact of dose modification guideline)* Of the 91 patients with grade ≥2 peripheral neuropathy, 64% had experienced improvement (n=8) or resolution (n=50) by their last follow-up. Median time to improvement or resolution was 110 days (range: 4-627). 72/91 patients had dose modification per guideline; 31 discontinued due to perpheral neuropathy (14 within the first three treatment cycles).

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							49/72 (68%) experienced improvement or resolution in a median of 110 days (range: 4-376). Among the 41 patients who had dose modifications but did not discontinue bortezomib, 71% (n=29) had resolution of peripheral neuropathy in a median of 78 days (range 9-376) and in the patients who discontinued treatement, 65% (n=20) experienced improvement (n=8) or resolution (n=12) in a median of 122 days (range 4-296). In the 19 patients who did not have dose modifications per guideline (protocol violation), 47% experienced resolution in a median of 106 days (range: 5-627) *Effect of dose modification for peripheral neuropathy on outcome* The occurence of peripheral neuropathy did not adversely affect response rate, median time to progression or median overall survival. No effect of dose reductions or modification was observed for response rate, median time to progression or median overall survival.

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
Truni et al (2011)	Prospective Case Series Study Single centre (Italy)	To investigate the therapeutic potential of prolonged treatment with Palmitoylethanolamide (PEA) on pain and nerve function	N=30 consecutive patients with multiple myeloma and painful neuropathy (score of at least 4 on Bouhassira's DN4 screening tool for neuropathic pain). 10 patients excluded due to insufficient DN4 score or because other sources of neuropathy could not be ruled out. <u>*Exclusions*</u> • Possible alternative reason other than multiple myeloma and chemotherapy • Coexistence of other neuropathies, sensory disturbances due to other neurological diseases • Cognitive impairment All patients were undergoing treatment consisting of bortezomib and thalidomide and were examined after a mean treatment duration of 3 months (range 1-5).	Palmitoylethanolamide (PEA)	N/A	No details	Not clear No patient interrupted bortezomib/thalidomide treatment. There were dose reductions in 4 patients Following 2 months of treatment with PEA, mean pain scores were reduced(4.5±1.2 versus 3.4±1.0 p<0.002). The amplitude of foot-LEPs (Mean Scores 5.6±7.9 versus 8.1±9.2, p=0.0234), sural-SNAPs (Mean Scores 3.5±4.7 versus 4.7±5.1, p=0.0269) and peroneal-CMAPs (Mean Scores 3.8±1.9 versus 4.5±2.4, p=0.0171) were significantly increased. The amplitude of hand-LEPs, ulnar-SNAPs and ulnar-CMAPs was increased though not significantly. Warmth thresholds did not change (p<0.5) Changes in clinical and neurophyiological variables were similar when comparing responses in males verus females (p>0.2).

Study	Study Type/Setting	Aim	Population	Intervention	Comaprison	Follow-Up	Outcomes and Results
							Mean changes in clinical and neurophysiological variables were similar in the four patients who had reduced their chemotherapy dosage.

1

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3

Preventing thrombosis

Review Question

What is the most effective method for the prevention of thrombosis in patients with myeloma?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients diagnosed with myeloma and undergoing a potential thrombogenic therapy as initial treatment Patients diagnosed with myeloma and undergoing a potential thrombogenic therapy as ongoing treatment	• low molecular weight heparin • aspirin • vitamin K antagonist • new oral anticoagulants - Dabigatran etexilate - Rivaroxaban - Apixaban • antiplatelet drugs - Clopidogrel - Dipyridamole • fondaparinux • defibrotide • anti-coagulant and anti-platelet combination	• each other • no treatment	• arterial thrombosis • venous thrombosis • bleeding events • adverse events • death/mortality • HRQOL • compliance/adherence& patient acceptability

Evidence statements

Thrombosis

For the outcome of thrombosis there was very low to low quality evidence from mostly observational studies. From these studies it is clear that prophylaxis with aspirin, LMWH or VKA is effective in preventing thrombosis in myeloma patients as fewer thrombotic events occurred in patients receiving any of these interventions compared to patients that did not receive any prophylaxis. However it is unclear from these studies which intervention is most effective at preventing thrombosis. Most of these studies were not randomized as they were not designed to answer the question of thrombosis prophylaxis.

There was moderate quality evidence from two large RCTs studies (from the same research group) of thromboprophylaxis in myeloma. The first studied thromboprophylaxis with LMWH, aspirin or VKA in 667 newly diagnosed myeloma patients (Palumbo et al., 2011). Patients treated with thalidomide-containing regimens were randomly assigned in a 1:1:1 ratio to receive LMWH (enoxaparin 40 mg/d), aspirin (100 mg/d), or VKA (warfarin 1.25 mg/d). The investigators concluded that LMWH was better than VKA in reducing the incidence of thrombosis events but was no different from aspirin. In another study of newly diagnosed myeloma patients treated with lenalidomide (Larocca et al 2012), 342 patients were randomized to aspirin (100 mg/d) or LMWH (enoxaparin 40 mg/d). The data replicated the results from Palumbo et al in that there was no significant difference

in the incidence of thrombosis events between aspirin and LMWH. These RCTs are limited as the participants are not representative of the entire myeloma population as high risk individuals (patients at high risk of thromboembolic events such as patients with a previous history of thromboembolism, cardiac disease, infections, immobilization or surgery) were excluded.

Only 1 study (including 542 myeloma patients) stratified results according to risk for thrombosis (Leleu et al., 2013). They found the lowest incidence of thrombosis in the patients at highest risk (incidence of thrombosis 3% in high risk individuals, 6% in those at intermediate risk and 7% in those at low risk) because these patients received better and optimized prophylaxis with LMWH and VKA compared to low risk patients who mostly received aspirin.

Bleeding events

There was very low to low quality evidence from 2 observational studies and moderate quality evidence from 2 RCTs for incidence of bleeding events.

The data from the observational studies indicates that bleeding events are more likely in patients receiving prophylaxis with VKA, LMWH and aspirin compared to patients not receiving prophylaxis. The data also shows that VKA results in fewer bleeding events than aspirin and LMWH.

The data from the RCTs replicated this and also demonstrated a lower incidence of bleeding in patients receiving VKA compared to those receiving aspirin or LWMH. Patients receiving aspirin had the greatest risk of bleeding.

Mortality

Sudden death presumed to be a result of PE, MI or stroke was reported in 1 observational study and 1 RCT. There was no difference in the number of deaths between the different prophylactic interventions. However death was a rare event with too few events to make valid conclusions with regards to this outcome.

Adverse events, HRQOL, Compliance/adherence and patient acceptability

We did not find evidence for these outcomes.

Search Results

Characteristics of the 10 included papers:

- observational studies =8, RCTs =2
- treatment with thalidomide = 6, lenalidomide = 2, thalidomide or lenalidomide =1, not thalidomide or lenalidomide =1
- Newly diagnosed = 5, Refractory/relapsed = 1, Newly diagnosed+relapsed = 4
- Exclusion of high risk patients from 3 studies including the 2 RCTs
- Only 1 study looked at risk types
- Interventions examined were aspirin, LMWH and VKA. No studies regarding other interventions were identified.

Figure 9.3: Screening results

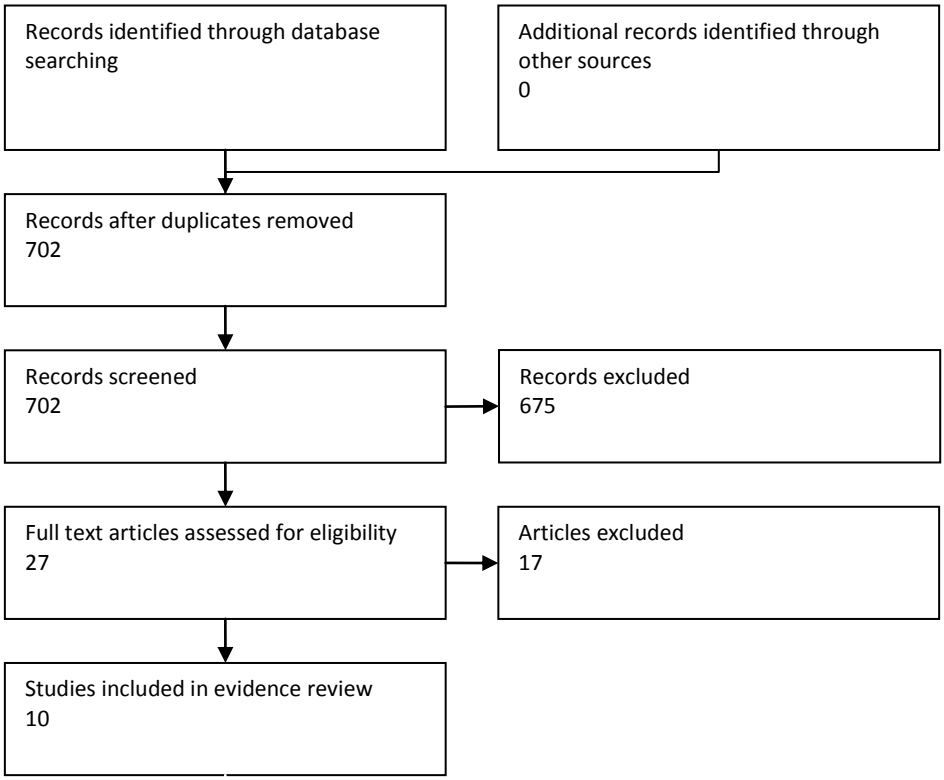

Table 9.12: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (no prophylaxis versus aspirin)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aspirin	nrophylaxis	Relative (95% CI)	Absolute	
incidence of thromboembolic events											
4	observational studies	no serious limitations	Serious[1]	no serious indirectness	no serious imprecision	none	587	861	-	-0.2% to 39% fewer patients receiving aspirin suffered a thromboembolic event compared to those receiving no prophylaxis.	⊕OOO VERY LOW
incidence of bleeding											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	81	-	4.9% fewer patients receiving no prophylaxis suffered a bleeding event compared to those receiving aspirin.	⊕⊕OO LOW

[1] heterogeneity between populations

Table 9.13: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (no prophylaxis versus vitamin K antagonists)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	no prophylaxis	VKA	Relative (95% CI)	Absolute	
incidence of thromboembolic events											
4	observational studies	no serious limitations	Serious[1]	no serious indirectness	no serious imprecision	none	934	412	-	-1.2% to 15.7% fewer patients receiving VKA suffered a thromboembolic event compared to those receiving no prophylaxis.	⊕OOO VERY LOW
incidence of bleeding											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	81	48	-	1.7% fewer patients receiving no prophylaxis suffered a bleeding event compared to those receiving VKA.	⊕⊕OO LOW
incidence of death											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	19	246	-	0.8% fewer patients receiving no prophylaxis died compared to those receiving LMWH.	⊕OOO VERY LOW

[1] heterogeneity between populations
[2] very low number of events

Table 9.14: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (no prophylaxis versus low molecular weight heparin)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	no prophylaxis	LMWH	Relative (95% CI)	Absolute	
incidence of thromboembolic events											
3	observational studies	no serious limitations	Serious[1]	no serious indirectness	no serious imprecision	none	308	274	-	5% to 9% fewer patients receiving LMWH suffered a thromboembolic event compared to those receiving no prophylaxis.	⊕OOO VERY LOW
incidence of bleeding											
2	observational studies	no serious limitations	Serious[1]	no serious indirectness	no serious imprecision	none	221	206	-	-4.7% to 0.6% fewer patients receiving LMWH suffered a bleeding event compared to those receiving no prophylaxis.	⊕OOO VERY LOW

[1] heterogeneity between populations

Table 9.15: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (aspirin versus vitamin K antagonists)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aspirin	VKA	Relative (95% CI)	Absolute	
incidence of thromboembolic events											
3	observational studies	no serious limitations	Serious[1]	no serious indirectness	no serious imprecision	none	679	146	-	-1% to 7% fewer patients receiving VKA suffered a thromboembolic event compared to those receiving aspirin.	⊕OOO VERY LOW
incidence of thromboembolic event											
1	randomized trials	Serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220	220	-	2.3% fewer patients receiving aspirin suffered a thromboembolic event compared to those receiving VKA.	⊕⊕⊕O MODERATE
incidence of bleeding											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	48	-	3.2% fewer patients receiving VKA suffered a bleeding event compared to those receiving aspirin.	⊕⊕OO LOW
incidence of bleeding											
1	randomized trials	Serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220	220	-	3.5% fewer patients receiving VKA suffered a bleeding event compared to those receiving aspirin.	⊕⊕⊕O MODERATE
incidence of death											
1	randomized trials	Serious[2,3,4]	no serious inconsistency	no serious indirectness	serious imprecision[5]	none	220	220	-	0.4% fewer patients receiving aspirin died compared to those receiving VKA.	⊕⊕OO LOW

[1] heterogeneity between populations; [2] Open-label trial (not blinded); [3] selection bias - high risk individuals excluded; [4] No placebo. However it would not be ethical to include a placebo with the high risk of thrombosis; [5] very low number of events

Table9.16: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (aspirin versus low molecular weight heparin)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	aspirin	LMWH	Relative (95% CI)	Absolute	
incidence of thromboembolic events											
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	472	108	-	4% to 7% fewer patients receiving LMWH suffered a thromboembolic event compared to those receiving aspirin.	⊕⊕OO LOW
incidence of thromboembolic events											
2	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	396	385	-	1.1% to 2.7% fewer patients receiving LMWH suffered a thromboembolic event compared to those receiving aspirin.	⊕⊕⊕O MODERATE
incidence of bleeding											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	307	88	-	0.2% fewer patients receiving LMWH suffered a bleeding event compared to those receiving aspirin.	⊕⊕OO LOW
incidence of bleeding											
2	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	396	385	-	-0.6%to 2.6% fewer patients receiving LMWH suffered a bleeding event compared to those receiving aspirin.	⊕⊕⊕O MODERATE
incidence of death											
1	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	220	219	-	There was no difference in the numbers of sudden deaths between patients receiving aspirin and those receiving LMWH.	⊕⊕OO LOW

[1] Open-label trial (not blinded).
[2] Selection bias - high risk individuals excluded.
[3] No placebo. However it would not be ethical to include a placebo with the high risk of thrombosis.
[4] very low number of events

Table9.17: GRADE profile: What is the most effective method for prevention of thrombosis in patients with myeloma (vitamin K antagonists versus low molecular weight heparin)?

Quality assessment	Summary of findings

							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA**	**LMWH**	**Relative (95% CI)**	**Absolute**	
incidence of thromboembolic events											
2	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	679	146	-	-3% to 16.7% fewer patients receiving LMWH suffered a thromboembolic event compared to those receiving VKA.	⊕⊕OO LOW
incidence of thromboembolic events											
1	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220	219	-	5% fewer patients receiving LMWH suffered a thromboembolic event compared to those receiving VKA.	⊕⊕⊕O MODERATE
incidence of bleeding											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	88	-	3% fewer patients receiving VKA suffered a bleeding event compared to those receiving LMWH.	⊕⊕OO LOW
incidence of bleeding											
1	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	220	219	-	0.9% fewer patients receiving VKA suffered a bleeding event compared to those receiving LMWH.	⊕⊕⊕O MODERATE
incidence of death											
1	randomized trials	Serious[1,2,3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	220	219	-	0.4% fewer patients receiving LMWH died compared to those receiving VKA.	⊕⊕OO LOW

[1] Open-label trial (not blinded).
[2] Selection bias - high risk individuals excluded.
[3] No placebo. However it would not be ethical to include a placebo with the high risk of thrombosis.
[4] very low number of events

1 ***Evidence table***

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Bagratuni et al., 2013</td>
<td>Prospective cohort study from single institution in Greece.</td>
<td>200 consecutive unselected myeloma patients treated with lenalidomide based regimes at a single institution

Previously untreated: 67 (34%)
Previously treated: 133 (66%)</td>
<td>• Low dose aspirin (100mg daily)

• LMWH

• vitamin K antagonist: Acenocoumarol (target INR 2-3)</td>
<td>• each other</td>
<td>
<table>
<tr><th></th><th>aspirin</th><th>LMWH</th><th>VKA</th><th>p</th></tr>
<tr><td>VTE</td><td>12/165 (7%)</td><td>0/20 (0%)</td><td>0/15 (0%)</td><td>0.097 aspirin vs. others</td></tr>
</table>
<table>
<tr><th></th><th>Previously untreated</th><th>Previously treated</th></tr>
<tr><td>VTE</td><td>9.4%</td><td>4.5%</td></tr>
</table>
</td>
<td>• Mix of newly diagnosed and relapsed/refractory patients

• Aim of study to assess clinical and genetic risk factors that may predispose to VTE. The study was not designed to answer the question of VTE prophylaxis.</td>
</tr>
<tr>
<td>Baz et al., 2005</td>
<td>Single institution Phase 2 clinical trial conducted by the Cleveland Clinic Foundation</td>
<td>105 myeloma patients receiving DVd-T (55 newly diagnosed, 50 relapsed/refractory)</td>
<td>• Low dose aspirin (81 mg orally) received from the start of DVd-T administration before the study began.

• Low dose aspirin (81 mg orally) received after at least 1 chemotherapy cycle with DVd-T after the study began and before the end of treatment with DVd-T administration</td>
<td>•no aspirin</td>
<td>After a median follow-up of 24 months:
<table>
<tr><th></th><th>Aspirin from start</th><th>Aspirin after start</th><th>Never took aspirin</th><th>p</th></tr>
<tr><td>VTE</td><td>11/58 (19%)</td><td>4/26 (15%)</td><td>11/19 (58%)</td><td>0.001</td></tr>
</table>
</td>
<td>• Mix of newly diagnosed and relapsed/refractory patients

• study was not randomised

• Study was not originally designed to answer the question of VTE prophylaxis. Study designed to evaluate the efficacy of DVd-T for myeloma. But because of high incidence of VTEs in first 35 enrolled patients the study protocol was amended to add aspirin.</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Cini et al., 2005</td>
<td>Retrospective analysis.

Data from phase 2, multicenter ‘Bologna 2002’ study.</td>
<td>266 newly diagnosed myeloma patients treated with Thalidomide–dexamethasone

Patients with a previous history of venous or arterial thrombosis were excluded.</td>
<td>VKA: fixed low-dose (1.25 mg⁄ day) warfarin</td>
<td>No prophylaxis</td>
<td>
<table>
<tr><th></th><th>VKA</th><th>No prophylaxis</th><th>p</th></tr>
<tr><td>VTE events</td><td>26/246 (10.6%)</td><td>5/19 (26.3%)</td><td>0.095</td></tr>
<tr><td>Patients-years rate of VTE</td><td>35.5%</td><td>86.2%</td><td>0.043</td></tr>
<tr><td>Deaths (possible fatal PE)</td><td>2</td><td>0</td><td></td></tr>
</table>
</td>
<td>Study was not randomized as the study was not designed to answer the question of VTE prophylaxis. No thromboprophylaxis was initially planned.
But 26.3% of the first 19 patients who were enrolled into the study had VTE events. Because of this high rate the study was subsequently amended to add thromboprophylaxis.</td>
</tr>
<tr>
<td>Kato et al., 2013</td>
<td>Retrospective cohort study of patients from 291 hospitals across Japan.</td>
<td>1035 refractory or relapsed myeloma patients treated with thalidomide-based regimens</td>
<td>• Aspirin (80-100 mg/d)

• VKA: Warfarin (0.5-5.0 mg/d)</td>
<td>No prophylaxis</td>
<td>Median follow-up period was 112 days (range 2-311 days).
<table>
<tr><th></th><th>aspirin</th><th>VKA</th><th>No prophylaxis</th></tr>
<tr><td>All VTE</td><td>3/207 (1.4%)</td><td>2/83 (2.4%)</td><td>9/747 (1.2%)</td></tr>
</table>
</td>
<td>•Short follow up period – 4 months

•Retrospective analysis

•Heterogeneous group of patients

•No randomization

•Rate of VTE is low so sample size too small for statistical validity

•Asian population – different rates of VTE to western populations</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Kessler et al., 2011</td>
<td>Observational study</td>
<td>258 newly diagnosed myeloma patients treated with VAD or VID.

In 13 centres across the Czech republic enrolled in the Czech myeloma group 2002 clinical trial.</td>
<td>LMWH once daily subcutaneously (dalteparin, nadroparin, or enoxaparin)</td>
<td>No prophylaxis</td>
<td>
<table>
<tr><th></th><th>LMWH</th><th>No prophylaxis</th><th>p</th></tr>
<tr><td>All VTE</td><td>4/118 (3.4%)</td><td>18/140 (12.9%)</td><td>0.007</td></tr>
<tr><td>Major bleeding</td><td>1/118 (0.8%)</td><td>2/140 (1.4%)</td><td></td></tr>
</table>
Subgroup of 102 patients from single centre:
<table>
<tr><th></th><th>No LMWH</th><th>LMWH < 70 IU/kg</th><th>LMWH > 70 IU/kg</th><th>p</th></tr>
<tr><td>All VTE</td><td>5/35 (14.3%)</td><td>3/39 (7.7%)</td><td>0/28 (0%)</td><td>0.002 (no vs. high)</td></tr>
</table>
</td>
<td>•Study was not randomized as the study was not originally designed to answer the question of VTE prophylaxis.

•Different LMWHs were used</td>
</tr>
<tr>
<td>Larocca et al., 2012</td>
<td>Prospective open label randomized substudy of a phase 3 trial conducted at 62 centres in Italy and Israel</td>
<td>342 newly diagnosed myeloma patients receiving lenalidomide based chemotherapy with no history of DVT or arterial thrombolic events within the past 12 months</td>
<td>• Aspirin 100 mg/d orally

• LMWH enoxaparin 40mg/d subcutaneously</td>
<td>Each other</td>
<td>6 months:
<table>
<tr><th></th><th>aspirin</th><th>LMWH</th><th>p</th></tr>
<tr><td>Grade 3 / 4 DVT and PE</td><td>4/176 (2.3%)</td><td>2/166 (1.2%)</td><td>0.452</td></tr>
<tr><td>Deep vein thrombosis</td><td>2/176 (1.1%)</td><td>2/166 (1.2%)</td><td></td></tr>
<tr><td>Pulmonary embolism</td><td>3/176 (1.7%)</td><td>0/166 (1.8%)</td><td></td></tr>
<tr><td>Arterial thrombosis</td><td>0/176 (0%)</td><td>0/166 (0%)</td><td></td></tr>
<tr><td>Major bleeding</td><td>0/176</td><td>0/166</td><td></td></tr>
<tr><td>Minor bleeding</td><td>0/176</td><td>1/166</td><td></td></tr>
</table>
</td>
<td>• High risk individuals not included

• Placebo comparison not included</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Leleu et al., 2013</td>
<td>Multi centre prospective observational study</td>
<td>524 myeloma patients treated with thalidomide (36%) or lenalidomide (64%) as either first (39%) or second or third (61%) line of chemotherapy.</td>
<td>• Aspirin 75-160 mg/d orally

• LMWH prophylactic dose subcutaneously

• VKA (target INR 2-3)

• No prophylaxis</td>
<td>Each other</td>
<td>VTE prophylaxis according to VTE risk group:
<table>
<tr><th></th><th>aspirin</th><th>LMWH</th><th>VKA</th><th>No prophylaxis</th></tr>
<tr><td>low</td><td>70%</td><td>6.5%</td><td>3%</td><td>20.5%</td></tr>
<tr><td>intermediate</td><td>58%</td><td>20%</td><td>6%</td><td>16%</td></tr>
<tr><td>high</td><td>18%</td><td>43%</td><td>34%</td><td>5%</td></tr>
</table>
VTE events were recorded in all risk types:
<table>
<tr><th></th><th>VTE</th></tr>
<tr><td>low</td><td>17 (7%)</td></tr>
<tr><td>intermediate</td><td>12 (6%)</td></tr>
<tr><td>high</td><td>2 (3%)</td></tr>
</table>
High risk patients had lowest incidence of VTE - better and optimized VTE prophylaxis with LMWH and VKA

12 months:
<table>
<tr><th></th><th>aspirin</th><th>LMWH</th><th>VKA</th><th>No prophylaxis</th><th>p</th></tr>
<tr><td>VTE</td><td>21/307 (7%)</td><td>3/88 (3%)</td><td>0/48 (0%)</td><td>7/81 (8%)</td><td>Aspirin v LMWH 0.62;

VKA vs. aspirin 0.03</td></tr>
<tr><td>Bleeding episode</td><td>9.3%</td><td>9.1%</td><td>6.1%</td><td>4.4%</td><td>0.9480</td></tr>
</table>
Bleeding episode serious in 0.7% of cases.</td>
<td>• not randomized observational study</td>
</tr>
<tr>
<td>Niesvizky et al., 2007</td>
<td>Study 1: retrospective analysis

Study 2: prospective</td>
<td>Study 1: 60 newly diagnosed or previously treated myeloma patients receiving thalidomide based treatment.</td>
<td>Aspirin (81 mg/d)</td>
<td>No prophylaxis</td>
<td>Report describing the use of low dose aspirin as thromboprophylaxis in 3 case series of myeloma patients.
2 of the studies had data comparing TE in patients who had aspirin and those who did not.

Study 1:</td>
<td><u>Study 1:</u>
• Mix of newly diagnosed and relapsed/refractory patients

• not randomised</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td></td>
<td>randomized sequential trial</td>
<td>Study 2: 29 newly diagnosed myeloma patients receiving Thalidomide+dexamethasone or dexamethasone alone</td>
<td></td>
<td></td>
<td>
<table>
<tr><th></th><th>Before aspirin</th><th>After aspirin</th></tr>
<tr><td>Grade 2 thrombosis</td><td>5/60 (8%)</td><td>0</td></tr>
<tr><td>Grade 3 or 4 thrombosis</td><td>6/60 (15%)</td><td>0</td></tr>
</table>

Study 2:
<table>
<tr><th></th><th>dexamethasone</th><th>Thalidomide + dexamethasone + aspirin</th><th>p</th></tr>
<tr><td>Grade 3 or 4 thrombosis</td><td>3/14 (21.4%)</td><td>1/15 (6.6%)</td><td>0.33</td></tr>
</table>
</td>
<td>• Study was not originally designed to answer the question of VTE prophylaxis. But after the occurrence of thrombotic events midway through the trial all patients then received aspirin.

<u>Study 2:</u>
• Small study sample size

• Thalidomide not in both groups. Thalidomide+dexamethasone+aspirin vs. dexamethasone</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Palumbo et al., 2011</td>
<td>RCT

open-label, phase III, randomized study conducted at 84 centers in Italy</td>
<td>659 patients newly diagnosed myeloma patients who received thalidomide-containing regimens.

Patients at high risk of thromboembolic events, such as patients with previous history of thromboembolism, severe cardiac disease, uncontrolled diabetes, infections, immobilization, or surgery, were not included.</td>
<td>• Aspirin 100 mg/d orally

• VKA: Warfarin 1.25 mg/d orally</td>
<td>LMWH (enoxaparin) 40 mg/d subcutaneously

.</td>
<td>6 months:
<table>
<tr><th></th><th>aspirin</th><th>VKA</th><th>LMWH</th><th>p</th></tr>
<tr><td>Grade 3 or 4 thromboembolic event</td><td>13/220 (5.9%)</td><td>18/220 (8.2%)</td><td>7/219 (3.2%)</td><td>0.173 aspirin vs. LMWH;

0.024 VKA vs. LMWH</td></tr>
<tr><td>Deep vein thrombosis</td><td>8/220 (3.6%)</td><td>14/220 (6.4%)</td><td>6/219 (2.7%)</td><td></td></tr>
<tr><td>Pulmonary embolism</td><td>4/220 (1.8%)</td><td>4/220 (1.8%)</td><td>0/219 (0%)</td><td></td></tr>
<tr><td>Arterial thrombosis</td><td>1/220 (0.5%)</td><td>0/220 (0%)</td><td>1/219 (0.5%)</td><td></td></tr>
<tr><td>Major bleeding</td><td>3/220 (1.4%)</td><td>0/220 (0%)</td><td>0/219 (0%)</td><td>0.83 aspirin vs. LMWH;

1.0 warfarin vs. LMWH</td></tr>
<tr><td>Minor bleeding</td><td>6/220 (2.7%)</td><td>1/220 (0.5%)</td><td>3/219 (1.4%)</td><td>0.316 aspirin vs. LMWH;

0.313 warfarin vs. LMWH</td></tr>
<tr><td>Sudden death</td><td>1/220 (0.5%)</td><td>0/220 (0%)</td><td>1/219 (0.5%)</td><td></td></tr>
</table>
25 months:
<table>
<tr><th></th><th>aspirin</th><th>VKA</th><th>LMWH</th><th>p</th></tr>
<tr><td>Grade 3 or 4 thromboembolic event</td><td>17/220 (7.7%)</td><td>21/220 (9.5%)</td><td>11/219 (5%)</td><td></td></tr>
<tr><td>Deep vein thrombosis</td><td>12/220 (5.5%)</td><td>17/220 (7.7%)</td><td>10/219 (4.6%)</td><td></td></tr>
<tr><td>Pulmonary embolism</td><td>4/220 (1.8%)</td><td>4/220 (1.8%)</td><td>0/219 (0%)</td><td></td></tr>
<tr><td>Arterial thrombosis</td><td>1/220 (0.5%)</td><td>0/220 (0%)</td><td>1/219 (0.5%)</td><td></td></tr>
<tr><td>Sudden death</td><td>1/220 (0.5%)</td><td>2/220 (0.9%)</td><td>1/219 (0.5%)</td><td></td></tr>
</table>
Sudden deaths: one patient died in the aspirin group (pulmonary embolism), two patients died in the warfarin group (acute myocardial infarction and cardiac arrest) and one patient died in the LMWH group (cardiac arrest).</td>
<td>Limitations:

• absence of a placebo group
(However, the inclusion of a placebo arm would not have been ethical because all patients enrolled onto this study were treated with thalidomide-containing regimens and could have an increased risk of thromboembolic events)

• open-label design

• no high risk patients included</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Zangari et al., 2004</td>
<td>open label prospective trial

USA</td>
<td>190 newly diagnosed myeloma patients receiving chemotherapy + thalidomide</td>
<td>• VKA: Warfarin: Low dose coumadin 1 mg/d

• LMWH: enoxaparin 40 mg/d</td>
<td>No prophylaxis</td>
<td>
<table>
<tr><th></th><th>LMWH</th><th>VKA</th><th>No prophylaxis</th></tr>
<tr><td>DVT</td><td>10/68 (14.7%)</td><td>11/35 (31.4%)</td><td>30/87 (34.4%)</td></tr>
</table>
</td>
<td>• Not randomized for prophylaxis</td>
</tr>
</table>

References of included studies

1. Bagratuni, T., Kastritis, E., Politou, M., Roussou, M., Kostouros, E., Gavriatopoulou, M., Eleutherakis-Papaiakovou, E., Kanelias, N., Terpos, E. & Dimopoulos, M. A. (2013) Clinical and genetic factors associated with venous thromboembolism in myeloma patients treated with lenalidomide-based regimens. American Journal of Hematology, 88: 765-770.
2. Baz, R., Li, L., Kottke-Marchant, K., Srkalovic, G., McGowan, B., Yiannaki, E., Karam, M. A., Faiman, B., Jawde, R. A., Andresen, S., Zeldis, J. & Hussein, M. A. (2005) The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clinic Proceedings, 80: 1568-1574.
3. Cini M, Zamagni E, Valdré L, Palareti G, Patriarca F, Tacchetti P, Legnani C, Catalano L, Masini L, Tosi P, Gozzetti A, Cavo M. (2010) Thalidomide-dexamethasone as up-front therapy for patients with newly diagnosed multiple myeloma: thrombophilic alterations, thrombotic complications, and thromboprophylaxis with low-dose warfarin. Eur J Haematol. 2010 Jun;84(6):484-92.
4. Kato, A., Takano, H., Ichikawa, A., Koshino, M., Igarashi, A., Hattori, K. & Nagata, K. (2013) A retrospective cohort study of venous thromboembolism(VTE) in 1035 Japanese myeloma patients treated with thalidomide; lower incidence without statistically significant association between specific risk factors and development of VTE and effects of thromboprophylaxis with aspirin and warfarin. Thrombosis Research, 131: 140-144.
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6. Larocca, A., Cavallo, F., Bringhen, S., Di, R. F., Falanga, A., Evangelista, A., Cavalli, M., Stanevsky, A., Corradini, P., Pezzatti, S., Patriarca, F., Cavo, M., Peccatori, J., Catalano, L., Carella, A. M., Cafro, A. M., Siniscalchi, A., Crippa, C., Petrucci, M. T., Yehuda, D. B., Beggiato, E., Di Toritto, T. C., Boccadoro, M., Nagler, A. & Palumbo, A. (2012) Aspirin or enoxaparin thromboprophylaxis for patients with newly diagnosed multiple myeloma treated with lenalidomide. Blood, 119: 933-939.
7. Leleu, X., Rodon, P., Hulin, C., Daley, L., Dauriac, C., Hacini, M., Decaux, O., Eisemann, J. C., Fitoussi, O., Lioure, B., Voillat, L., Slama, B., Al, J. A., Benramdane, R., Chaleteix, C., Costello, R., Thyss, A., Mathiot, C., Boyle, E., Maloisel, F., Stoppa, A. M., Kolb, B., Michallet, M., Lamblin, A., Natta, P., Facon, T., Elalamy, I., Fermand, J. P. & Moreau, P. (2013) MELISSE, a large multicentric observational study to determine risk factors of venous thromboembolism in patients with multiple myeloma treated with immunomodulatory drugs. Thrombosis & Haemostasis, 110: 844-851.
8. Niesvizky, R., Martinez-Banos, D., Jalbrzikowski, J., Christos, P., Furst, J., De, S. M., Mark, T., Pearse, R., Mazumdar, M., Zafar, F., Pekle, K., Leonard, J., Jayabalan, D. & Coleman, M. (2007) Prophylactic low-dose aspirin is effective antithrombotic therapy for combination treatments of thalidomide or lenalidomide in myeloma. Leukemia & Lymphoma, 48: 2330-2337.
9. Palumbo, A., Cavo, M., Bringhen, S., Zamagni, E., Romano, A., Patriarca, F., Rossi, D., Gentilini, F., Crippa, C., Galli, M., Nozzoli, C., Ria, R., Marasca, R., Montefusco, V., Baldini, L., Elice, F., Callea, V., Pulini, S., Carella, A. M., Zambello, R., Benevolo, G., Magarotto, V., Tacchetti, P., Pescosta, N., Cellini, C., Polloni, C., Evangelista, A., Caravita, T., Morabito, F., Offidani, M., Tosi, P. & Boccadoro, M. (2011) Aspirin, warfarin, or enoxaparin

thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. Journal of Clinical Oncology, 29: 986-993.

10. Zangari, M., Barlogie, B., Anaissie, E., Saghafifar, F., Eddlemon, P., Jacobson, J., Lee, C. K., Thertulien, R., Talamo, G., Thomas, T., Van, R. F., Fassas, A., Fink, L. & Tricot, G. (2004) Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. British Journal of Haematology, 126: 715-721.

Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. Aikens, G. B., Rivey, M. P. & Hansen, C. J. (2013) Primary venous thromboembolism prophylaxis in ambulatory cancer patients. [Review]. *Annals of Pharmacotherapy*, 47: 198-209.	Expert review.
2. Alexander, M., Kirsa, S. & Mellor, J. D. (2012) Thalidomide thromboprophylaxis in multiple myeloma: a review of current evidence. [Review]. *Asia-Pacific Journal of Clinical Oncology*, 8: 319-324.	Expert review.
3. Carrier, M., Le, G. G., Tay, J., Wu, C. & Lee, A. Y. (2011) Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. [Review]. *Journal of Thrombosis & Haemostasis*, 9: 653-663.	Study summarizes rates of VTE in patients with myeloma receiving thalidomide or lenalidomide based regimes. Use of thromboprophylaxis was associated with lower risk of VTE but comparisons between different types of thromboprophylaxis not done.
4. Cavallo, F. (2011). A phase iii study of enoxaparin vs aspirin as thromboprophylaxis for patients with newly diagnosed of multiple myeloma treated with lenalidomide-based regimens. Haematologica, Conference, S30.	Abstract from Palumbo (2011) trial.
5. Connors, J. M. (2014). Prophylaxis against venous thromboembolism in ambulatory patients with cancer. New England Journal of Medicine, 370, 2515-2519.	Expert review
6. Crusoe, E. D., Massarenti, M., Almeida, M., Cury, P., Higashi, F., Vieira, L. et al. (2014). Venous Thromboembolism Prophylaxis with Aspirin for Multiple Myeloma Patients Receiving Thalidomide Combination As First-Line Treatment. Blood, 124.	Non comparative study
7. Khorana, A. A. (2015). Prevention of venous thromboembolism in cancer outpatients: Guidance from the SSC of the ISTH: Reply. Journal of Thrombosis and Haemostasis, 13, 325-326.	Comment
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15. Phillips S., B. (2014). Over-the-counter aspirin use, comorbidities, and timing of aspirin therapy initiation in multiple myeloma patients. Pharmacoepidemiology and Drug Safety, Conference, var.	Does not compare thromboprophylaxis interventions
16. Reid, V. L. (2011). Effectiveness of aspirin thromboprophylaxis in patients with multiple myeloma on combination treatment with thalidomide. Haematologica, Conference, S126.	Does not compare thromboprophylaxis interventions.
17. Rome, S., Doss, D., Miller, K., Westphal, J. & IMF Nurse Leadership Board. (2008) Thromboembolic events associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. *Clinical Journal of Oncology Nursing*, 12: 21-28.	Consensus statement for the assessment and prevention of thromboembolic events from the International Myeloma Foundation's Nurse Leadership Board.

Checklists to identify risk of bias

Study identification: Larocca et al 2012					
Myeloma			Topic M		
Study Type			Randomised controlled trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across	Yes	No	Unclear	N/A

	groups)				
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? Antithrombotic prophylaxis was discontinued in any patient who developed DVT, PE, arterial thrombosis or any acute cardiovascular or bleeding event or patient who had a platelet count < 50,000/ul. Numbers not reported.				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A

D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Palumbo et al 2011					
Myeloma			Topic M		
Study Type			Randomised controlled trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an	Yes	No	Unclear	N/A

	equal length of time (or analysis was adjusted to allow for differences in length of follow-up)				
C2	a. How many participants did not complete treatment in each group? Antithrombotic prophylaxis was discontinued in any patient who developed thrombosis or bleeding or stopped thalidomide treatment. Aspirin: 35, warfarin: 46, LMWH: 26				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Bagratuni et al 2013					
Myeloma			**Topic M**		
Study Type			Prospective cohort study		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design	Yes	No	Unclear	N/A

	or analysis to balance the comparison groups for potential confounders				
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 0				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A

D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Baz et al 2005					
Myeloma			**Topic M**		
Study Type			Phase 2 clinical trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 3 patients were non-compliant with aspirin intake.				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of	Yes	No	Unclear	N/A

	those who did not complete treatment)				
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Study identification: Cini et al 2005					
Myeloma			**Topic M**		
Study Type			Retrospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention					

under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 1 patient refused the intervention.				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Kato et al 2013					
Myeloma			**Topic M**		
Study Type			Retrospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 0				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					

Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Kessler et al 2011					
Myeloma			**Topic M**		
Study Type			Observational study		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			

Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 0				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Study identification: Leleu et al 2013					
Myeloma			**Topic M**		
Study Type			Observational study		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A

A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 0				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A

D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Niesvizky et al 2007					
Myeloma			**Topic M**		
Study Type			Observational study		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? Not reported				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A

C3	a. For how many participants in each group were no outcome data available? Not reported				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

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Study identification: Zangari et al 2004					
Myeloma		**Topic M**			
Study Type		prospective			
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the	Yes	No	Unclear	N/A

	intervention(s) studied				
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 0				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Managing fatigue

Review Question

Which interventions are most effective in reducing fatigue in patients being treated for myeloma?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients who are or have been treated for myeloma	• Exercise/physical activity • pacing schedule • Prescription drugs (e.g. psychostimulants) • Non-prescription drugs, e.g. over-the-counter stimulant drinks • Complementary therapies • Dietary intervention • Spinal rehabilitation • Blood transfusion or EPO if anaemic • Rest • Sleep hygiene education	• Each other • Supportive care only	• Reduction of fatigue • Performance status • Daytime sleepiness • QOL • Exercise tolerance • Actimetry • Muscle function • Mobility – physical and social functioning • Dependency for activities of daily living • Adverse events • PROMs

Evidence statements

Reduction of fatigue

Moderate quality evidence from a randomized trial (Coleman et al, 2012) suggests that an individualized exercise program is not effective for reducing fatigue in myeloma patients. There was very little difference in the fatigues scores (FACT and POMS) between patients undertaking a home-based individualized exercise program (HBIEP), coming aerobic and strength resistance training, and the control group receiving the current best practice recommendation to walk 20 minutes three times a week (usual care).

Moderate quality evidence from a randomized trial (Berenson et al, 2015) including 42 patients, suggests that moderately fatigued patients with myeloma treated with placebo for 28 days show similar improvements in self-reported fatigue to those treated with armodafinil.

Performance (aerobic capacity)

Moderate quality evidence from a randomized trial (Coleman et al, 2012) suggests that an individualized exercise program is not effective for improving aerobic capacity (measured by distance walked in 6 minutes) when compared to usual care (Coleman et al, 2012). Patients in the exercise program group walked on average an additional 50 feet compared to the usual care group but the difference was not statistically significant.

ECOG performance score

Moderate quality evidence from a randomized trial (Dammacco et al., 2001) suggests that that epoetin alfa can improve ECOG performance score in myeloma patients when compared to placebo. 20% of patients receiving epoetin alfa showed a one-point improvement in ECOG performance score compared to 6% of those receiving placebo.

Daytime and night-time sleep (ActiGraph)

Moderate quality evidence from a randomized trial (Coleman et al, 2012) suggests that an individualized exercise program is not effective for improving sleep in myeloma patient. There was very little difference in minutes of daytime and nighttime sleep between patients undertaking the HBIEP, coming aerobic and strength resistance training, and the control group receiving the current best practice recommendation to walk 20 minutes three times a week (usual care).

QOL

Moderate quality evidence from a randomized trial (Dammacco et al., 2001) suggests that that epoetin alfa can improve QOL in myeloma patients when compared to placebo. Within-group changes from baseline to week 12 revealed statistically significant improvement in emotional reactions, social interaction, energy and ability to do daily activities in patients treated with epoetin alfa. Placebo-treated patients, in contrast, showed no significant improvement except in sleep. Between-group differences in effect on QOL were not detected.

Moderate quality evidence from a randomized trial (Berenson et al, 2015) including 42 patients, suggests that moderately fatigued patients with myeloma treated with placebo for 28 days show similar improvements in self-reported quality of life to those treated with armodafinil.

Adverse events

High quality evidence from a randomized trial (Dammacco et al., 2001) suggests that adverse events are similar in myeloma patients receiving epoetin alfa and myeloma patients receiving placebo. No differences were found for overall incidence of adverse events (72·5% epoetin alfa-treated; 75·0% placebo-treated). Type and frequency of individual adverse events were similar throughout the study. The most commonly reported adverse events in either treatment group were fever, pain and leucopenia.

Exercise tolerance, Muscle function, Mobility – physical and social functioning, Dependency for activities of daily living

The literature searches did not find evidence for these outcomes.

Search Results

Figure 9.3: Screening results

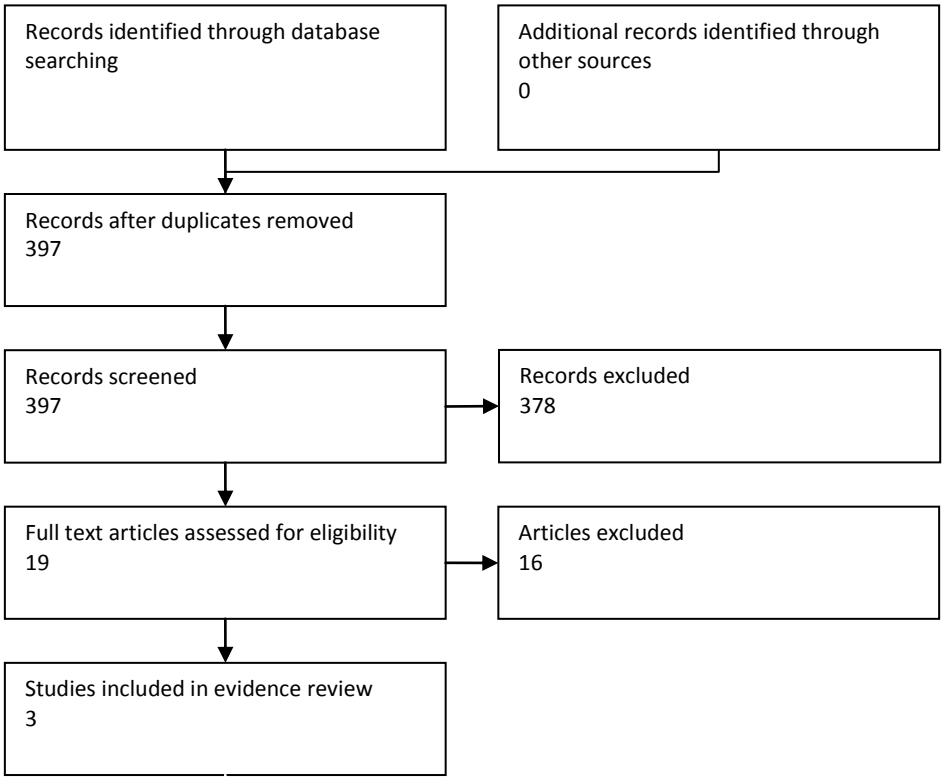


Table 9.18: GRADE profile: Which interventions are most effective in reducing fatigue in patients having treatment for myeloma (individualised exercise program versus usual care)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	an individualized exercise program	usual care	Relative (95% CI)	Absolute	
fatigue (POMS and FACT-F)											
1[2]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	75	-	The effect of exercise was minimal on decreasing fatigue: At the end of the 15 week experimental period patients in the intervention group had a mean FACT fatigue score of 31.34 (scores range from 0-52 with higher scores indicating less fatigue) and a mean POMS fatigue score of 10.63 (scores range from 0-28 with higher scores indicating less fatigue). Patients in the control group had a mean FACT fatigue score of 31.71 a mean POMS fatigue score of 10.92.	⊕⊕⊕O MODERATE
daytime and night-time sleep (actigraph)											
1[2]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	75	-	The effect of exercise was minimal on improving sleep: At the end of the 15 week experimental period patients in the intervention group had a mean of 411.7 minutes nighttime and 113.17 daytime sleep, whilst patients in the control group had a mean 414.33 minutes nighttime and 114 daytime sleep.	⊕⊕⊕O MODERATE
performance (aerobic capacity) – measured by distance walked in 6 minutes											
1[2]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	75	-	The effect of exercise was minimal on improving performance: At the end of the 15 week experimental period patients in the intervention group walked 1594.69 feet in 6 minutes compared to those in the control group who walked 1545.07 feet in 6 minutes.	⊕⊕⊕O MODERATE

[1] *The patients self-reported their compliance with the exercise program. Observation of the exercise and activity was not possible because this was a home-based program. Exercise was individualized for each patient so no consistent pattern of exercise across the population.* [2] *Coleman et al., 2012.*

Table 9.19: GRADE profile: Which interventions are most effective in reducing fatigue in patients having treatment for myeloma (epoetin alfa versus placebo)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	epoetin alfa	placebo	Relative (95% CI)	Absolute	
QOL											
1[2]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	72	-	Improvement in more QOL measures with epoetin than with placebo. No Absolute data reported.	⊕⊕⊕O MODERATE
ECOG performance score											
1[2]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	66	-	13.6% more patients in the intervention group had a 1-point improvement in performance score compared to the placebo group.	⊕⊕⊕O MODERATE
adverse events											
1[2]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/69 (72.5%)	57/76 (75%)	-	2.5% fewer patients in the intervention group experienced an adverse event, compared to the placebo group.	⊕⊕⊕⊕ HIGH

[1] *Changes in functional status and QOL in the study reported here were secondary efficacy assessments, and the study was not powered to measure absolute change, but rather statistical trends.*
[2] *Dammacco et al., 2001*

Table 9.20: GRADE profile: Which interventions are most effective in reducing fatigue in patients having treatment for myeloma (armodafinil versus placebo)?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	placebo-first	armodafinil	Relative (95% CI)	Absolute	
QOL (FACIT-G; higher scores better; measured after 28 days of treatment)											
1[2]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	23	19	-	FACIT-G was 75.8 (12.9)in placebo-first group and 68.5 (20.5) in the treatment only group (P=0.377)	⊕⊕⊕O MODERATE
Fatigue (BFI; lower scores better; measured after 28 days of treatment)											
1[2]	randomised	no serious	no serious	no serious	serious	none	23	19	-	BFI was 41.5 (18.4) in placebo-first group	⊕⊕⊕O

	trials	limitations	inconsistency	indirectness	imprecision[1]					and 48.8 (22.4) in the treatment only group (P=0.289)	MODERATE
serious adverse events (during 28 days of treatment)											
1[2]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	0/23	2/19	-	Overall toxicities were similar between the two groups. 4% of adverse events were deemed to be drug related.	⊕⊕⊕O MODERATE

[1] *Small sample size*
[2] *Berenson et al (2015)*

1 ***Evidence table***

<table>
<tr><th>Paper</th><th>Study type</th><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcomes</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Coleman et al., 2012</td><td>RCT</td><td>187 myeloma patients.

Outpatient setting of the Myeloma Institute for Research and Therapy at the Rockfellow Cancer Centre at the University of Arkansas for Medical Sciences.</td><td>Home-based individualized exercise program, combining aerobic and strength resistance training (HBIEP)

n=95
(outcomes for n=91)</td><td>Current best practice recommendation to walk 20 minutes three times a week (usual care).

n=92
(outcomes for n=75)</td><td>• Fatigue (POMS and FACT-F)

• Daytime and night-time sleep (ActiGraph)

• performance (aerobic capacity (6-Minute Walk Test))</td><td>Results suggested that no benefit was derived from exercise for reducing fatigue, improving sleep and improving performance in myeloma patients.</td><td>15-week experimental period

Limitations:
• The patients self-reported their compliance with the HBIEP. Observation of the exercise and activity was not possible because this was a home-based program.
Also, patients in the control group were not discouraged from exercising.

• Exercise was individualized for each patient so no consistent pattern of exercise across the population.</td></tr>
<tr><td>Berenson et al, 2015</td><td>RCT</td><td>50 patients with myeloma and moderate fatigue</td><td>Placebo (day 1 to day 28) followed by armodafinil (day 29 to 56) at 150 mg/daily</td><td>Armodafinil at 150 mg/daily for 56 days</td><td>• Fatigue (self reported using Epworth Sleepiness Scale, ESS; and BFI)
• Adverse events
• Anxiety and depression (using HADS)
• QOL measured using FACIT-F
• Cognitive tests –trail making test (TMT-B), symbol digits modality test (SDMT) and digit span</td><td>No significant difference between the placebo-first (PF) and treatment-only (TO) groups after 28 days

<table><tr><th>Patient reported outcomes</th><th>PF (n=23)</th><th>TO (n=19)</th><th>P</th></tr><tr><td>BFI</td><td>41.5 (18.4)</td><td>48.8 (22.4)</td><td>0.289</td></tr><tr><td>ESS</td><td>10.0 (4.6)</td><td>10.1 (5.1)</td><td>0.840</td></tr><tr><td>FACIT-G</td><td>75.8 (12.9)</td><td>68.5 (20.5)</td><td>0.377</td></tr><tr><td>Anxiety</td><td>5.5 (3.3)</td><td>6.9 (4.6)</td><td>0.945</td></tr><tr><td>Depression</td><td>6.6 (3.6)</td><td>10.3 (17.8)</td><td>0.316</td></tr></table></td><td>56 day double-blind placebo controlled cross-over study. Small sample size –powered to detect a 1 point difference on the BFI fatigue scale.</td></tr>
</table>

<table>
<tr>
<td></td><td></td><td></td><td></td><td></td><td></td>
<td>
<table>
<tr><td>Objective outcomes</td><td>PF (n=23)</td><td>TO (n=19)</td><td>P</td></tr>
<tr><td>digit span forward</td><td>10.4 (2.3)</td><td>10.6 (3.0)</td><td>0.636</td></tr>
<tr><td>Digit span backward</td><td>7.0 (2.6)</td><td>7.0 (2.6)</td><td>0.531</td></tr>
<tr><td>SDMT</td><td>40.8 (14.7)</td><td>42.4 (12.0)</td><td>0.699</td></tr>
<tr><td>TMT-B</td><td>159.8 (94.2)</td><td>158.4 (81.2)</td><td>0.954</td></tr>
</table>

Compared to baseline scores both placebo-first and treatment only groups showed similar improvements in fatigue (BFI and ESS scores), QOL (FACIT-G) and HADS anxiety. The placebo group showed significant improvement on eight other measures.
</td>
<td></td>
</tr>
<tr>
<td>Dammacco et al., 2001</td>
<td>RCT</td>
<td>145 patients with myeloma and anemia enrolled at 31 sites in 12 countries.</td>
<td>150IU/kg epoetin alfa received subcutaneously 3 times a week

n=69
(QOL outcomes for n=66)</td>
<td>matching volume of placebo received subcutaneously 3 times a week

n=76
(QOL outcomes for n=72)</td>
<td>• QOL (measured using 2 questionnaires:
- Nottingham health profile
- Cancer linear analogue scale assessment)

• ECOG performance scores (rated by the physician using a scale with values that ranges from 0=able to carry out all normal activities without restriction to 4 =completely disabled, cannot carry out nay self-care ad totally confined to bed or a chair)

• adverse events</td>
<td>During double-blind treatment there was significant ($p \leq 0{\cdot}05$) improvement in more QOL measures with epoetin than with placebo.
Epoetin: emotional reactions, social interaction, energy and ability to do daily activities
Placebo: sleep
Raw data not reported.

Significantly ($p = 0{\cdot}038$) more epoetin alfa vs. placebo patients had improved performance scores.

Adverse events were similar between treatment groups
<table>
<tr><td></td><td>intervention</td><td>placebo</td></tr>
<tr><td>One point improvement in performance score</td><td>13/66 (19.7%)</td><td>4/66 (6.1%)</td></tr>
<tr><td>Two-point deterioration</td><td>1/66 (1.5%)</td><td>5/66 (7.6%)</td></tr>
</table>
</td>
<td>12 week Double-blind Placebo-controlled study.
Patients completing the 12 weeks could enter a subsequent optional 12 week phase of open-label epoetin alfa treatment.
The improvement in QOL and performance observed during the double-blind phase was generally maintained during the open-label phase, and patients who were previously in the placebo showed an improvement after switching to epoetin.

Changes in functional status and QOL in the study reported here were secondary efficacy assessments, and the study was not powered to measure absolute change, but rather</td>
</tr>
</table>

						in physical ability			statistical trends. The primary efficacy evaluation was transfusion requirements.
						Incidence of Adverse events	50/69 (72.5%)	57/76 (75%)	

1
2

References of included studies

1. Berenson, J. R. (2015). A phase 3 trial of armodafinil for the treatment of cancer-related fatigue for patients with multiple myeloma. Supportive Care in Cancer, 23, 1503-1512.
2. Coleman, E. A., Goodwin, J. A., Kennedy, R., Coon, S. K., Richards, K., Enderlin, C., Stewart, C. B., McNatt, P., Lockhart, K. & Anaissie, E. J. (2012) Effects of exercise on fatigue, sleep, and performance: a randomized trial. Oncology Nursing Forum, 39: 468-477.
3. Dammacco F, Castoldi G, Rödjer S. (2001) Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol. 113(1), 172-179.

1 Excluded papers (after checking full text)

PAPER	REASONS FOR EXCLUSION
1. Battaglini, C. L. (2011) Physical activity and hematological cancer survivorship. [Review]. Recent Results in Cancer Research, 186: 275-304.	Book chapter. Review. Only 1 page on studies conducted in myeloma patients with reference to 2 papers but these studies look at feasibility of exercise and not studies of interventions to reduce fatigue.
2. Bilotti, E., Gleason, C. & McNeill, A. (2011) Routine Health Maintenance in Patients Living With Multiple Myeloma. Clinical Journal of Oncology Nursing, 15: 25-40.	Review and nursing guidelines. Only 1 paragraph on fatigue. No mention of interventions for reducing fatigue.
3. Bergenthal, N., Will, A., Streckmann, F., Wolkewitz, K. D., Monsef, I., Engert, A. et al. (2014). Aerobic physical exercise for adult patients with haematological malignancies. Cochrane.Database.of Systematic.Reviews..	Includes Coleman trial – but no additional myeloma trials.
4. Birgegard, G., Gascon, P. & Ludwig, H. (2006) Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY. European Journal of Haematology, 77: 378-386.	Study looking at prevalence of anaemia and relationship between anaemia and performance status. Study does not look at interventions for reducing fatigue.
5. Bourantas, K. (1996) Recombinant human erythropoietin for the treatment of anemia in patients with multiple myeloma. Journal of Experimental and Clinical Cancer Research, 15: 371-374.	Treatment of anaemia in 19 patients with myeloma with recombinant human erythropoietin. No comparator. Fatigue not studied. It is stated that the patients had an improved quality of life but it is not stated how this was measured.
6. Coleman, E. A., Hall, B. J., Coon, S. & Stewart, C. B. (2003) Facilitating exercise adherence for patients with multiple myeloma. Clinical journal of oncology nursing., 7: 529-534, 540.	Descriptive study about patient adherence to exercise and patient experiences. Study does not discuss how effective the intervention is in reducing fatigue.
7. Coleman, E. A., Coon, S. K., Mattox, S. G. & O'Sullivan, P. (2002) Symptom management and successful outpatient transplantation for patients with multiple myeloma. Cancer Nursing, 25: 452-460.	Descriptive retrospective study. Study does not discuss methods to reduce fatigue.
8. de Nijs, E. J. M., Ros, W. & Grijpdonck, M. H. (2008) Nursing intervention for fatigue during the treatment for cancer. Cancer Nursing, 31: 191-206.	Systematic review to search for nursing interventions (non pharmacological interventions) to reduce fatigue caused by cancer treatment. 18 studies included (10: exercise, 5: education and counselling, 2: distraction and relaxation, 1: sleep promotion). Only 1 study on myeloma – Coleman.
9. Felbel, S., Meerpohl, J. J., Monsef, I., Engert, A., & Skoetz, N. (2014). Yoga in addition to standard care for patients with haematological malignancies. Cochrane.Database.of Systematic.Reviews..	Includes a single trial in lymphoma patients.
10. Garcia, M. K., McQuade, J., Lee, R., Haddad, R., Spano, M., & Cohen, L. (2014). Acupuncture for Symptom Management in Cancer Care: an Update. Current Oncology Reports, 16.	No analysis according to type of cancer
11. Groeneveldt, L., Mein, G., Garrod, R., Jewell, A. P., Van, S. K., Stephens, R., D'Sa, S. P. & Yong, K. L. (2013) A mixed exercise training programme is feasible and safe and may improve quality of life and muscle strength in multiple myeloma survivors. BMC Cancer, 13: 31.	Single arm study - no comparator.
12. Hirashima, K. (1994) The phase III multicenter open trial of recombinant human	Not comparative study.

erythropoietin (EPOCH) on anemic patients associated with marrow failure. Japanese Pharmacology and Therapeutics, 22: 211-236.	Paper in Japanese.
13. Jones LW, Courneya KS, Vallance JK, Ladha AB, Mant MJ, Belch AR, Stewart DA, Reiman T. (2004) Association between exercise and quality of life in multiple myeloma cancer survivors. Support Care Cancer 12(11):780-8.	Retrospective observational study design. Not comparative study.
14. Skoetz, N. (2014). Aerobic physical exercise for patients with haemtological malignancies. A systematic review and meta-analysis. Haematologica, Conference, 517.	Abstract only – results not reported separately for myeloma
15. Skoetz, N., Bergenthal, N., Will, A., Streckmann, F., Elter, T., & Engert, A. (2014). Physical exercise improves fatigue in patients with haematological malignancies: A Cochrane systematic review and meta-analysis. Oncology Research.and Treatment., 37, 277.	Abstract only – results not reported separately for myeloma
16. Strong, A. (2006) Recommended Exercise Protocol to Decrease Cancer-related Fatigue and Muscle Wasting in Patients With Multiple Myeloma: An Evidence-based Systematic Review. Topics in Geriatric Rehabilitation, 22: 172-186.	Review. Includes 20 papers but they are a mix of different cancers. Only 1 paper is specific to myeloma. Coleman et al.

1 Checklists to identify risk of bias

2

Study identification: Coleman et al 2012					
Myeloma			Topic Q		
Study Type			Randomised controlled trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? A qualitative analysis of the weekly exercise and activity reports showed that four patients in the HBIEP group did not exercise at all and that 22 patients in the control group had exercised beyond what was required of them.				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? There was no outcome data available from 4 out of the 95 patients in the intervention group and 17 of the 92 patients in the control group.				

	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

Study identification: Dammacco et al., 2001					
Myeloma			Topic Q		
Study Type			Randomised controlled trial		
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					

B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? 64/ 69 (92·8%) epoetin alfa patients and 61/76 (80·3%) placebo patients completed the 12 weeks of double-blind treatment. Five patients who received epoetin alfa discontinued prematurely, two because of adverse events (death due to septic shock, *n* = 1; disease progression, *n* = 1), and three for personal reasons. Fifteen patients who received placebo discontinued prematurely, three because of adverse events (pneumonia, *n* = 1; death due to septic shock, *n* = 1; death due to acute renal failure, *n* = 1); six because of disease progression; and six for personal (*n* = 3) or other unspecified reasons (*n* = 3).				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? Quality of life in the double-blind phase was evaluated for 66/69 epoetin alfa and 72/76 placebo patients. Performance score in the double-blind phase was evaluated for 66/69 epoetin alfa and 66/76 placebo patients. Adverse event data was available for all participants.				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other	Yes	No	Unclear	N/A

	important confounding and prognostic factors				
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1
2
3
4

Chapter 10: Monitoring

Review Question:

What is the optimal follow-up protocol for patients with myeloma (including duration, frequency, investigations and onward referral)?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients diagnosed with myeloma: • Asymptomatic myeloma • Symptomatic patients not on active therapy • Symptomatic patients on long term therapies	Follow-up protocols involving combinations of: • serum and urine electrophoresis and/or free light-chain determination • β2-microglobulin • serum quantitative immunoglobulins • imaging procedures (CT, MRI, radiograph, skeletal survey, PET-CT) • Bone marrow aspiration and biopsy • flow cytometry	Any other protocols	• Overall survival • progression free survival • Health-related quality of life • Adverse events • PROMs • Patient experience
Additional comments on PICO			
Look for any papers comparing follow-up protocols. As well as looking at the follow up procedures also look at the timings of the follow-up.			

Evidence statements

No studies were identified that investigated follow-up protocols for patients with myeloma. One observational study was identified that reported on patient monitoring/follow up after first line autologous stem cell transplant (ASCT) and ten studies were identified that investigated individual follow-up tests and their accuracy in detecting disease in the follow-up setting. Diagnostic accuracy is not listed in our review protocol or PICO but on discussion with the sub-group for this topic it was agreed that this evidence was of interest and clinical relevance to determine how accurate these tests are in follow up setting.

Observational data from 1 study

Evidence was identified from a retrospective study (Zamarin et al., 2013) examining the patterns of relapse or progression of disease (R/POD) in 273 patients treated with induction therapy followed by ASCT. The authors made several observations the most relevant ones being:

- The overwhelming majority of R/POD was associated with concurrent serological R/POD, with only a small percentage of patients (2%) presenting with symptomatic clinical disease in the absence of serological R/POD.
- A total of 85% had asymptomatic R/POD, first detected by serological testing, whereas 15% had symptomatic R/POD with aggressive disease, early R/POD and short survival, with poor cytogenetics and younger age identified as risk factors

- Although occult skeletal lesions were found in 40% of asymptomatic patients tested following serological R/POD, yearly skeletal surveys and urine testing were poor at heralding R/POD.

Diagnostic accuracy

10 diagnostic accuracy studies (with 22 - 168 patients) were identified and included in the evidence review (Bannas et al., 2012; Cascini et al., 2013; Derlin et al., 2012; Derline et al., 2013; Elliott et al., 2011; Fallahi et al., 2005; Harrington et al., 2009; Horger et al., 2007; Mele et al., 2007; Villa et al., 2005). They investigated lab tests, CD56 immunohistochemistry, and imaging methods including WB-MRI, WBLD-MDCT, FDG PET-CT and TC99MIBI. The results for diagnostic accuracy including sensitivity, specificity, positive predictive value and negative predictive value can be seen in table 1. The data indicate that lab tests and WMLD-MDCT are the most effective tests for detecting disease in follow up with the highest sensitivity, specificity and accuracy, whilst TC99MIBI and FDG PET-CT appear to be least effective.

Table 10.1: Diagnostic accuracy of various follow-up tests for detecting disease/remission following treatment

(Note: variability in reference standard used in different studies)

Index tests	study	TP	FN	FP	TN	sensitivity	specificity	PPV	NPV	accuracy
Whole body MRI	Bannas et al., 2012	7	4	3	19	64%	86%	70%	83%	79%
	Cascini et al., 2013	9	0	8	12	100%	60%	33%	100%	72%
	Derlin et al., 2013	8	2	13	8	80%	38%	38%	80%	52%
FDG PET/CT	Elliott et al., 2011	12	6	2	17	67%	89%	86%	74%	78%
	Cascini et al., 2013	7	2	4	16	78%	80%	64%	9%	79%
	Derlin et al., 2012	NR	NR	NR	NR	55%	82%	82%	54%	66%
	Derlin et al., 2013	5	5	3	18	50%	86%	63%	78%	74%
WBLD-MDCT	Horger et al., 2007	411	2	1	25	99.5%	96.2%	99.8%	92.6%	99.3%
TC99MIBI bone scan	Fallahi et al., 2005	NR	NR	NR	NR	69%	100%	100%	61%	79%
	Villa et al., 2005	10	1	3	4	91%	57%	77%	80%	78%
	Mele et al., 2007	62	77	4	25	45%	86%	94%	25%	52%
Lab tests	Elliott et al., 2011	16	2	4	15	89%	79%	80%	88%	84%
	Horger et al., 2007	413	0	0	26	100%	100%	100%	100%	100%
Lab tests + PET/CT	Elliott et al., 2011	12	2	0	13	86%	100%	100%	87%	93%
CD56 immunohistochemistry	Harrington et al., 2009	59	15	3	50	80%	94%	95%	77%	86%

TP: true positive, FN: false negative, FP: false positive, TN: true negative, PPV: positive predictive value, NPV: negative predictive value, NR: not reported

Study quality

The QUADAS-2 assessment tool was used to evaluate risk of bias in these studies. Generally there was a low risk of bias across the studies and the studies were found to be applicable to the review question. For some of the studies the risk of bias is unclear as there was under-reporting in some studies with regards to the timing of the index and reference tests. Also some studies did not report the patient selection methods and so it was unclear whether a consecutive or random sample of patients had been recruited and if inappropriate exclusions had been avoided.

Other limitations of the included studies are that they are mostly single centre studies and many have small sample sizes. Furthermore, the patient populations studied are heterogeneous in that the patients included have undergone different treatments. However the studies aim to evaluate the performance of the diagnostic test for reevaluation of myeloma post treatment rather than efficacy of a specific treatment approach, and these differences in prior treatment may well reflect clinical reality.

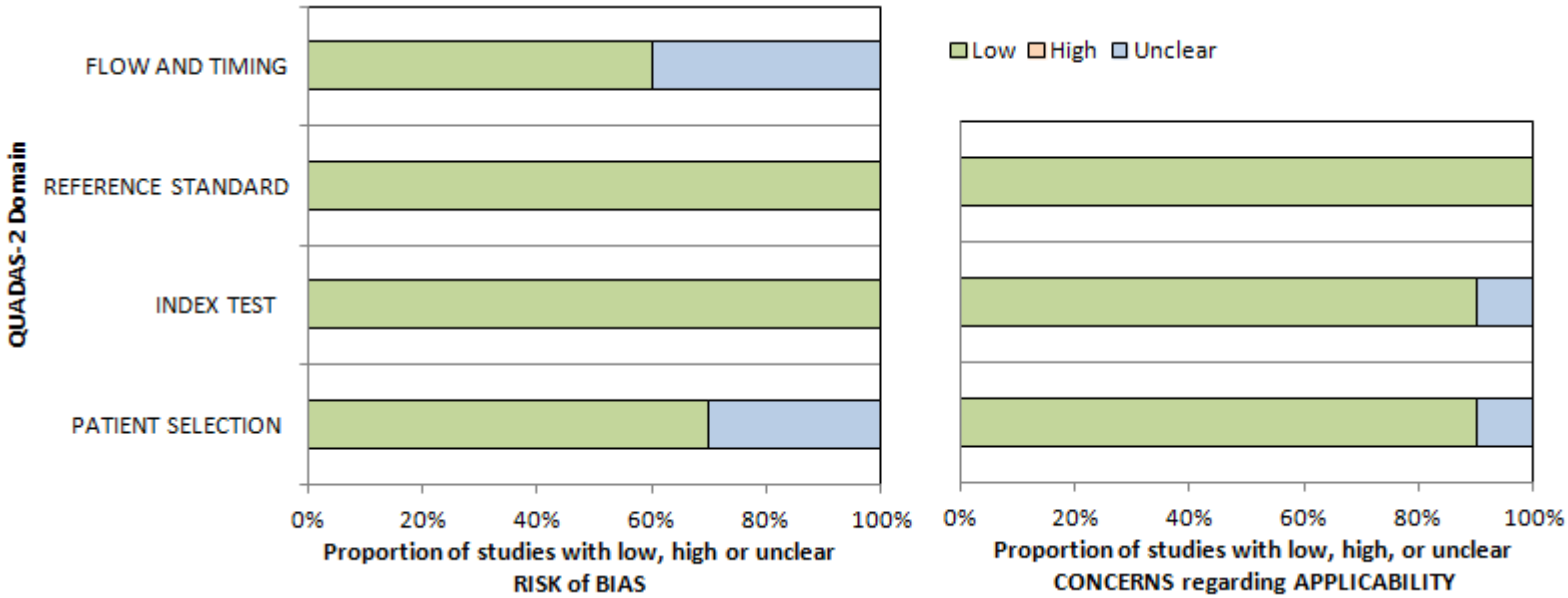
When comparing the results of the different diagnostic accuracy studies it is important to note that there is variability in the reference standards used in the different studies. Although a majority studies use the European group for blood and marrow transplantation criteria modified by the international uniform response criteria for multiple myeloma (panel of hematological and immunological parameters and bone marrow aspiration or biopsy where appropriate) there are some studies which use different criteria to establish the presence of disease.

Figure 10.1: Risk of bias and applicability for individual studies

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Bannas et al., 2012	☺	☺	☺	☺	☺	☺	☺
Cascini et al., 2013	☺	☺	☺	☺	☺	☺	☺
Derlin et al., 2012	☺	☺	☺	?	☺	☺	☺
Derlin et al., 2013	☺	☺	☺	☺	☺	☺	☺
Elliot et al., 2011	☺	☺	☺	?	☺	☺	☺
Fallahi et al., 2005	?	☺	☺	☺	☺	☺	☺
Harrington et al., 2010	?	☺	☺	?	☺	☺	☺
Horger et al., 2007	☺	☺	☺	?	☺	☺	☺
Mele et al., 2007	?	☺	☺	☺	☺	☺	☺
Villa et al., 2005	☺	☺	☺	☺	☺	☺	☺

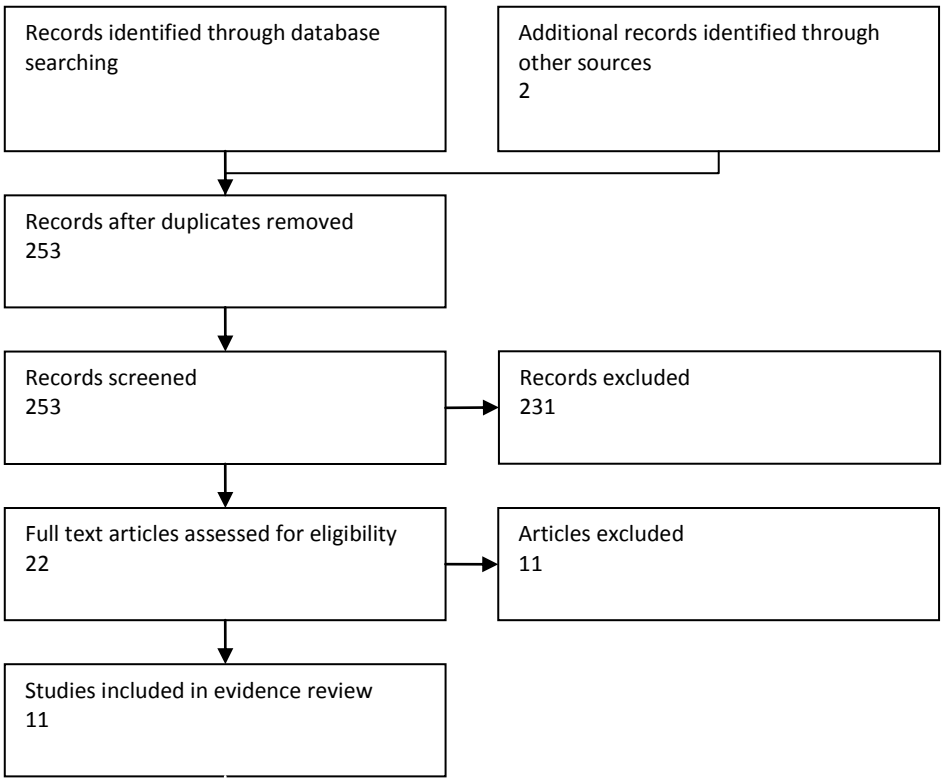
☺Low Risk ☹High Risk ? Unclear Risk

Figure 10.2: Risk of bias and applicability across studies



Search Results

Figure 10.3: Screening results



Evidence table

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Bannas et al., 2012

Germany

Retrospective study to compare tests for detecting persistent or relapsing disease after SCT</td>
<td>33 consecutive patients with myeloma who had received SCT (all 33 patients received autologous SCT, 26 additionally received allogeneic SCT)

Mean age 52 ± 11.8 years (range 31-73 years)

19 male; 14 female</td>
<td><u>whole body MRI</u>
multistation WMRI was performed with the integrated body coil in the spine position with 8 stations covering the whole body.

Time span between first diagnosis and first WBMRI was 5±3.7 years.
Mean time between SCT and first WBMRI was 2.4±2.2 years.
Time span between first and second WBMRI was 1.3±0.8 years.</td>
<td><u>Lab tests</u>
Patients with IgG or IA secreting myeloma: Monoclonal protein concentration measurements in serum

Patients in partial remission:
Serum protein electrophoresis was used for protein quantification

Patients in complete remission:
Immunofixation electrophoresis

Patients with light-chain secreting myeloma:
Quantitative measurements of free light chains in 24hr urine and serum</td>
<td>
<table>
<tr><th></th><th>WBMRI positive</th><th>WBMRI negative</th></tr>
<tr><td>Serum positive</td><td>7</td><td>4</td></tr>
<tr><td>serum negative</td><td>3</td><td>19</td></tr>
</table>
<table>
<tr><th></th><th>WBMRI</th></tr>
<tr><td>sensitivity</td><td>64%</td></tr>
<tr><td>specificity</td><td>86%</td></tr>
<tr><td>PPV</td><td>70%</td></tr>
<tr><td>NPV</td><td>83%</td></tr>
<tr><td>accuracy</td><td>79%</td></tr>
</table>
</td>
<td>Limitations:
• small sample size

• the patients included did not have an identical treatment protocol before SCT (however study aimed to assess diagnostic performance of WBMRI rather than efficacy of a specific treatment approach)</td>
</tr>
<tr>
<td>Cascini et al., 2013

Italy

Study to estimate diagnostic accuracy of tests</td>
<td>22 consecutive patients that underwent at least 1 reassessment after treatment (chemotherapy or autologous transplant)

range 48-83 years

10 male; 12 female</td>
<td><u>WBMRI</u>
All images were initially obtained in the coronal plane.
T1-weighted short tau inversion recovery images for 7 different body stations were acquired.
Spine was imaged in the sagittal plane using T1 weighted turbo spin echo T1 and STIR sequences.

<u>PET/CT</u>
FDG-PET/CT.
Whole body scan from head to toe was obtained using 9 to 12 consecutive field of view.

Imaging was done 2 months after the end of last treatment cycle</td>
<td><u>bone marrow aspiration or biopsy</u>
samples obtained from the posterior iliac crest</td>
<td>29 follow up assessments (as 7 patients underwent a second whole body assessment at a later date)
<table>
<tr><th></th><th>PET-CT positive</th><th>PET-CT negative</th></tr>
<tr><td>Bone marrow positive</td><td>7</td><td>2</td></tr>
<tr><td>Bone marrow negative</td><td>4</td><td>16</td></tr>
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<table>
<tr><th></th><th>WBMRI positive</th><th>WBMRI negative</th></tr>
<tr><td>Bone marrow positive</td><td>9</td><td>0</td></tr>
<tr><td>Bone marrow negative</td><td>8</td><td>12</td></tr>
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<table>
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<tr><td>specificity</td><td>80%</td><td>60%</td></tr>
<tr><td>PPV</td><td>64%</td><td>33%</td></tr>
<tr><td>NPV</td><td>89%</td><td>100%</td></tr>
<tr><td>accuracy</td><td>79%</td><td>72%</td></tr>
</table>
</td>
<td>Limitations:
• small sample size</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Derlin et al., 2012

Germany
(same group as Bannas et al., 2012 paper)

Retrospective study to determine the diagnostic performance of FGF PET-CT for detection of residual or recurrent disease after SCT.</td>
<td>99 patients with myeloma who had received SCT and had been referred for reevaluation (all 99 patients received autologous SCT, 72 additionally received allogeneic SCT)

Mean age 54.6 ± 9.7 years (range 31.4-72.7 years)

62 male; 37 female

Mean disease duration at time of PET/CT: 56.0±40.0 months
Range 5.4-186.5

Mean time interval between last SCT and imaging: 33.9±31.5 months (range 1.2-143.1).</td>
<td><u>FDG PET/CT</u>
After uptake period of 60nim imaging started with a low dose CT of the whole body. Then a total body emission data acquisition was performed in the caudocranial direction with 90s per bed position at the head and thorax, and 60s at the legs.</td>
<td>European group for blood and marrow transplantation criteria modified by the international uniform response criteria for multiple myeloma.
Panel of hematological and immunological parameters and underwent bone marrow aspiration or biopsy where appropriate.</td>
<td>
<table>
<tr><th></th><th>PET-CT positive</th><th>PET-CT negative</th></tr>
<tr><td>Gold standard positive</td><td>NR</td><td>NR</td></tr>
<tr><td>Gold standard negative</td><td>NR</td><td>NR</td></tr>
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Raw data for 2x2 table not reported

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<tr><td>sensitivity</td><td>54.6%</td></tr>
<tr><td>specificity</td><td>82.1%</td></tr>
<tr><td>PPV</td><td>82.3%</td></tr>
<tr><td>NPV</td><td>54.2%</td></tr>
<tr><td>Overall accuracy</td><td>65.5%</td></tr>
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</td>
<td>Limitations:

• raw data not provided for 2x2 table

• the patients included did not have an identical treatment protocol before SCT (however study aimed to evaluate performance of imaging for reevaluation of myeloma post SCT rather than efficacy of a specific treatment approach) and these differences in prior treatment may well reflect clinical reality.</td>
</tr>
<tr>
<td>Derlin et al., 2013

Germany
(same group as Bannas et al., 2012 paper)

Retrospective study to compare diagnostic performance of tests for determination of remission status after SCT.</td>
<td>31 consecutive patients with myeloma who had received SCT and had been referred for reevaluation (all 31 patients received autologous SCT, 24 additionally received allogeneic SCT)

Mean age 55 ± 9.9 years (range 38.6-73.3 years)

18 male; 13 female

Mean disease duration: 66.3±48.3 months
Range 5.4-168.3</td>
<td><u>WBMRI</u>
Multistack WBMRI was performed using the integrated body coil. Patients were imaged in the supine position with 8 stacks covering the entire body

<u>FDG PET/CT</u>
After uptake period of 60nim imaging started with a low dose CT of the whole body. Then a total body emission data acquisition was performed in the caudocranial direction with 90s per bed position at the head and thorax, and 60s at the legs.

Mean time interval between last SCT and imaging: 37.4±38.1 months (range 2.4-143.1).</td>
<td>European group for blood and marrow transplantation criteria modified by the international uniform response criteria for multiple myeloma.
Panel of haematological and immunological parameters and underwent bone marrow aspiration or biopsy where appropriate.</td>
<td>
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<tr><th></th><th>WBMRI positive</th><th>WBMRI negative</th></tr>
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<table>
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<tr><td>specificity</td><td>85.7%</td><td>38.1%</td></tr>
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<tr><td>NPV</td><td>78.3%</td><td>80%</td></tr>
<tr><td>Overall accuracy</td><td>74.2%</td><td>51.6%</td></tr>
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<td>Limitations:
• small sample size

• the patients included did not have an identical treatment protocol before SCT (however study aimed to evaluate performance of imaging for reevaluation of myeloma post SCT rather than efficacy of a specific treatment approach) and these differences in prior treatment may well reflect clinical reality.

• the definition of PET+ focal lesions as lesions corresponding to CT abnormalities might have reduced the sensitivity and consequently increased the false-negative rate, because there may be bone lesions without a corresponding pathology on CT. (However the authors prefer high specificity over high sensitivity to avoid unnecessary diagnostic (i.e., biopsy) or therapeutic procedures)</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Elliott et al., 2011

USA

Retrospective study to determine effectiveness of PET/CT and lab tests for detecting relapse/progression in myeloma</td>
<td>37 previously treated myeloma patients.

Median age 60.8
(range 43.9-78.9 years)

19 male; 18 female</td>
<td><u>PET/CT</u>
Whole body FDG-PET-CT

<u>Lab tests</u>
Serum chemistry
B2 microglobulin
Serum and urine protein electrophoresis with immunofixation
Serum free light chains

Median time from therapy to PET/CT imaging: 12 months (1-110)

Patients were followed for a median of 20.1 months (range 6.3-146.1)</td>
<td><u>2009 IMWG guidelines for the uniform reporting of clinical trials in myeloma.</u></td>
<td>After 12 months follow up:

<table>
<tr><th></th><th>Lab tests positive</th><th>Lab tests negative</th></tr>
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<tr><td>Gold standard negative</td><td>2</td><td>17</td></tr>
</table>

<table>
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<tr><td>specificity</td><td>89%</td><td>79%</td><td>100%</td></tr>
<tr><td>PPV</td><td>86%</td><td>80%</td><td>100%</td></tr>
<tr><td>NPV</td><td>74%</td><td>88%</td><td>87%</td></tr>
<tr><td>accuracy</td><td>78%</td><td>84%</td><td>93%</td></tr>
</table>
</td>
<td>Limitations:
• small sample size

• retrospective design resulted in heterogeneity of the data available including time intervals between lab draws and inconsistent use of bone marrow biopsies and non-PET/CT imaging.

• treatment strategies, post-treatment disease course and disease status at time of PET/CT scan were highly variable</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Fallahi et al., 2005

Iran

Study to determine the diagnostic value of TC99MIBI in differentiating active disease from remission.</td>
<td>43 myeloma patients.

Age 52+10 years

32 male; 11 female

Group A: Active disease: n=29
A1: new cases without previous treatment n=6
A2 previously treated with chemotherapy, radiotherapy or transplant n=23

Group B: Remission: n=14

All patients were followed for at least one year and reexamined every 3 months.</td>
<td><u>Tc99MIBI</u>
20mins following the intravenous injection of 555 MBq of ^{99m}Tc-MIBI, a whole body scan was carried out in the anterior and posterior projections.</td>
<td>Plasma protein electrophoresis
Serum immune-electrophoresis
Bone marrow biopsy
Complete peripheral blood count
Assessment of urinary excretion of Bence-Jones protein
ESR
Serum alkaline phosphatase</td>
<td>
<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>Reference standard positive</td><td>NR</td><td>NR</td></tr>
<tr><td>Reference standard negative</td><td>NR</td><td>NR</td></tr>
</table>
Raw data for 2x2 table not reported

<table>
<tr><th></th><th>Tc99MIBI</th></tr>
<tr><td>sensitivity</td><td>69%</td></tr>
<tr><td>specificity</td><td>100%</td></tr>
<tr><td>PPV</td><td>100%</td></tr>
<tr><td>NPV</td><td>61%</td></tr>
<tr><td>accuracy</td><td>79%</td></tr>
</table>
</td>
<td>Limitations:
• small sample size

• raw data not provided for 2x2 table

• treatment strategies differ amongst patients</td>
</tr>
<tr>
<td>Harrington et al., 2009

USA

Retrospective study to characterize potential of CD56 immunohistochemistry in residual disease monitoring</td>
<td>127 myeloma post-treatment bone marrow specimens from 111 myeloma patients who had undergone various treatment protocols

Median age 57.8 years
Range 35-78 years

65 male; 46 female</td>
<td><u>CD56 immunohistochemistry</u>
An indirect immunoperoxidase staining method was performed on Bouin-fixed, paraffin-embedded, 3-µm-thick tissue sections, using mouse anti-CD56 antibodies.</td>
<td><u>conventional criteria</u>
abnormal plasma cell morphologic features flow cytometry
light chain restriction by immunohistochemical studies</td>
<td>
<table>
<tr><th></th><th>CD56 positive</th><th>CD56 negative</th></tr>
<tr><td>Reference standard positive</td><td>59</td><td>15</td></tr>
<tr><td>Reference standard negative</td><td>3</td><td>50</td></tr>
</table>

<table>
<tr><th></th><th>CD56 immunohistochemistry</th></tr>
<tr><td>sensitivity</td><td>80%</td></tr>
<tr><td>specificity</td><td>94%</td></tr>
<tr><td>PPV</td><td>95%</td></tr>
<tr><td>NPV</td><td>77%</td></tr>
<tr><td>accuracy</td><td>86%</td></tr>
</table>
</td>
<td>Limitations:

• treatment strategies differ amongst patients</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Horger et al., 2007

Germany

Prospective study to establish the value of tests for follow-up</td>
<td>131 consecutive myeloma patients

Mean age 61.2 years
Range 40-86 years

73 male; 58 female</td>
<td><u>WBLD-MDCT</u>
CT was performed non-enhanced (without oral or intravenous contrast dye application) on an MDCT scanner.
The scan length was in all patients 1530.6 mm stretching from the roof of the skull down to the knees including the entire skull, axial skeleton, thoracic café and the arms down to the elbows.

<u>Hematological parameters/laboratory data</u>
Levels of serum Ig, hemoglobin, B2 microglobulin and creatinine. Protein electophoresis to detect bence-jones protein in urine.</td>
<td>European group for blood and marrow transplantation response criteria</td>
<td>Median interval of hematologic follow-up after diagnosis or after therapy was 3 months.
WBLD-CT follow-up lasted from 3 months to 40 months (median 20 months) between the first and last visits.

439 assessments were performed in131 patients.

<table>
<tr><th></th><th>Lab tests positive</th><th>Lab tests negative</th></tr>
<tr><td>Gold standard positive</td><td>413</td><td>0</td></tr>
<tr><td>Gold standard negative</td><td>0</td><td>26</td></tr>
</table>

<table>
<tr><th></th><th>WBLD-MDCT positive</th><th>WBLD-MDCT negative</th></tr>
<tr><td>Gold standard positive</td><td>411</td><td>2</td></tr>
<tr><td>Gold standard negative</td><td>1</td><td>25</td></tr>
</table>

<table>
<tr><th></th><th>Lab tests</th><th>WBLD-MDCT</th></tr>
<tr><td>sensitivity</td><td>100%</td><td>99.5%</td></tr>
<tr><td>specificity</td><td>100%</td><td>96.2%</td></tr>
<tr><td>PPV</td><td>100%</td><td>99.8%</td></tr>
<tr><td>NPV</td><td>100%</td><td>92.6%</td></tr>
<tr><td>Overall accuracy</td><td>100%</td><td>99.3%</td></tr>
</table>

For specific diagnosis hematological parameters proved correct in 84% of all examinations, whereas WBLD-MDCT resulted in correct assessment in 94% of all examinations:</td>
<td>Limitations:

• treatment strategies differ amongst patients</td>
</tr>
</table>

<table>
<tr><th>Paper</th><th>Population</th><th>Index tests</th><th>Reference Standard</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Mele et al., 2007

Italy

Multicentre study to determine the diagnostic value of TC99MIBI in differentiating active disease from remission</td>
<td>168 myeloma patients at follow up

Median age 63 years
Range 35-82 years

86 male; 82 female</td>
<td><u>TC99MIBI</u>
99mTc-MIBI at the dose 740MBq was administered in an antecubital vein and anterior and posterior whole body scans were obtained after 20 min using a large field of view gamma camera.</td>
<td>Clinical status at time of TC99MIBI was assessed by complete clinical and biochemical evaluations including complete blood count, renal and liver function tests, protein electrophoresis plus evaluation of monoclonal component (MC), urinary light chain excretion and 24-h proteinuria, erythrocyte sedimentation rate (ESR), lactate-dehydrogenase (LDH), C-reactive protein (CRP), b2-microglobulin (b2M) and bone marrow plasma cell infiltration. Response to therapy was evaluated according the criteria published by Blade et al (1998) – European group for blood and marrow transplant.</td>
<td>
<table>
<tr><th></th><th>TC99MIBI positive</th><th>TC99MIBI negative</th></tr>
<tr><td>Reference standard positive</td><td>62</td><td>77</td></tr>
<tr><td>Reference standard negative</td><td>4</td><td>25</td></tr>
</table>
<table>
<tr><th></th><th>Tc99MIBI</th></tr>
<tr><td>sensitivity</td><td>45%</td></tr>
<tr><td>specificity</td><td>86%</td></tr>
<tr><td>PPV</td><td>94%</td></tr>
<tr><td>NPV</td><td>25%</td></tr>
<tr><td>accuracy</td><td>52%</td></tr>
</table>
TC99MIBI has high specificity to identify absence of disease (patients in complete remission) but is less sensitive for the identification of residual disease when response is not complete.
</td>
<td>Limitations:

• unclear timing of tests and whether analysed blinded to each other

• treatment strategies differ amongst patients</td>
</tr>
</table>

Paper	Population	Index tests	Reference Standard	Results	Additional comments
Villa et al., 2005 Italy 5 year single centre experience to evaluate the diagnostic value of TC99MIBI in the detection of bone marrow involvement in follow up	110 consecutive patients in the whole study Mean age 62 years Range 41-87 years 58 male; 52 female 18 patients with active myeloma underwent at least 1 course of high dose alkylating agent chemotherapy supported by peripheral blood stem cells transplantation and were re-evaluated using TC99MIBI. Follow up was performed once in 12 patients and twice in 6 patients.	TC99MIBI Anterior and posterior whole body scans were obtained 20 minutes after the iv injection of 740MBq of TC99MIBI	Clinical status at time of TC99MIBI was assessed by complete clinical and biochemical evaluations including complete blood count, renal and liver function tests, protein electrophoresis and evaluation of monoclonal component (MC),serum immunoglobulin concentration, C-reactive protein (CRP), b2-microglobulin (b2M.), urinary light chain excretion, 24-h proteinuria, and bone marrow biopsy.	**TC99MIBI positive** / **TC99MIBI negative** **Reference standard positive**: 10 / 1 **Reference standard negative**: 3 / 4 **Tc99MIBI** sensitivity 90.9% specificity 57.1% PPV 76.9% NPV 80% accuracy 77.8%	**Limitations:** • small sample size • Interval between baseline and follow up scan was guided by clinical judgment and evaluation of biochemical analysis. Possible that short time from therapy to scan could result in false negative scan.

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Paper	Population	Methods	observations	Potential impact of observation on current practice
Zamarin et al., 2013 USA Retrospective observational study examining R/POD after first line ASCT	273 patients with myeloma who underwent ASCT as part of first line therapy. Mean age at diagnosis 57 years. 163 male; 110 female	The standard IMWG criteria for disease response, relapse and progression were used for determination of serological, urinary and clinical R/POD.	• The majority (98%) of R/POD is associated with serological evidence of R/POD. - Only 2% of patients had symptomatic R/POD without evidence of serological R/POD. • The majority (85%) of patients with R/POD have asymptomatic R/POD. Symptomatic disease is associated with younger age, poor cytogenetic and shorter PFS and post-R/POD survival. • New proposed criteria for relapse in patients with FLC only disease (currently there are no IMWG criteria available). • Annual skeletal survey was not useful in any patients to predict R/POD. • Urine testing was not useful to predict R/POD except in a few patients in CR. • The association between patterns of paraprotein at diagnosis and relapse is predictable and versatile. • A significant percentage of patients with asymptomatic serological R/POD actually have occult bone lesions (40%).	• Serological follow-up may be sufficient to monitor patients. • Younger patients with poor cytogenetics may need closer monitoring. • New criteria using FLC assay could be used to detect relapse even in patients with measurable M spike. • Annual skeletal survey is not recommended for routine monitoring. • Routine urine testing is possibly not recommended for routine monitoring predict R/POD except in a few patients in CR. • Allows to predict patterns of paraprotein at relapse and mitigates the current IMWG recommendation to 'follow patients using the same method' as at diagnosis. • Imaging at serological R/POD is recommended in asymptomatic patients, recommendation that departs from the current IMWG recommendation that 'CT, MRI and PET may be indicated according to clinical circumstances' at R/POD.

References of included studies

1. Bannas, P., Hentschel, H. B., Bley, T. A., Treszl, A., Eulenburg, C., Derlin, T., Yamamura, J., Adam, G., Stubig, T., Kroger, N., Weber, C. (2012) Diagnostic performance of whole-body MRI for the detection of persistent or relapsing disease in multiple myeloma after stem cell transplantation. *European Radiology,* 22: 2007-2012.
2. Cascini, G. L., Falcone, C., Console, D., Restuccia, A., Rossi, M., Parlati, A., Tamburrini, O. (2013) Whole-body MRI and PET/CT in multiple myeloma patients during staging and after treatment: personal experience in a longitudinal study. *Radiologia Medica,* 118: 930-948.
3. Derlin, T., Weber, C., Habermann, C.R., Herrmann, J., Wisotzki, C., Ayuk, F., Wolschke, C., Klutmann S., Kröger, N. (2012) 18F-FDG PET/CT for detection and localization of residual or recurrent disease in patients with multiple myeloma after stem cell transplantation. Eur J Nucl Med Mol Imaging 39(3), 493-500.
4. Derlin, T., Peldschus, K., Munster, S., Bannas, P., Herrmann, J., Stubig, T., Habermann, C. R., Adam, G., Kroger, N. & Weber, C. (2013) Comparative diagnostic performance of 8F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. *European Radiology,* 23: 570-578.
5. Elliott, B.M., Peti, S., Osman, K., Scigliano, E., Lee, D., Isola, L., Kostakoglu, L. (2011) Combining FDG-PET/CT with laboratory data yields superior results for prediction of relapse in multiple myeloma. *European Journal of Haematology,* 86: 289-298.
6. Fallahi, B., Saghari, M., Fard Esfahani, A., Eftekhari, M., Iravani, M., Beiki, D., Dabbagh Kakhki, V.R,, Sadeghi, R. (2005) The value of 99mTc-MIBI whole body scintigraphy in active and in remission multiple myeloma. *Hellenic Journal of Nuclear Medicine,* 8: 165-168.
7. Harrington, A. M., Hari, P., Kroft, S. H. (2009) Utility of CD56 immunohistochemical studies in follow-up of plasma cell myeloma. *American Journal of Clinical Pathology,* 132: 60-66.
8. Horger, M., Kanz, L., Denecke, B., Vonthein, R., Pereira, P., Claussen, C. D., Driessen, C. (2007) The benefit of using whole-body, low-dose, nonenhanced, multidetector computed tomography for follow-up and therapy response monitoring in patients with multiple myeloma. *Cancer,* 109: 1617-1626.
9. Mele, A., Offidani, M., Visani, G., Marconi, M., Cambioli, F., Nonni, M., Catarini, M., Brianzoni, E., Berbellini, A., Ascoli, G., Brunori, M., Agostini, V., Corvatta, L., Isidori, A., Spinelli, A., Gradari, M., Leoni, P. (2007) Technetium-99m sestamibi scintigraphy is sensitive and specific for the staging and the follow-up of patients with multiple myeloma: a multicentre study on 397 scans. *British Journal of Haematology,* 136: 729-735.
10. Villa, G., Balleari, E., Carletto, M., Grosso, M., Clavio, M., Piccardo, A., Rebella, L., Tommasi, L., Morbelli, S., Peschiera, F., Gobbi, M., Ghio, R. (2005) Staging and therapy monitoring of multiple myeloma by 99mTc- sestamibi scintigraphy: A five year single center experience. *Journal of Experimental and Clinical Cancer Research,* 24: 355-361.
11. Zamarin, D., Giralt, S., Landau, H., Lendvai, N., Lesokhin, A., Chung, D., Koehne, G., Chimento, D., Devlin, S.M., Riedel, E., Bhutani, M., Babu, D., Hassoun, H. (2013) Patterns of relapse and progression in multiple myeloma patients after auto-SCT: implications for patients' monitoring after transplantation. Bone Marrow Transplantation 48, 419–424.

Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. Caers, J., Withofs, N., Hillengass, J., Simoni, P., Zamagni, E., Hustinx, R. & Beguin, Y. (2014) The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. *Haematologica,* 99: 629-637.	Expert review
2. Decaux, O. (2013) Multiple myeloma in clinical practice: From diagnosis to treatment and follow-up. *Biochimica Clinica,* Conference: S65.	Abstract
3. [1]Dimopoulos et al. (2011) Consensus recommendations for standard investigative workup: report of the International MyelomaWorkshop Consensus Panel 3. Blood 117: 4701-4705.	International myeloma working group recommendations – based on consensus.
4. Durie, B. G., Harousseau, J. L., Miguel, J. S., Blade, J., Barlogie, B.,	Not relevant to PICO.

	Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G., Rajkumar, S. V. & International Myeloma Working Group. (2006) International uniform response criteria for multiple myeloma.[Erratum appears in Leukemia. 2007 May;21(5):1134], [Erratum appears in Leukemia. 2006 Dec;20(12):2220]. *Leukemia,* 20: 1467-1473.	Development of new response criteria for myeloma – based on consensus.
5.	Dutoit, J. C., Vanderkerken, M. A. & Verstraete, K. L. (2013) Value of whole body MRI and dynamic contrast enhanced MRI in the diagnosis, follow-up and evaluation of disease activity and extent in multiple myeloma. *European Journal of Radiology,* 82: 1444-1452.	Outcomes not relevant for PICO.
6.	Fenchel, M., Konaktchieva, M., Weisel, K., Kraus, S., Claussen, C. D. & Horger, M. (2010) Response assessment in patients with multiple myeloma during antiangiogenic therapy using arterial spin labeling and diffusion-weighted imaging: a feasibility study. *Academic Radiology,* 17: 1326-1333.	Feasibility study of 10 patients. Extended study of 19 patients reported in next paper. Outcomes not relevant for PICO.
7.	Fenchel, M., Konaktchieva, M., Weisel, K., Kraus, S., Brodoefel, H., Claussen, C. D. & Horger, M. (2010) Early response assessment in patients with multiple myeloma during anti-angiogenic therapy using arterial spin labelling: first clinical results. *European Radiology,* 20: 2899-2906.	Outcomes not relevant for PICO.
8.	Joshi, R., Horncastle, D., Elderfield, K., Lampert, I., Rahemtulla, A. & Naresh, K. N. (2008) Bone marrow trephine combined with immunohistochemistry is superior to bone marrow aspirate in follow-up of myeloma patients. *Journal of Clinical Pathology,* 61: 213-216.	No comparison to reference standard and so diagnostic accuracy cannot be calculated. No clinical outcomes of relevance.
9.	Lin, C., Luciani, A., Belhadj, K., Deux, J. F., Kuhnowski, F., Maatouk, M., Beaussart, P., Cuenod, C. A., Haioun, C. & Rahmouni, A. (2010) Multiple myeloma treatment response assessment with whole-body dynamic contrast-enhanced MR imaging. *Radiology,* 254: 521-531.	Outcomes not relevant to PICO
10.	Shortt, C. P., Carty, F. & Murray, J. G. (2010) The role of whole-body imaging in the diagnosis, staging, and follow-up of multiple myeloma. [Review] [44 refs]. *Seminars in Musculoskeletal Radiology,* 14: 37-46.	Expert review
11.	Wirk, B. (2011) The serum free light chain assay allows earlier detection of relapse/progression of multiple myeloma after autologous hematopoietic cell transplantation. *Blood,* Conference: 21.	Abstract

1 *Checklists to identify risk of bias*

Study: Bannas et al., 2012		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	33 patients with myeloma who had received SCT	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias.
B. Concerns regarding applicability		
Patient characteristics and setting	N=33 Inclusion criteria: patients with myeloma who had received SCT Exclusion criteria: claustrophobia, metallic implants or implanted electronic devices. Clinical setting: secondary/tertiary care. Germany.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		

A. Risk of bias		
Index test		**WBMRI**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**Serum lab tests**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Haematological parameters were determined at same time point as imaging.	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		No – different tests were done depending on whether the patient had disease (and depending on type of myeloma) or was in remission.
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

1

2

3

Study: Cascini et al., 2013		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	22 patients that underwent at least 1 reassessment after treatment	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias.
B. Concerns regarding applicability		
Patient characteristics and setting	N=22 Inclusion criteria: patients with myeloma who had undergone at least 1 reassessment after treatment Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern

INDEX TEST		
A. Risk of bias		
Index test		**WBMRI**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Index test		**PET/CT**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	**Serum lab tests**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	WBMRI and PET/CT performed within 2 weeks of each other. Bone marrow aspirate or biopsy procedures were performed at least 15 days before imaging.	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

1

Study: Derlin et al., 2012		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	99 patients with myeloma who had received SCT	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias.
B. Concerns regarding applicability		
Patient characteristics and setting	N=99 Inclusion criteria: - Image data digitally available for retrospective analysis - Prior autologous or allogeneic SCT	

	- Time interval between PET/CT and assessment of haematological and immunologic parameters < 2 weeks Exclusion criteria: - Inability or unwillingness to provide informed consent for retrospective analysis of the data - Chemotherapy in the preceding 8 weeks - Radiation therapy in the preceding 8 weeks Clinical setting: secondary/tertiary care. Germany.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**PET/CT**
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**European group for blood and marrow transplantation criteria modified by the international uniform response criteria for multiple myeloma**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	Not reported
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk of bias
Comments	n/a

1

Study: Derlin et al., 2013	
PATIENT SELECTION	
A. risk of bias	
Patient sampling	31 patients with myeloma who had received SCT
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	Low risk of bias.
B. Concerns regarding applicability	

Patient characteristics and setting	N=31 Inclusion criteria: - Image data digitally available for retrospective analysis - Prior autologous or allogeneic SCT - Time interval between PET/CT and MRI < 4 weeks - Time interval between PET/CT and assessment of haematological and immunologic parameters < 2 weeks Exclusion criteria: - Inability or unwillingness to provide informed consent for retrospective analysis of the data - Chemotherapy in the preceding 8 weeks - Radiation therapy in the preceding 8 weeks - claustrophobia, metallic implants or implanted electronic devices - elevated serum creatinine concentrations Clinical setting: secondary/tertiary care. Germany.
Are there concerns that the included patients and setting do not match the review question?	Low concern
INDEX TEST	
A. Risk of bias	
Index test	**WBMRI**
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
Index test	**PET/CT**
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern
REFERENCE STANDARD	
A. risk of bias	
Reference standard(s)	**European group for blood and marrow transplantation criteria modified by the international uniform response criteria for multiple myeloma**
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk of bias
B. Concerns regarding applicability	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Low concern
FLOW AND TIMING	
A. risk of bias	
Flow and timing	WBMRI and PET/CT performed within 2 weeks of each other. Bone marrow aspirate or biopsy procedures were performed at least 15 days before imaging.
Was there an appropriate interval between index test and	Yes

reference standard?	
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk of bias
Comments	n/a

1

Study: Elliot et al., 2011		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	37 previously treated myeloma patients	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias.
B. Concerns regarding applicability		
Patient characteristics and setting	N=37 Inclusion criteria: - PET/CT imaging performed specifically for the assessment of myeloma - Relevant laboratory data performed with 3 weeks of PET/CT Exclusion criteria: - PET/CT performed for a reason other than to evaluate myeloma - Plasmacytomas were the only evidence of disease and identified only on PET/CT and identified only on PET/CT - Individual PET/CT scans were excluded it treatment was administered within the one month prior to the PET/CT Clinical setting: secondary/tertiary care. USA.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**FDG-PET-CT**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Index test		**Lab tests**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
REFERENCE STANDARD		
A. risk of bias		
Reference standard(s)	2009 IMWG guidelines for the uniform reporting of clinical trials in myeloma	
Is the reference standard likely to correctly classify the target condition?		Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Lab tests were performed with 3 weeks of PET/CT but the timing of the reference standard is unclear	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Unclear risk of bias
Comments	n/a	

1

Study: Fallahi et al., 2005		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	43 patients with myeloma	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclear risk of bias.
B. Concerns regarding applicability		
Patient characteristics and setting	N=43 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Iran.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Reference standard(s)	**Lab tests and Bone marrow biopsy**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

FLOW AND TIMING		
A. risk of bias		
Flow and timing	TC99MIBI was performed day after reference standard	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

1

Study: Harrington et al., 2010		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	111 previously treated myeloma patients	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclear risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=111 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. USA.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		CD56 immunohistochemistry
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Reference standard(s)	**Conventional criteria**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Not reported	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Unclear risk of bias
Comments	n/a	

1

Study: Horger et al., 2007		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	131 myeloma patients	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=131 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Germany.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**WBLD-MDCT**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Index test		**Hematological parameters/laboratory data**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Reference standard(s)	**European group for blood and marrow transplantation response criteria**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Mean time interval between assessing haematologic parameters and performing WBLD-MDCT was -0.1 days (sd 17.8 days). In 54% of patients both examinations were performed on the same day. Unclear when reference standard test were performed.	
Was there an appropriate interval between index test and reference standard?		Unclear
Did all patients receive the same reference standard?		Yes

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk of bias
Comments	n/a

1

Study: Mele et al., 2007		
PATIENT SELECTION		
A. risk of bias		
Patient sampling	168 myeloma patients	
Was a consecutive or random sample of patients enrolled?		Unclear
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Unclear
Could the selection of patients have introduced bias?		Unclear risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=169 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Reference standard(s)	**clinical and biochemical evaluations/ European group for blood and marrow transplant criteria**	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Clinical status was assessed at same time as TC99MIBI scan	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

2

Study: Villa et al., 2005
PATIENT SELECTION
A. risk of bias

Patient sampling	18 myeloma patients	
Was a consecutive or random sample of patients enrolled?		Yes
Was a case-control design avoided?		Yes
Did the study avoid inappropriate exclusions?		Yes
Could the selection of patients have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Patient characteristics and setting	N=18 Inclusion criteria: not reported Exclusion criteria: not reported Clinical setting: secondary/tertiary care. Italy.	
Are there concerns that the included patients and setting do not match the review question?		Low concern
INDEX TEST		
A. Risk of bias		
Index test		**TC99MIBI**
Were the index test results interpreted without knowledge of the results of the reference standard?		Yes
Could the conduct or interpretation of the index test have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
Reference standard(s)	complete clinical and biochemical evaluations	
Is the reference standard likely to correctly classify the target condition?		Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?		Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk of bias
B. Concerns regarding applicability		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
FLOW AND TIMING		
A. risk of bias		
Flow and timing	Clinical status was assessed at same time as TC99MIBI scan	
Was there an appropriate interval between index test and reference standard?		Yes
Did all patients receive the same reference standard?		Yes
Were all patients included in the analysis?		Yes
Could the patient flow have introduced bias?		Low risk of bias
Comments	n/a	

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2

3

Chapter 11: Managing relapsed myeloma

Second autologous stem cell transplant

Review Question:
In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy?

Question in PICO format

Population	Intervention	Comparator	Outcomes
Patients with relapsed or refractory myeloma grouped according to - Age - Performance status - Comorbidities (charlson score, ACE-27) - Renal impairment - Genetic abnormalities - Time from first autologous transplant to retreatment - Number of prior lines of therapy	• Second autologous stem cell transplant	• Other therapies (excluding allogeneic stem cell transplant) • No therapy	• Overall survival • Progression free survival • Health related quality of life • Adverse events • Treatment related mortality • Treatment related morbidity • PROMs • Patient/carer/family acceptability

Evidence statements

Comparative studies

From the literature search one RCT was identified (Cook et al., 2014). The study was a multicentre, randomised, open-label, phase 3 study comparing high-dose melphalan plus salvage autologous stem cell transplant (ASCT) (n=89) with weekly cyclophosphamide (n=85) in patients with relapsed multiple myeloma who had previously undergone ASCT and provides moderate quality evidence that time to progression is longer following treatment with salvage ASCT. Results of the predefined subgroup analysis of time to progression in Cook et al (2014) suggest that salvage ASCT is more effective than cyclophosphamide, irrespective of the quality of response to PAD re-induction and the concentration of β2-microglobulin at registration. Furthermore, ASCT was more effective than cyclophosphamide irrespective of the response duration to the initial ASCT, although time to progression was longer (TTP 24 months) in patients with a response lasting longer than 24 months after their first ASCT than in those with a response of 24 months or less (TTP 13 months). The relative effectiveness of salvage ASCT and cyclophosphamide in patients with adverse cytogenetics was uncertain due to the small number of patients with an adverse cytogenetic risk profile (n=13). Follow up in this study was not long enough (median 34 months) to confidently assess the effect of salvage therapy on survival.

Very low to low quality evidence from 4 retrospective comparative studies including 1134 patients suggests that outcomes are better (OS and/or PFS are longer) following treatment with a second

ASCT compared to salvage systematic chemotherapy or alternative treatments in patients with relapsed myeloma who had previously undergone ASCT and belonging to the following subgroups: patients who respond well following ASCT1, (Cook et al., 2011), patients with longer time to progression after ASCT1 (Alvares et al., 2006; Cook et al., 2011), patients with a younger age (Cook et al., 2011), patients with a poor prognosis (as determined by time to progression after ASCT1 and ISS) (Yhim et al., 2013). Grovdal et al (2015) reported that both overall survival and time to next treatment were longer with a second ASCT than with either conventional cytotoxic chemotherapy or novel drugs (proteosome inhibitors or immunomodulatory drugs). There is the potential for selection bias in these retrospective comparative studies as the choice of therapy after relapse is often governed by a complex list of unmeasured factors that can potentially affect outcomes and not all patients will be suitable for salvage ASCT. Two studies (Cook et al., 2011 and Yhim et al., 2013) matched patients in the intervention and comparator groups for a number of potential risk factors in an attempt to overcome selection bias. However, only a randomised trial can exclude such bias completely.

No evidence was identified for the outcomes treatment related morbidity and mortality, health related quality of life, adverse events, patient/carer/family acceptability and PROMs.

Prognostic studies

Moderate quality evidence from non-comparative retrospective studies that reported predictive factors (high quality prognostic factor studies but downgraded as comparative studies are better for answering the review question) suggest that in relapsed myeloma patients time to progression following an initial ASCT is an important predictor of survival following salvage ASCT. All 11 studies reported that a longer TTP after first ASCT was associated with longer PFS and/or OS after salvage ASCT. However the studies were inconsistent with regard to the length of remission that predicted improved survival outcomes, with reports of increased PFS and/or OS if TTP was more than 12 months (Olin et al., 2009; Fenk et al., 2011; Wirk et al., 2013), 18 months (Chow et al., 2013; Sellner et., 2013), 21.5 months (Auner et al., 2013) and 24 months (Jimenez-Zepeda et al., 2012; Lemieux et al., 2013; Michaelis et al., 2013).

Evidence also indicated a lack of response to initial ASCT (Olin et al., 2009), higher number of treatment regimens before second ASCT (Olin et al., 2009; Shah et al., 2012; Gonsalves et al., 2013), higher plasma cell labelling index at second ASCT (Gonsalves et al., 2013), elevated LDH at second ASCT (Sellner et al., 2013), adverse cytogenetics (Shah et al., 2012; Sellner et., 2013) age >60 (Lemieux et al., 2013) or age >65 (Olin et al., 2009), and being of african-american ethnicity (Shah et al., 2012) was predictive of worse survival outcomes. Whilst disease status (> PR) at salvage ASCT (Auner et al., 2013) and ISS stage I before salvage ASCT (Sellner et al., 2013) was predictive of better survival outcomes.

Myeloma subtype was also found to be an important predictor of survival. However it is unclear which subtype is associated with better or worse outcomes as one study reported an association between the IgG subtype and worse outcomes (Shah et al., 2012) whilst another study demonstrated that patients with non IgG subtype had worse outcomes (Sellner et., 2013).

All the evidence was in relation to survival outcomes and no evidence was identified for the outcomes treatment related morbidity and mortality, health related quality of life, adverse events, patient/carer/family acceptability and PROMs.

Table 11.1: independent predictive factors for outcomes following salvage ASCT

	Auner et al., 2013	Chow et al., 2013[a]	Fenk et al., 2011	Gonsalves et al., 2013	Jimenez-Zepeda et al., 2012	Lemieux et al., 2013	Michaelis et al., 2013	Olin et al., 2009	Sellner et., 2013	Shah et al., 2012	Wirk et al., 2013
	n=83	**n=30**	**n=55**	**n=98**	**n=81**	**n=81**	**n=187**	**n=41**	**n=200**	**n=44**	**n=27**
Response to ASCT1	n/a	n/a	X	X	X	?	n/a	Lack of response to ASCT1: shorter PFS	X	n/a	n/a
TTP after ASCT1	TTP >21.5 months: longer PFS	TTP >18 months: longer OS and PFS	TTP >12 months: longer OS and PFS	Longer TTP: longer OS and PFS	TTP >24 months: longer OS and PFS	TTP >24 months: longer OS and PFS	TTP >36 months: longer OS and PFS	TTP >12 months: longer OS	TTP >18 months: longer OS and PFS	Longer TTP: longer OS	TTP >12 months: longer OS and PFS
Time between ASCT1 and ASCT2	n/a	n/a	n/a	X	n/a	?	X	X	n/a	n/a	X
prior therapies	n/a	n/a	X	Higher number of treatments before ASCT2: shorter PFS	X	?	n/a	>5 prior lines of therapy: shorter PFS and OS	X	Higher number of treatments before ASCT2: shorter OS	X
Disease status at ASCT2	status >PR: longer OS and PFS	n/a	n/a	X	n/a	?	X	X	n/a	n/a	X
age	X	X	X	X	X	Age>60: shorter OS	X	Age>65: shorter PFS	X	X	X
gender	X	X	n/a	n/a	n/a	?	X	n/a	X	X	X
B2 microglobulin	n/a	n/a	X	X	X	?	n/a	X	n/a	n/a	X
cytogenetics	n/a	n/a	n/a	X	X	?	n/a	X	Adverse FISH: shorter PFS and OS	Adverse FISH: shorter OS	X
ISS stage	n/a	ISS at diagnosis predictive of survival	X	X	n/a	?	n/a	n/a	ISS stage I before ASCT2: longer OS	X	X
Durie-Salmon stage	n/a	n/a	n/a	n/a	n/a	?	X	n/a	n/a	n/a	X
ethnicity	X	n/a	n/a	n/a	n/a	?	n/a	n/a	n/a	African-American: shorter OS	
Performance score	n/a	n/a	n/a	n/a	n/a	?	X	n/a	n/a	n/a	X
Immunochemical type	X	X	n/a	n/a	n/a	?	X	n/a	Non-immunoglobulin G isotype: shorter PFS	IgG subtype: shorter OS	X
Plasma cell labelling index	n/a	n/a	n/a	Higher PLCI at ASCT2: shorter PFS	n/a	?	n/a	n/a	n/a	n/a	n/a
haemoglobin	n/a	n/a	X	X	n/a	?	n/a	X	n/a	n/a	n/a
creatinine	n/a	n/a	n/a	X	X	?	n/a	X	n/a	n/a	n/a
albumin	n/a	n/a	n/a	n/a	X	?	n/a	X	n/a	n/a	X
C-reactive protein	n/a	n/a	X	X	n/a	?	n/a	n/a	n/a	n/a	n/a
Serum lactate dehydrogenase	n/a	n/a	X	X	X	?	n/a	X	Elevated LDH at ASCT2: shorter OS	n/a	n/a

[a] *Results from univariate analysis. Multivariate analysis was not performed; X: Not predictive.; n/a: Factor not investigated or too few numbers of patients to include in analysis.*

?: Lemieux et al., 2013 reported results but did not report a list of factors included in the analysis

Table 11.1: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus alternative treatment in patients with a relapse-free survival > 18 months from ASCT1)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	alternative treatment	Relative (95% CI)	Absolute	Quality
median OS											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	43	-	Median OS was 1.7 years longer in patients that underwent salvage ASCT compared to patients that underwent other salvage treatments.	⊕OOO VERY LOW

[1] *published as letter: limited study details and not peer-reviewed (Alvares et al., 2006)*

Table 11.2: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients < 54 years at ASCT1)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	Quality
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	-	Median OS was 1.75 years longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕⊕OO LOW

Table 11.3: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients 55 - 65 years at ASCT1)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	Quality
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	?	?	-	Median OS was 1.7 years longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕OOO VERY LOW

[1] *number of patients in subgroup unclear (maximum 46)*

Table 11.4: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients > 65 years at ASCT1)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	Quality
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	?	?	-	Median OS was not significantly different in patients that underwent salvage ASCT and patients that underwent salvage chemotherapy.	⊕OOO VERY LOW

[1] *number of patients in subgroup unclear (maximum 46)*

Table 11.5: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients with a duration of response greater than 18 months post ASCT1)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	Quality
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	59	-	Median OS was 2.1 years longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕⊕OO LOW

Table 11.6: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients with achievement of at least a PR (CR/PR) following ASCT1)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	Quality
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	91	-	Median OS was 2 years longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕⊕OO LOW

Table 11.7: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients with poor responding disease to ASCT1 (no response, minimal disease or progressive disease))?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	
median OS from relapse											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	15	15	-	Median OS was 1 year longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕OOO VERY LOW

[1] *small sample size*

Table 11.8: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients with a good prognosis (TTP >18 months after ASCT1 and ISS 1 or II))?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	
median PFS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	13	34	-	Median OS was no different in patients that underwent salvage chemotherapy and patients that salvage ASCT.	⊕OOO VERY LOW
median OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	13	34	-	Median PFS was 23.7 months longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕OOO VERY LOW

[1] *small number of patients in the intervention group (ASCT2)*

Table 11.9:GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus salvage systematic chemotherapy in patients with a poor prognosis (TTP <18 months after ASCT1 and/or ISS III))?

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ASCT2	salvage systematic chemotherapy	Relative (95% CI)	Absolute	
median OS											
1	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	35	110	-	Median OS was 32.7 months years longer in patients that underwent salvage ASCT compared to patients that underwent salvage chemotherapy.	⊕OOO VERY LOW
median PFS											
1	observational	no serious	no serious	no serious	serious[1]	none	35	110	-	Median PFS was 6.6 months longer in patients that underwent salvage	⊕OOO

	studies	limitations	inconsistency	indirectness						ASCT compared to patients that underwent salvage chemotherapy.	VERY LOW

[1] *small number of patients in the intervention group (ASCT2)*

Table 11.10: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus cyclophosphamide in patients with a first response to ASCT1 longer than 24 months)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ASCT2**	**cyclophosphamide**	**Relative (95% CI)**	**Absolute**	**Quality**
median time to progression											
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	64	64	-	Median TTP was 13 months longer in patients that underwent salvage ASCT compared to patients that underwent cyclophosamide.	⊕⊕⊕O MODERATE

[1] *choice of cyclophosphamide might be questioned in current treatment landscape.*

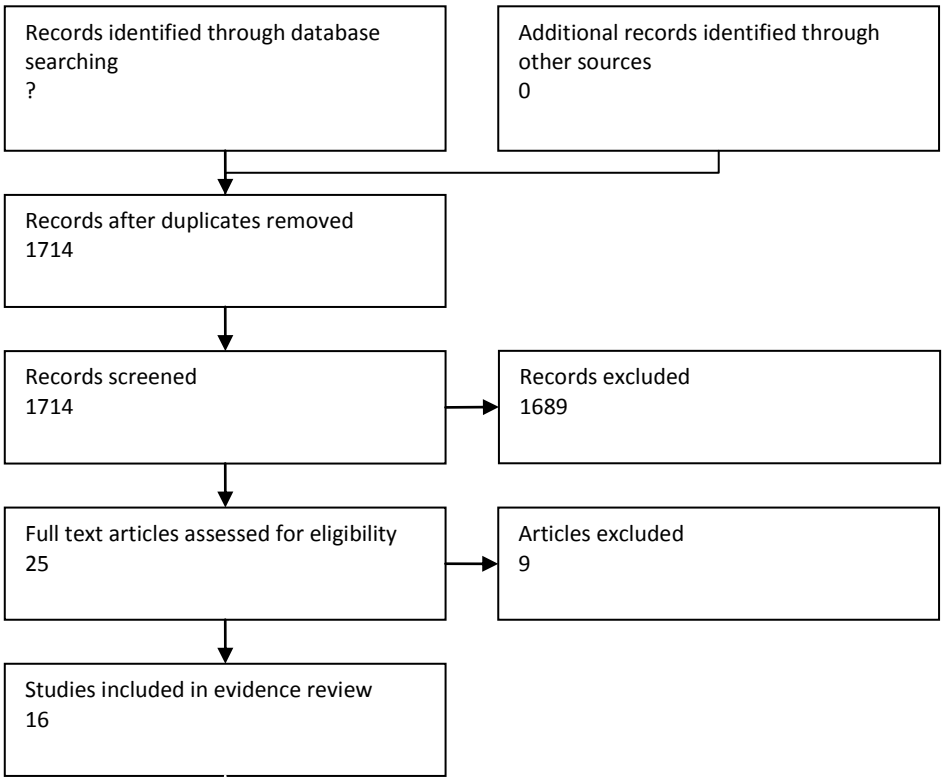
Table 11.11: GRADE profile: In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy (ASCT2 versus cyclophosphamide in patients with a first response to ASCT1 of 24 months or less)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ASCT2**	**cyclophosphamide**	**Relative (95% CI)**	**Absolute**	**Quality**
median time to progression											
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	25	21	-	Median TTP was 4 months longer in patients that underwent salvage ASCT compared to patients that underwent cyclophosamide.	⊕⊕⊕O MODERATE

[1] *choice of cyclophosphamide might be questioned in current treatment landscape.*

Search Results

Figure 11.1: Screening result



Five of the included studies were comparative and assessed second autologous transplant in comparison to systemic chemotherapy (n=3), oral cyclophosphamide (n=1) or any other treatment (n=1) in specific subgroups of patients. Eleven of the studies were non-comparative studies that reported factors predicting outcome following second autologous stem cell transplant.

1 ***Evidence table***

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td>Alvares et al., 2006

Retrospective analysis
Single-centre

UK</td><td>Patients with relapsed myeloma who had previously undergone ASCT.

median time to relapse of 2.6 years

median follow-up of patients receiving a first ASCT was 8 years</td><td>second auto transplant
n=83</td><td>alternative treatment
n=83

18 interferon, 8 thalidomide regime, 8 cyclophosphamide regime, 8 melphalan, 2 velcade, 9 local radiotherapy, and 30 no treatment</td><td>Patients with a relapse-free survival of ≥18 months from first ASCT
<table><tr><th></th><th>n</th><th>Median OS</th></tr><tr><td>Salvage ASCT</td><td>63</td><td>4.6 years</td></tr><tr><td>Other treatment</td><td>43</td><td>2.9 years</td></tr><tr><td></td><td></td><td>p=0.33</td></tr></table></td><td>Not in database.

Letter so limited study details reported and study has not been peer-reviewed.</td></tr>
<tr><td>Auner et al., 2013

Retrospective study
Single-centre

UK</td><td>Patients with relapsed myeloma who had previously undergone ASCT.</td><td>salvage ASCT
n=83

59 male, 24 female

median age 61 (32 – 75)

Median interval between ASCT1 and SCT2 was 35.4 months (95% CI 9-93)</td><td>n/a</td><td>Factors analysed:
Age at salvage ASCT, patient gender, myeloma subtype, disease status at ASCT2, time to relapse/progression after ASCT1, and ethnicity

Multivariate analysis:
Disease status (> PR) at salvage ASCT was associated with better OS.
Disease status (> PR) at salvage ASCT and time to progression/relapse ≥ 21.5 months after first ASCT were associated with better PFS.

Multivariate analysis of risk factors for OS and PFS after second ASCT
<table><tr><th></th><th>n</th><th>RR</th><th>95%CI</th><th>p</th></tr><tr><td>Overall survival</td><td></td><td></td><td></td><td></td></tr><tr><td>Disease status at ASCT2</td><td></td><td></td><td></td><td></td></tr><tr><td>>PR</td><td>16</td><td>1</td><td></td><td></td></tr><tr><td>PR</td><td>41</td><td>2.96</td><td>0.8-9.9</td><td>0.079</td></tr><tr><td><PR</td><td>21</td><td>8.34</td><td>2.4-29.0</td><td>0.001</td></tr><tr><td>PFS</td><td></td><td></td><td></td><td></td></tr><tr><td>Disease status at ASCT2</td><td></td><td></td><td></td><td></td></tr><tr><td>>PR</td><td>16</td><td>1</td><td></td><td></td></tr><tr><td>PR</td><td>41</td><td>0.83</td><td>0.4-1.7</td><td>0.61</td></tr><tr><td><PR</td><td>21</td><td>2.64</td><td>1.2-5.7</td><td>0.012</td></tr><tr><td>PFS after ASCT1</td><td></td><td></td><td></td><td></td></tr><tr><td>< 21.5 months</td><td>36</td><td>1</td><td></td><td></td></tr><tr><td>≥ 21.5 months</td><td>42</td><td>0.51</td><td>0.3-0.9</td><td>0.013</td></tr></table></td><td>Non-comparative study but reports predictive factors.</td></tr>
<tr><td>Chow et al., 2013</td><td>Patients with relapsed myeloma who had previously undergone ASCT.</td><td>salvage ASCT
n=30</td><td>n/a</td><td>Factors analysed:
Age, ISS stage, patient gender, myeloma subtype, PFI post-initial ASCT, responses to reinduction and ASCT, use of novel agents, and maintenance therapy</td><td>Non-comparative study but reports predictive factors.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Retrospective study
Single-centre

Australia</td>
<td></td>
<td>13 male, 17 female

median age at diagnosis 55 (31 – 70)

median follow up of 32 months after salvage ASCT</td>
<td></td>
<td>postsalvage ASCT.

Progression free interval (PFI) after initial ASC predicted survival outcomes in a time-dependent manner.
<table>
<tr><th></th><th>PFI <18 months</th><th>PFI 18-36 months</th><th>PFI >36 months</th></tr>
<tr><td>n</td><td>5</td><td>13</td><td>12</td></tr>
<tr><td>median PFS</td><td>4.21 months</td><td>13.8 months</td><td>49.1 months</td></tr>
<tr><td>median OS</td><td>10.7 months</td><td>30.9 months</td><td>86.1 months</td></tr>
</table>
ISS at diagnosis was associate with survival benefit after salvage ASCT

Use of novel agents in reinduction, maintenance therapy and response status post-salvage ASCT did not influence PFS following salvage ASCT.</td>
<td>Not multivariate analysis.</td>
</tr>
<tr>
<td>Cook et al., 2011

Case-matched retrospective study
Multi-centre

UK</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT

median follow-up 48 months (range 8 -136)</td>
<td>Second auto-SCT n=106

73 male, 33 female

median age at diagnosis 53 (25 – 72)

median age at 1st ASCT 54 (26 – 75)</td>
<td>salvage systemic chemotherapy n=106

66 male, 35 female

median age at diagnosis 53 (25 – 70)

median age at 1st ASCT 54 (25 – 76)

Controls were matched on age at first transplantation, status at first transplantation, and length of remission after first transplantation. It was also decided to match for year of transplantation (in 4-year intervals) to account for</td>
<td>age ≤54 years at first ASCT
<table>
<tr><th></th><th>Median OS from relapse (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>3.5 years (2.7-4.6)</td></tr>
<tr><td>Salvage chemotherapy</td><td>1.75 years (1.1-2.1)</td></tr>
<tr><td></td><td>p=0.0019</td></tr>
</table>
age 55-65 years at first ASCT
<table>
<tr><th></th><th>Median OS from relapse (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>2.7 years (2.2-3.4)</td></tr>
<tr><td>Salvage chemotherapy</td><td>1 year (0.2-2.7)</td></tr>
<tr><td></td><td>p=0.0015</td></tr>
</table>
age >65 years at first ASCT
<table>
<tr><th></th><th>Median OS from relapse (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>1.1 years (0.1-3.4)</td></tr>
<tr><td>Salvage</td><td>0.7 years (0.2-2.7)</td></tr>
</table></td>
<td>The reinduction regimens, both pre-ASCT and in the CCT cohort, were heterogeneous.

Insufficient data on cytogenetic analysis and b2MG at diagnosis and at relapse to permit confidence in a comparative analysis.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td>procedural and supportive care changes.</td><td>
<table>
<tr><td>chemotherapy</td><td></td></tr>
<tr><td></td><td>p=0.92</td></tr>
</table>
Duration of response greater than 18 months post first ASCT
<table>
<tr><td></td><td>Median OS</td></tr>
<tr><td>Salvage ASCT</td><td>3.9 years (3.1-4.8)</td></tr>
<tr><td>Salvage chemotherapy</td><td>1.8 years (1.1-2.3)</td></tr>
<tr><td></td><td>p=0.0011</td></tr>
</table>
Achievement of at least a PR (CR/PR) following first ASCT
<table>
<tr><td></td><td>Median OS</td></tr>
<tr><td>Salvage ASCT</td><td>3.1 years (2.5-3.7)</td></tr>
<tr><td>Salvage chemotherapy</td><td>1.1 years (1.0-1.8)</td></tr>
<tr><td></td><td>p<0.0001</td></tr>
</table>
Poor responding disease to first ASCT (no response, minimal disease or progressive disease)
Low numbers n=15
<table>
<tr><td></td><td>Median OS</td></tr>
<tr><td>Salvage ASCT</td><td>2 years (0.2 -3.1)</td></tr>
<tr><td>Salvage chemotherapy</td><td>1 year (0.4-2.0)</td></tr>
<tr><td></td><td>p=0.394</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Cook et al., 2014

Multicentre, randomised, open-label, phase 3 study

UK</td>
<td>Patients aged at least 18 years with myeloma who needed treatment for first progressive or relapsed disease at least 18 months after a previous ASCT from 51 centres across the UK</td>
<td>single infusion of intravenous melphalan 200 mg/m² followed by salvage ASCT after 24–48 h
n=89

65 male, 24 female

median age 61 (40–73)

median follow-up of 34 months (IQR 19–48)</td>
<td>oral cyclophosphamide (400mg/m² per week for 12 weeks)
n=85

61 male, 24 female

median age 61 (40–73)

median follow-up of 23 months (IQR 25–31)</td>
<td>Subgroup analysis of time to progression.
HRs for risk of disease progression in the melphalan plus salvage ASCT group compared with the cyclophosphamide group:

* Adverse risk was defined by the presence of a t(4;14) translocation, t(14;16) translocation, or TP53 deletion; standard risk was defined by the absence of adverse markers.
† Numbers for each subgroup do not add up to 174 overall because not all patients had the information needed for the subgroup analysis.

High-dose melphalan plus salvage ASCT was not better than cyclophosphamide in patients with an adverse cytogenetic risk profile by iFISH. However, the small number of patients with an adverse cytogenetic risk makes the interpretation of this result difficult.

Patients with a first response to the initial ASCT lasting longer than 24 months
<table>
<tr><th></th><th>n</th><th>median time to progression (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>64</td><td>24 months (18–27)</td></tr>
<tr><td>cyclophosphamide</td><td>64</td><td>11 months (10–12)</td></tr>
<tr><td></td><td></td><td>p<0·0001</td></tr>
</table>
Patients with a first response of 24 months or less
<table>
<tr><th></th><th>n</th><th>median time to progression (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>25</td><td>13 months (10–20)</td></tr>
<tr><td>cyclophosphamide</td><td>21</td><td>9 months (8–12)</td></tr>
<tr><td></td><td></td><td>p<0·0037</td></tr>
</table>
</td>
<td>The study was stopped early because it crossed a stopping boundary for efficacy at an interim analysis. RCTs that are stopped early for efficacy have been suggested to overestimate the effect size. However the primary endpoint analysis was undertaken when 125 (50%) of the required 249 events had been reported, suggesting that the estimated effect could be at most minimally inflated.

The choice of cyclophosphamide might be questioned in the current treatment landscape.
(the study was designed in 2006)

The follow-up is not sufficiently long enough to confidently assess the effect of salvage therapy on survival.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Fenk et al., 2011

Retrospective study
Single-centre

Germany</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT.</td>
<td>salvage ASCT
n=55

35 male, 21 female

median age at diagnosis 51 (36 – 69)</td>
<td>n/a</td>
<td>Factors analysed:
Age, ISS stage, B2 microglobulin, CRP, LDH, thromboyctes, haemoglobin, CR/vgPR after ASCT1, EFS after ASCT1, prior lines of therapy, conditioning regime, maintenance therapy, year of transplant

Multivariate analysis:
duration of remission of more than 12 months after the first transplant was the only predictive factor for both EFS and OS.

Multivariate analysis of EFS and OS
<table>
<tr><th></th><th colspan="2">EFS</th><th colspan="2">OS</th></tr>
<tr><th></th><th>HR (95%CI)</th><th>p</th><th>HR</th><th>p</th></tr>
<tr><td>age (< > 60 years)</td><td></td><td></td><td>0.2 (0.2-1.4)</td><td>0.3</td></tr>
<tr><td>ISS stage at relapse (1 vs. 2/3)</td><td>2.7 (1-7.7)</td><td>0.1</td><td></td><td></td></tr>
<tr><td>Thromboyctes (< > 140 x 10^3/L)</td><td>1.2 (0.4-3.4)</td><td>0.7</td><td>3.1 (1.1-8.7)</td><td>0.03</td></tr>
<tr><td>Haemoglobin (< > 10g/dL)</td><td>0.6 (0.2-1.7)</td><td>0.3</td><td></td><td></td></tr>
<tr><td>EFS after ASCT1 (< > 12 months)</td><td>0.1 (0.01-0.2)</td><td>0.0001</td><td>4.4 (1.7-11.4)</td><td>0.002</td></tr>
</table>
Duration of remission following initial ASCT predicted survival outcomes:
<table>
<tr><th></th><th><12 months</th><th>13-24 months</th><th>25-36 months</th></tr>
<tr><td>median EFS</td><td>4 months</td><td>15 months</td><td>15 months</td></tr>
<tr><td>median OS</td><td>7 months</td><td>40 months</td><td>78 months</td></tr>
</table>
</td>
<td>Non-comparative study but reports predictive factors.</td>
</tr>
<tr>
<td>Gonsalves et al., 2013

Retrospective study
Single centre

USA</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT.</td>
<td>salvage ASCT
n=98

median age at ASCT2 60 (35 – 74)

median time between ASCT1 and ASCT2 was 46 months (range: 10–130)

average follow up 60 months</td>
<td>n/a</td>
<td>Prognostic examined included: age, response to ASCT1, TTP after ASCT1, time interval between ASCT1 and ASCT2, number of prior lines of therapy, responsive disease at the time of salvage transplant, BM plasma cell percentage, presence of high-risk FISH, conditioning regimen, and pre-transplant International Staging System (ISS) stage, plasma cell labelling index (PCLI), serum M spike, urine M spike,haemoglobin, creatinine, creatinine clearance, C-reactive protein and lactate dehydrogenase (LDH).

multivariable analysis:
shorter TTP after ASCT1, not achieving a CR after ASCT2, higher number of treatment regimens before ASCT2 and a higher plasma cell labelling index at ASCT2 predicted for shorter PFS. However, only a shorter TTP after ASCT1 predicted for a shorter OS post ASCT2.</td>
<td>Non-comparative study but reports predictive factors.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
factors associated with PFS
<table>
<tr><th>factor</th><th>RR</th><th>p</th></tr>
<tr><td>TTP after ASCT1</td><td>0.11
(0.01-0.96)</td><td>0.046</td></tr>
<tr><td>CR after ASCT2</td><td>0.6
(0.4-0.9)</td><td>0.03</td></tr>
<tr><td>number of treatments before ASCT2</td><td>5.1
(1.1-22.1)</td><td>0.04</td></tr>
<tr><td>plasma cell labelling index percentage</td><td>11.6
(1.8-58)</td><td>0.01</td></tr>
</table>
factors associated with OS
<table>
<tr><th>factor</th><th>RR</th><th>p</th></tr>
<tr><td>TTP after ASCT1</td><td>0.05
(0.003-0.4)</td><td>0.004</td></tr>
</table>
Time to progression after ASCT1 and its effect on survival outcomes after ASCT2
<table>
<tr><th></th><th><12 months</th><th><18 months</th><th><24 months</th><th><36 months</th></tr>
<tr><td>n</td><td>9</td><td>25</td><td>47</td><td>68</td></tr>
<tr><td>median PFS</td><td>5.6 months
(3-8)</td><td>7.1 months
(6-8)</td><td>7.3 months
(6-10)</td><td>7.6 months
(7-12)</td></tr>
<tr><td>median OS</td><td>12.6 months
(4-23)</td><td>19.4 months
(10-42)</td><td>22.7 months
(13-62)</td><td>30.5 months
(19-62)</td></tr>
</table>
(range)
</td><td></td></tr>
<tr><td>Jimenez-Zepeda et al., 2012

Retrospective study
Single-centre

Canada</td><td>Patients with relapsed myeloma who had previously undergone ASCT.</td><td>salvage ASCT
n=81

49 male, 32 female

median age 55
(30– 67)

Median follow-up 36 months</td><td>n/a</td><td>
Factors analysed:
age, response to initial ASCT, prior therapies, maintenance, time to relapse after ASCT1, abnormal cytogenetics, high-dose regimen, B2 microglobulin, creatinine, albumin, lactate dehydrogenase.

B2 microglobulin and cytogenetics were not informative because of high percentage of missing values

Multivariate analysis: Improved PFS and OS if interval between ASCT1 and ASCT2 >24 mo.
<table>
<tr><th></th><th>≤24 months</th><th>>24 months</th><th>p</th></tr>
<tr><td>median PFS</td><td>9.83 months</td><td>17.3 months</td><td>0.03</td></tr>
<tr><td>median</td><td>28.47 months</td><td>71.3 months</td><td>0.006</td></tr>
</table>
</td><td>Non-comparative study but reports predictive factors.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table><tr><td>OS</td><td></td><td></td><td></td></tr></table></td><td></td></tr>
<tr><td>Grovdal et al., 2015

Retrospective study
Multi-centre

Nordic countries</td><td>Patients with relapsed myeloma who had previously undergone ASCT.</td><td>Total N=564 received a second-line treatment.

Second ASCT (N=111)</td><td>Re-treatment with conventional cytotoxic chemotherapy (N=91)
Novel drugs (proteosome inhibitors or immuno-modulatory drugs)</td><td><table><tr><td></td><td>Second ASCT</td><td>Cytotoxic Chemo</td><td>Novel drugs</td><td>P</td></tr><tr><td>median OS</td><td>4.0 years</td><td>2.5 years</td><td>3.3 years</td><td><0.001</td></tr><tr><td>median TTNT</td><td>2.4 years</td><td>2.1 years</td><td>2.3 years</td><td>P=0.02</td></tr></table>TTNT – time to next treatment.</td><td>ASCT patients significantly younger (P<0.001) & higher haemoglobin levels (P=0.017), however second ASCT was still a prognostic factor for survival in multivariate analysis accounting for this.</td></tr>
<tr><td>Lemieux et al., 2013

Retrospective study
Multi-centre

France</td><td>Patients with relapsed myeloma who had previously undergone ASCT.</td><td>Salvage ASCT
n=81

47 male, 34 female

median age at diagnosis 55 (30 – 67)

median time between first and salvage ASCT was 47 months (range 13-168)

median follow up time for living patients: 7 years (range 2.1-16.6)</td><td>n/a</td><td>Factors analysed: not reported

Multivariate analysis of prognostic factors found that three independent factors unfavourably affected PFS: a short duration of response to the first ASCT with cut-off value of 24 months, a response less than a VGPR after salvage therapy, and no maintenance treatment after salvage ASCT.

Age over 60 years and a short duration of response after the first ASCT were the two factors adversely affecting OS.

factors associated with PFS after salvage ASCT<table><tr><th>factor</th><th>HR</th><th>p</th></tr><tr><td>Duration of response after ASCT1 <24mo</td><td>2.25 (1.02-4.98)</td><td>0.04</td></tr><tr><td>Duration of response after ASCT1 <40mo</td><td>2.46 (1.40-4.32)</td><td>0.001</td></tr><tr><td>Response after salvage ASCT <VGPR</td><td>1.97 (1.02-3.80)</td><td>0.04</td></tr><tr><td>No maintenance therapy after salvage ASCT</td><td>3.40 (1.72-6.69)</td><td>0.0004</td></tr></table>factors associated with OS from diagnosis<table><tr><th>factor</th><th>HR</th><th>p</th></tr><tr><td>Age >60 years</td><td>4.00 (1.50-10.71)</td><td>0.006</td></tr></table></td><td>Non-comparative study but reports predictive factors.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Duration of response after ASCT1 <24mo</td><td>14.90 (3.98-55.70)</td><td><0.0001</td></tr>
<tr><td>Duration of response after ASCT1 <40mo</td><td>4.67 (2.04-10.70)</td><td>0.0003</td></tr>
</table>
factors associated with OS from salvage ASCT
<table>
<tr><th>factor</th><th>HR</th><th>p</th></tr>
<tr><td>Age >60 years</td><td>3.62 (1.39-9.42)</td><td>0.008</td></tr>
<tr><td>Duration of response after ASCT1 <24mo</td><td>8.25 (2.93-23.22)</td><td><0.0001</td></tr>
<tr><td>Duration of response after ASCT1 <40mo</td><td>4.45 (1.93-10.24)</td><td>0.0004</td></tr>
</table>
PFS and OS after salvage ASCT was associated with time to progression after ASCT1
<table>
<tr><th></th><th>≤40 months</th><th>>40 months</th><th>p</th></tr>
<tr><td>median PFS</td><td>14 months</td><td>26.4 months</td><td>0.001</td></tr>
<tr><td>Median OS</td><td>40.8 months</td><td>87.6 months</td><td><0.05</td></tr>
</table>
<table>
<tr><th></th><th>≤24 months</th><th>>24 months</th><th>p</th></tr>
<tr><td>median PFS</td><td>9 months</td><td>18 months</td><td>0.0096</td></tr>
<tr><td>Median OS</td><td>28.8 months</td><td>86.4 months</td><td><0.05</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Michaelis et al., 2013

Retrospective study
Multi-centre

international</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT

Data from the centre for international blood and marrow transplant research registry.</td>
<td>salvage ASCT
n=187
from 55 centres in north America

118 male, 69 female

Median age at AHCT2 was 59 years (range, 28 to 72)

median interval</td>
<td>n/a</td>
<td>The variables considered in the multivariate analysis were age, sex, Karnofsky performance score, Durie-Salmon stage, and immunochemical subtype of MM, disease status before AHCT2, conditioning regimen for ASCT2 (melphalan alone versus others), interval from ASCT1 to relapse/progression, interval from AHST1 to AHST2, and the year of AHST2.

In multivariate analyses, those relapsing ≥36 months after AHCT1 had a lower risk of relapse/progression after ASCT2 and superior progression-free and overall survival.

Patients who underwent AHCT2 after 2004 had superior survival.

Multivariate analysis of risk factors for relapse/progression, treatment failure</td>
<td>Non-comparative study but reports predictive factors.</td>
</tr>
</table>

Study	Population	Intervention	Comparator	Results	Additional comments
		between transplants was 32 months (range 6-122 months) median patient follow-up was 47 months (range, 3 to 97)		**(inverse of PFS), and OS** **outcome** **n** **HR** **95% CI** **p** **Relapse/progression** ≥ 36 mo 36 1 < 36 mo 151 1.58 1.03-2.41 0.036 **Treatment failure/PFS** ≥ 36 mo 36 1 < 36 mo 151 1.52 1.01-2.30 0.045 **Overall mortality/survival** ≥ 36 mo 36 1 < 36 mo 151 1.91 1.12-3.28 0.019 **Year of ASCT** 1995-2004 100 1 2005-2008 87 0.61 0.40-0.94 0.026	

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Olin et al., 2009

Retrospective study
Single-centre

USA</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT.</td>
<td>salvage ASCT
n=41

32 male, 9 female

median age at diagnosis: 50 (25 – 69)

median age at time of ASCT: 54 (28 – 73)

median time between transplants: 37 months (range 3-91 months)

median follow-up: 15 months (range 1-91)</td>
<td>n/a</td>
<td>Prognostic variables prior to the ASCT2 which were examined for significance include: age, response to initial ASCT, TTP after initial ASCT, time interval between the first and second transplants, number of prior lines of therapy, prior receipt of specific therapies (thalidomide, lenalidomide, bortezomib), responsive disease at the time of salvage transplant, abnormal cytogenetics, conditioning regimen, and pretransplant haemoglobin, creatinine, albumin and LDH.

B2 microglobulin was not informative because of a high percentage of missing values.

Factors predictive of poor PFS:
> 5 prior lines of therapy, lack of response to initial transplant and age >65 years were predictive of poor PFS

Factors predictive of poor OS:
>5 prior lines of therapy and TTP after initial transplant <12 months were predictive of poor OS

Multivariate analysis of PFS and OS
<table>
<tr><th></th><th colspan="2">PFS</th><th colspan="2">OS</th></tr>
<tr><th></th><th>HR (95%CI)</th><th>p</th><th>HR (95%CI)</th><th>p</th></tr>
<tr><td>Prior lines of therapy (>5 lines n=10 vs. <5 n=31)</td><td>5.2 (2.2-12.5)</td><td><0.001</td><td>3.9 (1.4-10.9)</td><td>0.008</td></tr>
<tr><td>Age (>65 n=7 vs. <65 n=34)</td><td>3.6 (1.1-12.1)</td><td>0.04</td><td>-</td><td>-</td></tr>
<tr><td>Response to initial ASCT (vs. CR/VGPR n=12)
PR (n=21)
SD/PR (n=8)</td><td>
1.4 (0.5-3.9)
7.4 (2.0-27.5)</td><td>
0.57
0.003</td><td>
-
-</td><td>
-
-</td></tr>
<tr><td>TTP after initial ASCT (<12mo n=14 vs. >12 n=27)</td><td>-</td><td>-</td><td>2.4 (1.1-5.5)</td><td>0.04</td></tr>
</table>
</td>
<td>Non-comparative study but reports predictive factors.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr>
<td>Sellner et al., 2013

Retrospective study
Single centre

Germany</td>
<td>Patients with relapsed myeloma who had previously undergone ASCT.</td>
<td>salvage ASCT
n=200

116 male, 84 female

median age at ASCT2 60 (range 29 – 72)

median follow-up after ASCT: 57.1 months (95% CI, 52.7 -63.6).</td>
<td>n/a</td>
<td>Prognostic variables before salvage ASCT examined for their impact on PFS and OS included age; gender; multiple myeloma isotype; number of upfront transplantations (single vs tandem ASCT); number of prior regimens; exposure to novel agents such as thalidomide, lenalidomide, and bortezomib; use of maintenance therapy after upfront and salvage ASCT; initial PFS after upfront ASCT; response to upfront ASCT as to reinduction before salvage ASCT; ISS stage at diagnosis and before salvage ASCT; and lactate dehydrogenase levels at the time of diagnosis and before salvage ASCT.

multivariate analysis:
Lack of response to reinduction therapy, short initial PFS time after upfront ASCT, and non-immunoglobulin G isotype were identified as independent predictors for adverse PFS.

Short initial PFS time after upfront ASCT, no use of bortezomib or lenalidomide for reinduction, elevated lactate dehydrogenase levels at salvage ASCT, and an ISS stage of II or III before salvage ASCT were found to be independent predictors for OS.

Cytogenetics:
The prognostic impact of chromosomal aberrations on PFS and OS was assessed for a subgroup of patients with available cytogenetic data.
gain of 1q21 in 41 of 71 patients (58%)
deletion of 17p13 in 14 of 80 patients(18%)
t(4;14) in 9 of 80 patients (11%)

The presence of del(17p13), t(4;14), and +1q21 was associated with adverse impact on both PFS and OS.
However, due to the low numbers of patients, this effect did not reach statistical significance when each subgroup was analyzed individually.

<table>
<tr><th></th><th>median PFS</th><th>4-year OS rate</th></tr>
<tr><td>adverse FISH:
+1q21, t(4;14), and del(17p13)</td><td>13.2 months</td><td>52%</td></tr>
<tr><td>absence of cytogenetic abnormalities</td><td>25.6 months</td><td>71%</td></tr>
<tr><td></td><td>p=0.03</td><td>p=0.09</td></tr>
</table>
</td>
<td>Non-comparative study but reports predictive factors.</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Multivariate analysis of PFS and OS
<table>
<tr><th></th><th colspan="2">PFS</th><th colspan="2">OS</th></tr>
<tr><th></th><th>HR (95%CI)</th><th>p</th><th>HR (95%CI)</th><th>p</th></tr>
<tr><td>Response to reinduction (<PR vs >PR)</td><td>1.64 (1.12-2.41)</td><td>0.01</td><td>-</td><td>-</td></tr>
<tr><td>Remission duration after ASCT1
12-18 mo vs >18 mo
0-12 mo vs >18 mo</td><td>
1.71 (1.08-2.72)
1.68 (0.69-4.07)</td><td>0.04</td><td>
2.66 (1.59-4.45)
2.54 (1.26-5.09)</td><td><0.001</td></tr>
<tr><td>Reinduction with lenalidomide or bortezomib vs thalidomide or chemotherapy</td><td>-</td><td>-</td><td>0.15 (0.04-0.64)</td><td>0.01</td></tr>
<tr><td>LDL level at ASCT2</td><td>-</td><td>-</td><td>1.26 (1.01-1.56)</td><td>0.04</td></tr>
<tr><td>Paraprotein type
Bence Jones vs IgG
IgA vs IgG
Other vs IgG</td><td>
2.15 (1.18-3.93)
1.26 (0.83-1.93)
2.55 (1.10-5.90)</td><td>0.02</td><td>-</td><td>-</td></tr>
<tr><td>ISS stage prior to ASCT2
II vs I
III vs I</td><td>-</td><td>-</td><td>
2.06 (1.22-3.49)
2.39 (1.29-4.44)</td><td>0.003</td></tr>
</table></td><td></td></tr>
<tr><td>Shah et al., 2012

Retrospective study
Single-centre

USA</td><td>Patients with relapsed myeloma who had previously undergone ASCT</td><td>salvage ASCT
n=44

24 male, 20 female

median age at salvage transplant was 55 years (range 38–73)

median time between the first auto-HCT and</td><td>n/a</td><td>In each multivariate regression model, the covariates included age, gender, race, log(CD34+ cell dose), time to progression after first therapy sequence, number of prior therapies before salvage auto-HCT, ISS stage, immunoglobulin subtype, and date of transplant (before or after January 1, 2003)

Multivariate analysis results:
shorter TTP after first transplant, larger number of prior therapies, race being African-American, and IgG subtype were significantly associated with worse OS.

Detection of high-risk chromosomal abnormalities showed a trend towards a</td><td>Non-comparative study but reports predictive factors.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td>the salvage auto-HCT was 30 months (range 2–78)

median follow up time from salvage transplant in surviving patients was 41 months.</td><td></td><td>shorter OS (p=0.07).
Small sample size - 11 patients had high risk cytogenetic abnormalities.</td><td></td></tr>
<tr><td>Wirk et al., 2013

Retrospective study
Single centre

USA</td><td>Patients with relapsed myeloma who had previously undergone ASCT</td><td>salvage ASCT
n=27

16 male, 11 female

median age 62 (32 – 69)

median interval from ASCT1 to ASCT2 was 30 months

median months of follow up from diagnosis 57 (19-115)</td><td>n/a</td><td>The following factors were analysed for their impact on OS: time from autoHCT1 to salvage HCT2 < 1 year vs. ≥ 1 year or < 2 years vs. ≥ 2 years, time from autoHCT1 to relapse < 1 year vs. ≥ 1 year or < 18 months vs. ≥ 18 months, and the following factors at autoHCT2: age, gender, KPS < 70% vs.≥ 70%, HCT CI < 2 vs. ≥ 2, stage by Durie-Salmon and International Staging System, B2M < 3.5 mg/L vs. ≥ 3.5 mg/L, albumin < 3.5 g/dL vs. ≥ 3.5 g/dL, immunochemical type of MM, induction chemotherapy with conventional vs. novel agents, number of lines of chemotherapy, chemosensitivity vs. chemoresistance, standard vs. intermediate vs. high risk cytogenetics, disease status CR/VGPR vs. others, time from autoHCT1 to relapse, type of relapse bone marrow vs. extramedullary, time from relapse to autoHCT2. Additionally, the authors analyzed best response after HCT2 CR/VGPR vs. others, time from diagnosis to autoHCT1, conditioning before autoHCT2 melphalan vs. others, stem cell source before HCT2, maintenance therapy after HCT2 none vs. given, autoHCT2 in first or greater relapse, year of HCT2 < 2006 vs. ≥ 2006, time from HCT2 to relapse, and relapse after HCT2 yes vs. no.

multivariate analysis:

factors associated with OS
<table>
<tr><th>factor</th><th>HR</th></tr>
<tr><td>time from ASCT1 to relapse < 1 year vs. ≥ 1year</td><td>24.81 (2.4-249.9)</td></tr>
<tr><td>no maintenance therapy vs. given after ASCT2</td><td>12.19 (2.5-249.9)</td></tr>
</table>
factors associated with PFS
<table>
<tr><th>factor</th><th>HR</th></tr>
<tr><td>time from ASCT1 to relapse < 1 year vs. ≥ 1year</td><td>18.55 (2.28-150.57)</td></tr>
</table>
PFS and OS was associated with time to progression after ASCT1
<table>
<tr><th></th><th>< 1 year</th><th>≥ 1year</th></tr>
</table></td><td>Non-comparative study but reports predictive factors.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Results</th><th>Additional comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>n</td><td>12</td><td>15</td></tr>
<tr><td>median OS</td><td>15 months (range 1-53)</td><td>Not yet reached at 143 months</td></tr>
<tr><td>Median PFS</td><td>5 months (range 1-49)</td><td>not yet reached at 88 months</td></tr>
</table>
no factors impacted NRM
</td><td></td></tr>
<tr><td>Yhim et al., 2013

Retrospective study: matched-pair analysis

Korea</td><td>Patients with relapsed myeloma who had previously undergone ASCT.

median follow-up of 55.3 months (range, 3.4–140.0 months</td><td>Salvage second ASCT
n=48

32 male, 16 female

median age at relapse 54.5
(39.0 – 65.1)</td><td>salvage systemic chemotherapy alone
n=144

Matched 1:3 to the salvage ASCT group for nine potential prognostic factors.

74 male, 70 female

median age at relapse 55.7
(33.4 – 68.5)</td><td>Good prognosis subgroup: TTP >18 months after first ASCT and ISS I or II.
Poor prognosis subgroup: TTP ≤18 months after first ASCT and/or ISS III.

Good prognosis subgroup
<table>
<tr><th></th><th>n</th><th>Median OS (95% CI)</th><th>Median PFS (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>13</td><td>75.3 months (55.2–88.0)</td><td>48.1 months (17.4–78.8)</td></tr>
<tr><td>Salvage chemotherapy</td><td>34</td><td>77.3 months</td><td>24.4 months (15.2–33.7)</td></tr>
<tr><td></td><td></td><td>p=0.919</td><td>p=0.118</td></tr>
</table>
Poor prognosis subgroup
<table>
<tr><th></th><th>n</th><th>Median OS (95% CI)</th><th>Median PFS (95% CI)</th></tr>
<tr><td>Salvage ASCT</td><td>35</td><td>49.9 months (19.4–80.4)</td><td>13.0 months (10.0–16.1)</td></tr>
<tr><td>Salvage chemotherapy</td><td>110</td><td>17.2 months (11.5–22.9)</td><td>6.4 months (5.2–7.6)</td></tr>
<tr><td></td><td></td><td>p=0.026</td><td>p=0.010</td></tr>
</table>
</td><td>Limitations:
• retrospective data

• small number of patients in the salvage ASCT group

• choice of therapy after relapse is often governed by a complex list of unmeasured factors that can potentially affect outcomes. Although the study adjusted for potential risk factors by a matched-pair analysis, only a randomized trial comparing second auto-SCT to systemic chemotherapy alone can exclude potential selection bias.</td></tr>
</table>

References of included studies

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2. Auner HW, Szydlo R, Rone A, Chaidos A, Giles C, Kanfer E, Macdonald DH, Marin D, Milojkovic D, Pavlu J, Apperley JF, Rahemtulla A. (2013) Salvage autologous stem cell transplantation for multiple myeloma relapsing or progressing after up-front autologous transplantation. Leuk Lymphoma 54(10), 2200-2204.
3. Chow, A. W., Lee, C. H., Hiwase, D. K., To, L. B. & Horvath, N. (2013) Relapsed multiple myeloma: who benefits from salvage autografts? Internal Medicine Journal, 43: 156-161.
4. Cook, G., Liakopoulou, E., Pearce, R., Cavet, J., Morgan, G. J., Kirkland, K., Lee, J., Davies, F. E., Hall, R., Rahemtulla, A., Russell, N., Marks, D. I. & British Society of Blood & Marrow Transplantation Clinical Trials Committee. (2011) Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. Biology of Blood & Marrow Transplantation, 17: 1638-1645.
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8. Grovdal, M., Nahi, H., Gahrton, G., Liwing, J., Waage, A., Abildgaard, N. et al. (2015). Autologous stem cell transplantation versus novel drugs or conventional chemotherapy for patients with relapsed multiple myeloma after previous ASCT. Bone Marrow Transplantation, 50, 808-812.
9. Jimenez-Zepeda, V. H., Mikhael, J., Winter, A., Franke, N., Masih-Khan, E., Trudel, S., Chen, C., Kukreti, V. & Reece, D. E. (2012) Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biology of Blood & Marrow Transplantation, 18: 773-779.
10. Lemieux, E., Hulin, C., Caillot, D., Tardy, S., Dorvaux, V., Michel, J., Gastinne, T., Rossi, C., Legouge, C., Touzeau, C., Planche, L., Loirat, M., Lafon, I. & Moreau, P. (2013) Autologous stem cell transplantation: an effective salvage therapy in multiple myeloma. Biology of Blood & Marrow Transplantation, 19: 445-449.
11. Michaelis, L.C., Saad, A., Zhong, X., et al. (2013) Salvage second hematopoietic cell transplantation in myeloma. Biology of Blood & Marrow Transplantation, 19: 760-766.
12. Olin, R. L., Vogl, D. T., Porter, D. L., Luger, S. M., Schuster, S. J., Tsai, D. E., Siegel, D. L., Cook, R. J., Mangan, P. A., Cunningham, K. & Stadtmauer, E. A. (2009) Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplantation, 43: 417-422.
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Table 4: Excluded papers (after checking full text)

Paper	Reasons for exclusion
1. Atanackovic, D. & Schilling, G. (2013) Second autologous transplant as salvage therapy in multiple myeloma. [Review]. *British Journal of Haematology,* 163: 565-572.	Expert review.
2. Burzynski, J. A., Toro, J. J., Patel, R. C., Lee, S., Greene, R. E., Ochoa-Bayona, J. L., Frei, C. R. & Freytes CO. (2009) Toxicity of a second autologous peripheral blood stem cell transplant in patients with relapsed or recurrent multiple myeloma. *Leukemia & Lymphoma,* 50: 1442-1447.	Non-comparative study and no predicative factors reported.
3. Byrne, M. (2014). Tandem Autologous Stem Cell Transplantation for Multiple Myeloma Patients Based on Response to Their First Transplant-A Prospective Phase II Study. Clinical Medicine Insights, Oncology. 8, 101-105.	Patients selected for second ASCT based on response to first ASCT.
4. Mehta, J., Tricot, G., Jagannath, S., Ayers, D., Singhal, S., Siegel, D., Desikan, K., Munshi, N., Fassas, A., Mattox, S., Vesole, D., Crowley, J. & Barlogie, B. (1998) Salvage autologous or allogeneic transplantation for multiple myeloma refractory to or relapsing after a first-line autograft? *Bone Marrow Transplantation,* 21: 887-892.	Not relevant to PICO. Second ASCT compared to allogeneic transplant which is excluded from the PICO.
5. Morris, C., Iacobelli, S., Brand, R., Bjorkstrand, B., Drake, M., Niederwieser, D., Gahrton, G. & Chronic Leukaemia Working Party Myeloma Subcommittee, E. G. f. B. a. M. T. (2004) Benefit and timing of second transplantations in multiple myeloma: clinical findings and methodological limitations in a European Group for Blood and Marrow Transplantation registry study. *Journal of Clinical Oncology,* 22: 1674-1681.	Not relevant to PICO. Comparison of second transplant after relapse vs tandem transplant upfront.
6. Oyan, B., Koc, Y., Ozdemir, E., Kars, A., Turker, A., Tekuzman, G. & Kansu, E. (2009) High complete remission rate and durable remissions achieved with rational use of autologous stem-cell transplantation, thalidomide maintenance, and non-myeloablative allogeneic transplantation in patients with multiple myeloma. *Clinical Transplantation,* 23: 839-847.	Small sample size. Only 3 patients underwent second autologous transplant.
7. Smethurst, D. P. (2012). Aggregated analysis of reported efficacy for salvage autologous stem-cell transplantation for myeloma. Annals of Oncology, Conference, ix354-ix355.	Conference abstract – insufficient information to fully appraise the study.
8. Tan, Y., Xu, S. N., Li, X., & Chen, J. P. (2014). Non-myeloablative stem cell transplantation in the treatment of multiple myeloma after first autologous stem cell transplantation: a systematic review (Provisional abstract). Database.of Abstracts.of Reviews.of Effects., 306-311.	Chinese language
9. Vangsted, A. J. (2010). Improved survival of multiple myeloma patients with late relapse after high-dose treatment and stem cell support, a population-based study of 348 patients in Denmark in 1994-2004. European Journal of Haematology, 85, 209-216.	Comparison not in PICO

Table 5: Checklists to identify risk of bias

5a. comparative studies

Study identification: Alvares et al 2006					
Myeloma			**Topic I**		
Study Type			Retrospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? unclear				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? unclear				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between	Yes	No	Unclear	N/A

	groups in terms of those for whom outcome data were not available)				
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

Study identification: Cook et al 2011					
Myeloma			**Topic I**		
Study Type			Retrospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					

Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? n/a				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? n/a				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

Study identification: Cook et al 2014					
Myeloma		**Topic I**			
Study Type		Randomised controlled trial			
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of	Yes	No	Unclear	N/A

	allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)				
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? ASCT2: 6 patients received no treatment: 3 had progressive disease between randomisation and ASCT, 1 patient not well enough for ASCT, 1patient withdrew post randomisation but before ASCT), 1 unknown Cyclophosphamide: 1 patient received no treatment (clinician decided on alternative treatment)				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A

D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

Study identification: Yhim et al 2013					
Myeloma			**Topic I**		
Study Type			Retrospective analysis		
A. Selection bias (systematic differences between the comparison groups)					
A1	The method of allocation to treatment groups was unrelated to potential confounding factors (that is, the reason for participant allocation to treatment groups is not expected to affect the outcome[s] under study)	Yes	No	Unclear	N/A
A2	Attempts were made within the design or analysis to balance the comparison groups for potential confounders	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? n/a				
	b. The groups were comparable for treatment completion (that is, there	Yes	No	Unclear	N/A

	were no important or systematic differences between groups in terms of those who did not complete treatment)				
C3	a. For how many participants in each group were no outcome data available? n/a				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

1

Study identification: Grovdal et al 2015					
Myeloma			**Topic I**		
Study Type			Observational study		
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomization was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			

Likely direction of effect: - younger fitter patients selected for ASCT2 which would favour ASCT2 outcomes					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group? None – patients were selected based on treatment they already had – so the completion rate is unknown				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? 0				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available)	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect: unclear.					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					

5b. single intervention prognostic studies

Auner et al., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Chow et al., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	No*
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

**results are from univariate analysis. Multivariate analysis not done.*

Fenk et al., 2011		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

1

Gonsalves et al., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

2

Jimenez-Zepeda et al., 2012		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

3

Lemieux et al., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

4

Michaelis eta l., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes

1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

1
2

Olin et al., 2009		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

3

Sellner et al., 2013		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

4

Shah et al., 2012		
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

5

Wirk et al., 2013

1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Search strategies

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 1 – Communication & Support **Literature search summary**

What are the specific information and support needs of patients with myeloma and their families and carers?

1. Literature search details

Search 1 – Myeloma population

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	706	121	23/05/2014
Premedline	May 22, 2014	39	13	23/05/2014
Embase	1974 -	1746	343	23/05/2014
Cochrane Library	As per database	67	11	23/05/2014
Web of Science (SCI & SSCI)	1970 -	768	94	28/05/2014
AMED	1985 -	15	7	23/05/2014
Psycinfo	1806 -	59	17	23/05/2014
Cinahl	1937 -	22	20	23/05/2014

Total References retrieved (after de-duplication): 435

Search 2 – Haematological cancer population

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1096	226	17/06/2014
Premedline	June 16, 2014	38	16	17/06/2014
Embase	1974 -	1249	320	19/06/2014
Cochrane Library	As per database	332	35	18/06/2014
Web of Science (SCI & SSCI)	1970 -	861	156	18/06/2014

AMED	1985 -	22	14	17/06/2014
Psycinfo	1806 -	66	47	17/06/2014
Cinahl	1937 -	25	18	17/06/2014

Total References retrieved (after de-duplication): 550

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 exp Hematologic Neoplasms/
8 (haematolog$ or hematolog$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
9 or/1-8
10 patient-centred$.tw.
11 "patient-reported outcom$".tw.
12 PROMS.tw.
13 Consumer Satisfaction/
14 exp Consumer Participation/
15 exp Personal Satisfaction/
16 exp Patient Participation/
17 exp Attitude to Health/
18 exp "Patient Acceptance of Health Care"/
19 Patient Compliance/
20 exp Patient Satisfaction/
21 ((client$ or patient$ or user$ or carer$ or consumer$ or customer$) adj2 (attitud$ or priorit$ or perception$ or preferen$ or expectation$ or choice$ or perspective$ or view$ or satisfact$ or opinion$ or concern$ or issue$)).tw.
22 or/10-21
23 Choice Behavior/
24 Decision Making/
25 Decision Support Techniques/
26 decision$.tw.
27 (choic$ or preference$).tw.
28 or/23-27
29 Patient Compliance/
30 Informed Consent/
31 Treatment Refusal/
32 exp Consumer Satisfaction/
33 exp Consumer Participation/
34 exp Health Education/
35 or/29-34
36 28 and 35
37 ((patient$ or consumer$) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
38 ((man or men) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
39 ((personal or interpersonal or individual) adj (decision$ or choice$ or prefer$ or participat$)).tw.
40 or/37-39
41 Pamphlets/
42 pamphlet$.tw.
43 (leaflet$ or diary or diaries or booklet$ or guidebook$).tw.

44 sheet$.tw.
45 Cues/
46 cue$.tw.
47 (prompt$ or coach$).tw.
48 (checklist$ or check list$).tw.
49 (written or write).tw.
50 question$.tw.
51 (card$ or helpcard$).tw.
52 (video$ or tape$ or cd$ or film$ or dvd$ or telephone$ or phone$ or computer$ or internet or electronic).tw.
53 *internet/
54 or/41-53
55 Communication/
56 communicat$.tw.
57 Patient Education/
58 ((patient$ or consumer$) adj3 (educat$ or skill$ or teach$ or train$ or coach$)).tw.
59 55 or 56
60 57 or 58
61 59 and 60
62 54 or 61
63 (preconsultation$ or pre-consultation$).tw.
64 Office Visits/
65 (office adj3 visit$).tw.
66 consult$.tw.
67 (medical adj3 interview$).tw.
68 waiting room$.tw.
69 scheduled appointment$.tw.
70 ((prior adj3 visit$) or previsit$).tw.
71 "Appointments and Schedules"/
72 or/63-71
73 62 and 72
74 (information adj3 need$).tw.
75 information material$.tw.
76 (patient$ adj3 information).tw.
77 (information adj3 web$1).tw.
78 (information adj3 print$).tw.
79 (information adj3 electronic$).tw.
80 or/74-79
81 73 or 80
82 40 and 81
83 nurs$.mp.
84 (key adj worker).tw.
85 CNS.tw.
86 or/83-85
87 Physician-Patient Relations/ or Hospital-Patient Relations/ or Nurse-Patient Relations/ or Professional-Patient Relations/
88 exp Psychotherapy/
89 exp Cognitive Therapy/
90 exp Counseling/
91 exp Self-Help Groups/
92 exp Social Support/
93 exp Hotlines/
94 exp Telephone/
95 exp Internet/
96 ((hot or help$ or tele$) adj line$).mp.
97 (internet or website$).mp.
98 ((cognit$ or group$ or psycho$) adj (therap$ or supp$ or session$)).mp.
99 ((self help$ or supp$ or counsel$) adj (group$ or session$)).mp.
100 or/87-98
101 22 or 82 or 86 or 100
102 9 and 101

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected. An initial search for the myeloma patient population was undertaken first, and then extended to haematological cancers in case there was no myeloma-specific literature of which in the end there was.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search. date limit of 2014 onwards. The Haematological Cancers search for this topic was not re-run as the GDG only wanted myeloma.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	751 – 74 sifted	5	08/06/2015
Premedline (5 June, 2015)	46	5	08/06/2015
Embase	2074 – 433 sifted	40	08/06/2015
Cochrane Library	78 (full)	0	08/06/2015
Web of Science (SCI & SSCI)	849 – 99 sifted	8	08/06/2015
AMED	17 – 2 sifted	0	08/06/2015
Psycinfo	68 – 9 sifted	2	08/06/2015
Cinahl	28 – 6 sifted	3	08/06/2015

Total References retrieved (after de-duplication): 50

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 2 – Laboratory Investigations Literature search summary

What is the optimal laboratory testing strategy for suspected myeloma?

1. Literature search details

Database name	Dates Covered	No of records found	No of references retrieved	Finish date of search
Medline	1946 -	1649	1649	23/07/2014
Premedline	22 July, 2014	21	21	23/07/2014
Embase	1974 -	960	960	24/07/2014
Cochrane Library	As per database	102	102	24/07/2014
Web of Science (SCI & SSCI)	1970 -	5172	5172	24/07/2014

Total References retrieved (after de-duplication): 7904 then sifted down to 3509

Medline search strategy *(This search strategy is adapted to each database)*

1. exp multiple myeloma/
2. exp neoplasms, plasma cell/
3. exp plasmacytoma/
4. (myelom* or plasmacytom*).tw.
5. (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6. "Monoclonal Gammopathy of Undetermined Significance"/
7. MGUS.tw.
8. monoclonal gammopath*.tw.
9. or/1-8
10. exp Bone Marrow Examination/
11. Bone Marrow/pa [Pathology]
12. (bone marrow adj3 (biops* or immunophenotyp* or aspirat*)).tw.
13. (trephine adj3 biops*).tw.
14. immunophenotyp*.tw.
15. exp Electrophoresis/
16. (protein* adj2 electrophoresis).tw.
17. immunofix*.tw.
18. exp Bence Jones Protein/
19. exp Immunoglobulin Light Chains/
20. light chain*.tw.
21. bence jones.tw.
22. exp Immunodiffusion/
23. cytogenetics/
24. exp Immunoelectrophoresis/
25. exp Diagnosis, Differential/
26. ((laboratory or lab) adj2 (test or tests or testing)).tw.
27. pa.fs.
28. or/10-27

29. 9 and 28
30. exp "Sensitivity and Specificity"/
31. sensitivity.tw.
32. specificity.tw.
33. ((pre-test or pretest) adj probability).tw.
34. post-test probability.tw.
35. predictive value$.tw.
36. likelihood ratio$.tw.
37. or/30-36
38. 29 and 37

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Search filter applied (as per search strategy detailed above). No date limits applied on the search. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1728 – 128 sifted	122	08/06/2015
Premedline (8 June, 2015)	19	19	08/06/2015
Embase	1164 – 238 sifted	217	08/06/2015
Cochrane Library	131 – 25 sifted	25	08/06/2015
Web of Science (SCI & SSCI)	5563 – 407 sifted	380	08/06/2015

Total References retrieved (after de-duplication): 628 then sifted down to 289

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 2 – Laboratory Investigations Literature search summary

Can investigations done at the diagnosis of myeloma, including trephine biopsy, immunophenotyping and cytogenetic and molecular genetic tests accurately predict treatment outcomes (for example, can they identify patients with a poor prognosis for whom an alternative treatment approach may be preferable)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2005 onwards	2900	836	11/11/2014
Premedline	22 Oct, 2014	120	26	23/10/2014
Embase	2005 onwards	3128	1392	17/03/2015
Cochrane Library	As per database	1626	79	14/11/2014
Web of Science (SCI & SSCI)	2005 onwards	3862	1224	27/03/2015

Total References retrieved (after de-duplication): 2457

Medline search strategy *(This search strategy is adapted to each database)*

1. exp multiple myeloma/
2. exp neoplasms, plasma cell/
3. exp plasmacytoma/
4. (myelom* or plasmacytom*).tw.
5. (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6. "Monoclonal Gammopathy of Undetermined Significance"/
7. MGUS.tw.
8. monoclonal gammopath*.tw.
9. or/1-8
10. exp Bone Marrow Examination/
11. Bone Marrow/pa [Pathology]
12. (bone marrow adj3 (biops* or immunophenotyp*)).tw.
13. In Situ Hybridization, Fluorescence/
14. Cytogenetics/
15. exp Immunohistochemistry/
16. exp Immunoglobulins/
17. light chain*.tw.
18. heavy chain*.tw.
19. exp Flow Cytometry/
20. exp Immunophenotyping/
23. exp beta 2-Microglobulin/
26. (risk adj (group* or categor*)).tw.
27. (high-risk or high risk).tw.

28. fluorescence in situ hybridization.tw.
29. cytogenetic*.tw.
30. immunohistochem*.tw.
31. (flow adj cytometr*).tw.
32. or/10-31
33. 9 and 32
34. exp Cohort Studies/
35. exp Mortality/
36. exp Morbidity/
37. natural history.ti,ab.
38. prognos$.ti,ab.
39. course.ti,ab.
40. predict$.ti,ab.
41. exp "Outcome Assessment (Health Care)"/
42. outcome$1.ti,ab.
43. (inception adj cohort$1).ti,ab.
44. Disease Progression/
45. exp Survival Analysis/
46. exp Prognosis/
47. or/34-46
48. 33 and 47
49. limit 48 to yr="2005 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Search filter applied (as per search strategy detailed above). Date limit of 2005 onwards applied with agreement with GDG. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	Sifted 165	18	08/06/2015
Premedline (8 June, 2015)	165	23	08/06/2015
Embase	Sifted 447	33	08/06/2015
Cochrane Library	Sifted 321	0	08/06/2015
Web of Science (SCI & SSCI)	Sifted 309	32	08/06/2015

Total References retrieved (after de-duplication): 91

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 3 – Imaging Investigations Literature search summary

- **What is the optimal imaging strategy for patients with suspected myeloma?**
- **What is the most effective imaging to guide treatment decisions in patients with newly diagnosed myeloma?**

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000 -	817	267	14/08/2014
Premedline	July 15, 2014	186	29	14/08/2014
Embase	2000 -	2376	438	14/08/2014
Cochrane Library	As per database	76	19	14/08/2014
Web of Science (SCI & SSCI)	2000 -	1671	409	14/08/2014

Total References retrieved (after de-duplication): 635

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Radiography/
9 (radiograph$ or xray or x-ray).mp.
10 exp Ultrasonography/
11 (ultrasound$ or ultrasonograph$ or sonogra$ or ultrasonic or echogra$ or echotomogra$).mp.
12 exp Radionuclide Imaging/
13 (radionuclide adj1 (scan$ or imaging)).tw.
14 scintigraph$.mp.
15 exp Magnetic Resonance Imaging/
16 magnet$ resonance.mp.
17 (MRI or MRI$1 or NMR$1).tw.
18 (MR adj (imag$ or scan$)).tw.
19 (magnet$ adj (imag$ or scan$)).tw.
20 (magneti?ation adj3 imaging).tw.
21 exp Tomography/
22 exp Tomography, X-Ray Computed/
23 PET$1.tw.
24 PET-CT.tw.
25 (comput$ adj1 tomogra$).tw.
26 ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan$ or imag$ or tomogra$)).tw.

27 (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).mp.
28 ((CT or CAT) adj (scan$ or imaging or examination)).tw.
29 (PET adj (scan$ or imag$ or examination)).tw.
30 positron emission tomograph$.mp.
31 (bone adj3 (scan$ or imag$)).mp.
32 (skelet$ adj3 survey).tw.
33 MIBI.tw.
34 or/8-33
35 7 and 34
36 limit 35 to yr="2000 -Current"

2. Health Economics Literature search details

Topic D1 was selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma and no further searches were requested by the health economist.

3. Any further comments

Basic exclusions filter only and, with the agreement of the GDG, a date limit of 2000 onwards applied due to developing imaging techniques. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	862 – 124 sifted	18	08/06/2015
Premedline (5 June 2015)	221	26	08/06/2015
Embase	1769 – 703 sifted	101	08/06/2015
Cochrane Library	108 - 36 sifted	1	08/06/2015
Web of Science (SCI & SSCI)	1841 – 254 sifted	52	08/06/2015

Total References retrieved (after de-duplication): 120

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 4 – Smouldering Myeloma Literature search summary

What are the most effective primary management strategies (including observation) for patients with asymptomatic myeloma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	707	136	08/12/2014
Premedline	Dec 3, 2014	86	9	04/12/2014
Embase	1974 -	1380	203	16/12/2014
Cochrane Library	As per database	39	22	18/12/2014
Web of Science (SCI & SSCI)	1970 -	1507	242	19/12/2014

Total References retrieved (after de-duplication): 382

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp asymptomatic diseases/ or exp asymptomatic infections/
9 asymptom*.tw.
10 (smouldering or smoldering).tw.
11 SMM.tw.
12 "clinically silent".tw.
13 (indolent adj (stage or disease)).tw.
14 (early adj (stage* or disease*)).tw.
15 or/8-14
16 7 and 15

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

1

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	699 – 79 sifted	4	08/06/2015
Premedline (5 June, 2015)	99	8	08/06/2015
Embase	1527 – 398 sifted	25	08/06/2015
Cochrane Library	52 –14 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	1584 – 199 sifted	25	08/06/2015

Total References retrieved (after de-duplication): 34

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 5 – Service Organisation Literature search summary

What is the optimal configuration of local and regional haematology services for management of myeloma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	2396	455	20/11/2014
Premedline	Nov 19, 2014	130	19	20/11/2014
Embase	1974 -	2701	502	24/11/2014
Cochrane Library	As per database	138	19	25/11/2014
Web of Science (SCI & SSCI)	1970 -	5090	370	02/12/2014
AMED	1985 -	33	21	20/11/2014
Psycinfo	1806 -	62	32	20/11/2014

Total References retrieved (after de-duplication): 1022

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 Hematologic Diseases/
9 exp Hematologic Neoplasms/
10 (h?ematolog$ adj1 malignan$).tw.
11 (h?ematolog$ adj1 neoplas$).tw.
12 or/8-11
13 Physicians Practice Patterns/
14 exp Interprofessional Relations/
15 multiprofession$.tw.
16 (multi-profession$ or multi profession$).tw.
17 multidisciplinary.tw.
18 (multi-disciplinary or multi disciplinary).tw.
19 interprofession$.tw.
20 (inter-professional$ or inter profession$).tw.
21 crossdisciplinary.tw.
22 (cross-disciplinary or cross disciplinary).tw.
23 Oncologic Nursing/
24 nurs$ specialist$.tw.
25 oncology$ nurs$.tw.
26 exp Patient Care Team/
27 assessment$ team$.tw.
28 specialist$ team$.tw.
29 skill$ mix$.tw.
30 (skillmix$ or skill$-mix$).tw.
31 cancer network$.tw.
32 team meetings$.tw.
33 management plan$.tw.
34 Patient-Centered Care/
35 Continuity of Patient Care/
36 exp Delivery of Health Care, Integrated/
37 (integrated adj2 care).tw.
38 teamwork$.tw.
39 (team-work$ or team work$).tw.
40 MDT.tw.
41 exp Hospitals, Special/
42 Oncology Service, Hospital/
43 Specialism/
44 specialist$.tw.
45 (speciali?ed or speciali?ing).tw.
46 (special$ adj (unit$ or centre$ or center$ or hospital$ or clinic$1)).tw.
47 (special$ adj (facilit$ or team$ or service$)).tw.
48 (single adj (unit$ or centre$ or center$ or clinic$1)).tw.
49 ((haematolog$ or hematolog$) adj (unit$ or centre$ or center$ or clinic$1)).tw.
50 ((haematolog$ or hematolog$) adj (facilit$ or team$ or service$)).tw.
51 ((specialist$ or speciali?ed) adj2 experience).tw.
52 ((bone tumo?r$ or bone disease$ or spinal disease$) adj (unit$ or centre$ or center$ or service$)).tw.
53 (radiolog$ adj (unit$ or centre$ or center$ or service$)).tw.
54 ((radiotherap$ or radiation or irradiation) adj (unit$ or centre$ or center$ or service$)).tw.
55 (transplant$ adj (unit$ or centre$ or center$ or service$)).tw.
56 (dental$ adj (unit$ or centre$ or center$ or service$ or clinic$)).tw.
57 (renal disease$ adj (unit$ or centre$ or center$ or service$)).tw.
58 ((supportive or palliative) adj2 (unit$ or centre$ or center$ or service$ or network$)).tw.
59 ((cancer or oncology) adj (unit$ or centre$ or center$ or service$ or team$)).tw.

60 (non-specialist$ or nonspecialist$).tw.
61 exp Long-Term Care/og [Organization & Administration]
62 exp "Delivery of Health Care"/
63 ("service delivery" or "service provision").tw.
64 (access$ adj2 service$).tw.
65 or/13-64
66 7 or 12
67 65 and 66

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	2469 – 143 sifted	3	18/06/2015
Premedline (5 June 2015)	144	6	18/06/2015
Embase	2811 – 495 sifted	14	18/06/2015
Cochrane Library	150 – 15 sifted	0	18/06/2015
Web of Science (SCI & SSCI)	5325 – 262 sifted	10	18/06/2015
AMED, Psycinfo	Nothing new	Nothing new	18/06/2015

Total References retrieved (after de-duplication): 26

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 6 – Managing newly diagnosed myeloma First-line treatment — Literature search summary

- **Which patients with newly diagnosed myeloma should be considered for autologous stem cell transplantation?**
- **In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy?**

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000 onwards	1704	507	23/09/2014
Premedline	12 Sept, 2014	235	122	15/09/2014
Embase	2000 onwards	1556	710	02/10/2014
Cochrane Library	As per database	599	599	30/09/2014

Total References retrieved (after de-duplication): 1573

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Stem Cell Transplantation/
9 exp Bone Marrow Transplantation/
10 (allograft* or autograft* or allo-graft* or auto-graft*).tw.
11 (allotransplant* or allo-transplant* or autotransplant* or auto-transplant*).tw.
12 ((allogen* or allo-gen* or autolog*) adj5 (transplant* or graft* or rescue*)).tw.
13 (homograft* or homo-graft* or homotransplant* or homo-transplant*).tw.
14 (bone marrow adj2 (transplant* or graft* or rescue*)).tw.
15 ((stem cell* or stem-cell*) adj2 (transplant* or graft* or rescue*)).tw.
16 (ASCT or ABMT or SCT or BMT or HSCT or HBMT).tw.
17 exp Transplantation, Autologous/
18 exp Transplantation, Homologous/
19 exp Transplantation Conditioning/
20 exp Hematopoietic Stem Cell Mobilization/
21 (nonmyeloablat$* or non-myeloablat* or myeloablat*).tw.
22 (reduced intens* or full intens* or high intens*).tw.
23 (mini-transplant* or minitransplant*).tw.
24 (RIC or MAC).tw.
25 (graft adj2 host).tw.
26 GVHD.tw.
27 exp Graft vs Host Disease/

28 or/8-27
29 7 and 28
30 limit 29 to yr="2000 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Systematic review, RCT and observational filters were used. Date limit of 2000 onwards applied with agreement with GDG. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1769 – sifted 226	29	08/06/2015
Premedline (8 June, 2015)	309	53	08/06/2015
Embase	1838 – sifted 436	78	08/06/2015
Cochrane Library	769 – sifted 143	4	08/06/2015
Web of Science (SCI & SSCI)	Topic I – 809 total Topic F & J – 1798 total	Topic I - 157 Topic F & J - 25	08/06/2015 08/06/2015

Total References retrieved (after de-duplication): 162

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Managing newly diagnosed myeloma - Primary plasma cell leukaemia **Literature search summary**

Topic G: What are the most effective treatments for patients with primary plasma cell leukaemia?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	524	109	14/11/2014
Premedline	Nov 12, 2014	35	11	14/11/2014
Embase	1974 -	798	160	14/11/2014
Cochrane Library	As per database	4	1	14/11/2014
Web of Science (SCI & SSCI)	1970 -	720	146	14/11/2014

Total References retrieved (after de-duplication): 242

Medline search strategy *(This search strategy is adapted to each database)*
1 exp Leukemia, Plasma Cell/
2 (plasma adj cell adj leukemia).tw.
3 (plasma adj cell adj leukaemia).tw.
4 or/1-3

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	519 – 27 sifted	1	08/06/2015
Premedline (5 June, 2015)	38	0	08/06/2015
Embase	899 – 160 sifted	21	08/06/2015

Cochrane Library	7 – 2 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	731 – 42 sifted	4	08/06/2015

Total References retrieved (after de-duplication): 22

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 8 – Managing Acute Renal Disease due to Myeloma — Literature search summary

What is the optimal management of acute renal disease in patients with myeloma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1994 onwards	960	323	07/01/2015
Premedline	7 Jan, 2015	136	34	08/01/2015
Embase	1994 onwards	2210	622	14/01/2015
Cochrane Library	As per database	107	47	07/01/2015
Web of Science (SCI & SSCI)	1994 onwards	1888	482	16/01/2015

Total References retrieved (after de-duplication): 897

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Plasmapheresis/
9 exp Plateletpheresis/
10 (plasmapheres* or plateletpheres$ or thrombocytopheres$).tw.
11 (plasma adj3 exchange).tw.
12 exp Renal Replacement Therapy/
13 exp Peritoneal Dialysis, Continuous Ambulatory/
14 (h?emodialys?s or dialysis or h?emofiltration or h?emodiafiltration or CAPD).tw.
15 (CRRT or CVVH or CVVHD or CVVHDF or SCUF).tw.
16 (renal adj3 replace$).tw.
17 ((kidney or renal) adj2 (fail$ or impair$ or insufficien$ or dysfunction$ or injur$ or disease)).tw.

18 or/8-17
19 7 and 18
20 "myeloma kidney".tw.
21 "cast nephropathy".tw.
22 or/19-21
23 limit 22 to yr="1994 -Current"

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only. Date limit of last 20 years placed upon on the search at the recommendation of the GDG. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	962 – 29 sifted	3	08/06/2015
Premedline (5 June, 2015)	141	14	08/06/2015
Embase	2422 – 227 sifted	51	07/05/2015
Cochrane Library	126 – 26 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	2245 – 210 sifted	21	08/06/2015

Total References retrieved (after de-duplication): 67

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 9 – Preventing and Managing Bone Disease Literature search summary

- **What is the most effective method of preventing bone disease in patients with myeloma?**
- **What are the most effective treatments (other than chemotherapy) for non-spinal bone disease in patients with myeloma (including radiotherapy and surgical intervention)?**
- **Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma, and in which circumstances and order should they be offered?**

1. Literature search details

Topic L1 – L3 Bisphosphonates

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	673	198	21/05/2014
Premedline	May 20, 2014	11	8	21/05/2014
Embase	1974 -	951	324	21/05/2014
Cochrane Library	As per database	378	161	22/05/2014
Web of Science (SCI & SSCI)	1970 -	446	115	22/05/2014

Topic L1 – L3 Denosumab

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	151	52	15/05/2014
Premedline	May 14, 2014	8	7	15/05/2014
Embase	1974 -	154	84	15/05/2014
Cochrane Library	As per database	19	10	15/05/2014
Web of Science (SCI & SSCI)	1970 -	129	70	15/05/2014

Total References retrieved (after de-duplication): 604 in all

Topic L1 Anabolic Therapy

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	(1672) 313	39	22/05/2014
Premedline	May 21, 2014	54	6	22/05/2014

Embase	1974 -	(4303) 928	64	30/05/2014
Cochrane Library	As per database	267	37	22/05/2014
Web of Science (SCI & SSCI)	1970 -	(1557) 793	71	30/05/2014

Topic L1 Exercise

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	172	18	20/05/2014
Premedline	May 19, 2014	3	0	20/05/2014
Embase	1974 -	297	40	20/05/2014
Cochrane Library	As per database	18	11	20/05/2014
Web of Science (SCI & SSCI)	1970 -	98	30	20/05/2014

Topic L1 Calcium and Vitamin D

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	910	50	15/05/2014
Premedline	May 14, 2014	28	2	15/05/2014
Embase	1974 -	748	40	30/05/2014
Cochrane Library	As per database	57	13	16/05/2014
Web of Science (SCI & SSCI)	1970 -	663	31	30/05/2014

Total References retrieved (after de-duplication): 268 in all

Topic L2 and L3

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1863	360	21/07/2014
Premedline	July 18, 2014	160	35	21/07/2014
Embase	1974 -	2969	620	22/07/2014
Cochrane Library	As per database	197	24	21/07/2014

Web of Science (SCI & SSCI)	1970 -	1290	354	21/07/2014

Total References retrieved (after de-duplication): 942

Medline search strategy *(This search strategy is adapted to each database)*
Bisphosphonates Search
1 exp Diphosphonates/
2 exp Organophosphorus Compounds/
3 exp Phosphoric Acids/
4 (bisphosphonat$ or diphosphonat$).af.
5 etidron$.af.
6 didron$.af.
7 difosfen.af.
8 osteodidronel.af.
9 osteum.af.
10 "disodium dihydrogen(1-hydroxyethylidene)diphosphonate".af.
11 pamidronate.af.
12 APD.af.
13 aredia.af.
14 "disodium 3-amino-1-hydroxypropylidenebisphosphonate".af.
15 clodronate.af.
16 bonefos.af.
17 loron.af.
18 ascredar.af.
19 lodronat.af.
20 lytos.af.
21 ostac.af.
22 clastoban.af.
23 clasteon.af.
24 difosfonal.af.
25 ossiten.af.
26 mebonat.af.
27 "disodium (dichloromethylene) diphosphonate tetrahydrate".af.
28 tiludron$.af.
29 skelid.af.
30 "disodium dihydrogen{[(p-chlorophenyl)thio]methylene}diphosphonate hemihydrate".af.
31 risedron$.af.
32 actonel.af.
33 "sodium trihydrogen[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonate".af.
34 alendron$.af.
35 fosamax.af.
36 adronat.af.
37 alendros.af.
38 dronal.af.
39 "aminohydroxybutylidene diphosphonic acid".af.
40 neridron$.af.
41 AHDP.af.
42 "(6-amino-1-hydroxyhexylidene)diphosphonic acid".af.
43 zoledron$.af.
44 zometa.af.
45 ibandron$.af.
46 bondronat.af.
47 "(1-hydroxy-3-[methylpentylamino]propylidene)diphosphonic acid".af.
48 olpadron$.af.
49 OPD.af.
50 "(3-dimethylamino-1-hydroxypropylidene)bisphosphonate".af.
51 incadron.af.

52 YM175.af.
53 YM 175.af.
54 minodron$.af.
55 YM529.af.
56 YM 529.af.
57 or/1-56
58 exp Multiple Myeloma/
59 exp Neoplasms, Plasma Cell/
60 exp Plasmacytoma/
61 (myeloma* or plasmacytoma).tw.
62 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
63 Kahler*.tw.
64 or/58-63
65 57 and 64

Denosumab Search
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp RANK Ligand/
9 (denosumab or prolia or xgeva).tw.
10 4EQZ6YO2HI.rn.
11 or/8-10
12 7 and 11

Anabolic Therapy Search
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 (bortezomib or velcade).tw.
9 (carfilzomib or kyprolis).tw.
10 (anabolic adj bone).tw.
11 (bone adj anabolic).tw.
12 (bone adj prevent$).tw.
13 (prevent$ adj bone).tw.
14 or/8-13
15 7 and 14

Exercise Search
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Exercise/ or exp Exercise Therapy/
9 exp Sports/
10 Physical Fitness/
11 (exercis$ or sport$).mp.
12 physical fitness.mp.
13 physical activit$.mp.

14 or/8-13
15 7 and 14

Calcium & Vitamin D Search
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Calcium/
9 exp Calcium, Dietary/
10 calcium.tw.
11 exp Vitamin D/
12 (vitamin D or vitamin D2 or vitamin D3).tw.
13 (calcitriol or cholecalciferol or colecalciferol or ergocalciferol$ or alphacalcidol or alfacalcidol or hydroxycholecalciferol or dihydrotachysterol).tw.
14 exp Ergocalciferols/
15 exp Cholecalciferol/
16 or/8-15
17 7 and 16

L2-L3 (Surgery etc) Search
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Kyphoplasty/
9 exp Vertebroplasty/
10 (vertebroplast$ or kyphoplast$ or lordoplast$).tw.
11 exp Fracture Fixation/
12 exp Orthopedic Procedures/
13 ((vertebra$ or cement$) adj3 augment$).tw.
14 (pinning or plating or fixation or bracing).tw.
15 (spinal adj3 (surgery or rehabilitation)).tw.
16 or/8-15
17 7 and 16
18 exp Bone Neoplasms/
19 exp neoplasm metastasis/
20 exp "bone and bones"/
21 19 and 20
22 ((bone$ or skelet$ or spinal or vertebra$ or osseous or osteo$) adj3 (disease$ or lesion$ or tumor$ or tumour$ or second$ or metast$ or spread$)).mp.
23 18 or 21 or 22
24 exp hypercalcemia/
25 exp Fractures, Bone/
26 exp spinal cord compression/
27 (hypercalc$ or fractur$ or break$ or compress$).mp.
28 or/24-27
29 exp neoplasms/
30 28 and 29
31 exp Osteolysis/
32 (bone$ or skelet$ or spinal or spine or vertebra$ or osseous or osteo$ or fractur$ or compress$).mp.
33 23 or 30 or 31 or 32
34 7 and 33
35 exp Pain/ or exp Pain Management/

36 pain.ti,ab.
37 35 or 36
38 34 and 37
39 exp Radiotherapy/
40 exp Radiation/
41 (radiotherapy or radiation or irradiation).tw.
42 or/39-41
43 7 and 42 and 33
44 17 or 38 or 43

2. Health Economics Literature search details

Topics L1 and L2 were not selected, but Topic L3 was selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma and no further searches were requested by the health economist.

3. Any further comments

Systematic review and RCT filters applied to the bisphosphonates search. On all other searches, basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	688 (bisphos) – 29 sifted 165 (denosumab) – 20 sifted 369 (anabolic) - 61 sifted 929 (calcium/vitd) – 33 sifted 183 (exercise) – 12 sifted 1907 (surgery etc) – 94 sifted	15	08/06/2015
Premedline (8 June, 2015)	10 (bisphos) 8 (denosumab) 69 (anabolic) 28 (calcium/vitd) 5 (exercise) 200 (surgery etc)	27	08/06/2015
Embase	1003 (bisphos) – 91 sifted 484 (denosumab) – 114 sifted 1287 (anabolic) – 200 sifted 1581 (calcium/vitd) – 67 sifted 343 (exercise) – 413 sifted 4337 (surgery etc) – 710 sifted	133	08/06/2015
Cochrane Library	426 (bisphos) – 49 sifted 34 (denosumab) – 6 sifted 360 (anabolic) – 78 sifted 82 (calcium/vitd) – 9 sifted 20 (exercise) – 5 sifted 221 (surgery etc) – 15 sifted	12	08/06/2015
Web of Science (SCI & SSCI)	514 (bisphos) – 135 sifted 148 (denosumab) – 21 sifted 860 (anabolic) – 149 sifted 703 (calcium/vitd) – 49 sifted 113 (exercise) – 13 sifted 1361 (surgery etc) – 106 sifted	55	08/06/2015

Total References retrieved (after de-duplication): 151

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 10 – Preventing and Managing Complications – preventing infection — Literature search summary

What is the most effective prophylactic strategy for infection in patients with myeloma (including immunoglobulin, antibiotics, growth factors and vaccinations)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1514	260	23/01/2015
Premedline	21 Jan, 2015	160	13	22/01/2015
Embase	1974 -	2253	468	27/01/2015
Cochrane Library	As per database	444	89	20/01/2015
Web of Science (SCI & SSCI)	1970 -	1996	370	05/02/2015

Total References retrieved (after de-duplication): 746

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Colony-Stimulating Factors/
9 (RHG?CSF$ or RH-G?CSF$ or RHGM?CSF$ or RH-GM?CSF$ or RMETHUG$ or RHMETHUG$ or R-METHUG$ or RH-METHUG$ or R?METHUG?CSF$ or RHUG$ or RHUG?CSF$ or RHUGM$ or RHUGM?CSF$ or GCSF$ or G-CSF$ or G?CSF$ or GM-CSF$ or GMCSF$ or GM?CSF$).tw.
10 (granulo?yt$ adj3 fa?tor$).tw.
11 (ma?rophag$ adj3 fa?tor$).tw.
12 (h?emato$ adj3 growth$ adj3 factor$).tw.
13 (colon$ adj3 stimulat$ adj3 factor$).tw.
14 (filgrastim$ or neupogen).tw.
15 (filgrastim$ or peg?filgrastim$ or neupogen or neulasta or nivestim or ratiograstim or Zarzio or religrast$ or nugraf$ or lenograstim$ or regrarmostim$ or ecograrmostim$ or molgrarmostim$ or sargrarmostim$ or nartograstim$ or pegnartograstim$ or leukine or leucomax or granocyte or Euprotin or leridistim$ or macrogen$ or Mielogen$).tw.
16 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 exp Anti-Bacterial Agents/
18 exp Antibiotic Prophylaxis/

19 (antibiotic$ or antimicrobial$ or anti-microbial$ or antimycobacterial$ or anti-mycobacterial$ or antibacterial$ or anti-bacterial$).mp.
20 exp Quinolones/
21 (ciprofloxacin or ofloxacin or norfloxacin or pefloxacin or moxifloxacin or levofloxacin or gemifloxacin or gatifloxacin).mp.
22 exp Trimethoprim-Sulfamethoxazole Combination/
23 trimethoprim-sulfamethoxazole.mp.
24 TMP-SMZ.mp.
25 Co-trimoxazole$.tw.
26 exp Sulfonamides/
27 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 exp Vaccination/
29 vaccin*.tw.
30 28 or 29
31 exp Immunoglobulins/
32 (Immunoglobulin$ or gammaglobulin$ or gamma globulin$ or immune globulin$ or omrigam or sandoglobulin* or ivig or hyperimmune* or Alphaglobin or Endobulin or Gamimune or Gamimmune or Gamimune N or Gamimmune N or Intraglobin F or Venimmune or Venoglobulin-I or Venoglobulin I or VenoglobulinI or Venoglobulin or Iveegam or Intraglobin or Gammagard or Gammonativ or Globulin-N or Globulin N or GlobulinN).tw.
33 31 or 32
34 exp Antiviral Agents/
35 exp Antifungal Agents/
36 (antiviral$ or anti-viral$ or antifungal$ or anti-fungal$).mp.
37 34 or 35 or 36
38 exp Pneumocystis Infections/
39 exp Pneumocystis/
40 (pcp or pneumocystis).mp.
41 38 or 39 or 40
42 prevention & control.fs.
43 exp Chemoprevention/
44 prevention.tw.
45 (prophylaxis or prophylactic or chemoprophylaxis).mp.
46 42 or 43 or 44 or 45
47 exp Infection/
48 infection$.tw.
49 exp Neutropenia/
50 (neutropen* or neutropaen*).tw.
51 47 or 48 or 49 or 50
52 16 or 27 or 30 or 33 or 37 or 41 or 51
53 7 and 46 and 52
54 7 and 30
55 7 and 51 and 52
56 53 or 54 or 55

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Systematic review, RCT and observational filters were used. No date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references	No of references	Finish date of

	found	retrieved	search
Medline (and check on Pubmed)	1567 – 34 sifted	3	08/06/2015
Premedline (5 June 2015)	175	3	08/06/2015
Embase	2355 – 151 sifted	41	08/06/2015
Cochrane Library	479 – 48 sifted	2	08/06/2015
Web of Science (SCI & SSCI)	2101 – 187 sifted	16	08/06/2015

Total References retrieved (after de-duplication): 53

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 10 – Preventing and Managing Complications - Managing peripheral neuropathy

Literature search summary

What is the most effective way to manage neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	1483	1483	14/07/2014
Premedline	14/07/2014	72	72	14/07/2014
Pubmed	2013 -	136	136	18/07/2014
Embase	1974 -	2478	2478	14/07/2014
Cochrane Library	As per database	75	75	15/07/2014
Web of Science (SCI & SSCI)	1970 -	2696	2696	15/07/2014
Psychinfo	1806 -	29	29	15/07/2014
AMED	1985 -	3	3	15/07/2014
Cinahl	1937 -	171	171	15/07/2014

Total References retrieved (after de-duplication): 4019, then sifted down to 688

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Multiple Myeloma/
2. exp Neoplasms, Plasma Cell/
3. exp Plasmacytoma/
4. (myeloma* or plasmacytoma).tw.
5. (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6. Kahler*.tw.
7. or/1-6
8. exp Peripheral Nervous System Diseases/
9. (neuropath* or polyneuropath*).tw.
10. ((autonom* or motor* or sensor* or spin* or peripher*) adj2 (nerve* or neuritis)).tw.
11. (nerve* adj2 pain).tw.
12. exp Neuralgia/
13. exp Neuritis/
14. CIPN.tw.
15. (chemo* adj3 neuropath*).tw.
16. or/8-15
17. 7 and 16

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

1

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1568 – 111 sifted	5	08/06/2015
Premedline (5 June, 2015)	83	5	08/06/2015
Embase	2812 – 470 sifted	40	08/06/2015
Cochrane Library	155 – 73 sifted	2	08/06/2015

Cinahl	193 – 32 sifted	3	08/06/2015
Psychinfo	31 – 4 sifted	0	08/06/2015
AMED	3 – 0 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	2917 – 279 sifted	33	08/06/2015

Total References retrieved (after de-duplication): 64

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 10 – Preventing and managing complications - Preventing Thrombosis

Literature search summary

What is the most effective method for prevention of thrombosis in patients with myeloma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	724	162	16/06/2014
Premedline	June 13, 2014	38	9	16/06/2014
Embase	1974 -	2864	504	25/06/2014
Cochrane Library	As per database	85	48	16/06/2014
Web of Science (SCI & SSCI)	1970 -	908	261	17/06/2014
AMED	1985 -	2	0	16/06/2014
Psycinfo	1806 -	3	0	16/06/2014
Cinahl	1937 -	34	2	17/06/2014

Total References retrieved (after de-duplication): 641

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Venous Thromboembolism/
9 exp Venous Thrombosis/

10 exp Pulmonary Embolism/
11 ((venous or vein) adj (thrombosis or thrombus or thromboembolism)).tw.
12 ((pulmonary or lung) adj6 (embolism or emboli)).tw.
13 (dvt or vte).tw.
14 (thrombosis or thrombus or thromboembolism).tw.
15 or/8-14
16 7 and 15
17 exp Anticoagulants/
18 exp Fibrinolytic Agents/
19 exp Platelet Aggregation/
20 exp Antithrombins/
21 (anticoagula$ or anti coagula$ or antithromb$ or anti thromb$ or antiemboli$ or anti emboli$ or thrombin inhibit$ or direct thrombin).ti,ab.
22 Aspirin/
23 (aspirin or acetylsalicylic acid or antiplatelet or anti platelet or ASA).mp.
24 (Dabigatran or dabigatran etexilate or Rendix or Pradaxa).mp.
25 (Rivaroxaban or Xarelto).mp.
26 (Apixaban or Eliquis).mp.
27 (Clopidogrel or Plavix).mp.
28 (Dipyridamole or Permole or Persantine).mp.
29 Dipyridamole/
30 (fondaparinux or Fondaparin sodium or idraparinux or arixtra).mp.
31 (Defibrotide or Defitelio or Gentium).mp.
32 VKA.mp.
33 vitamin K antagonist$.mp.
34 heparin/ or heparin, low-molecular-weight/
35 (Heparin or Lipo-Hepin or Liquaemin or Panheparin or LMWH).mp.
36 thromboprophylaxis.mp.
37 exp Warfarin/
38 exp Coumarins/
39 (acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).tw.
40 or/17-39
41 7 and 40
42 16 or 41

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	750 – 47 sifted	5	08/06/2015
Premedline (8 June, 2015)	60	4	08/06/2015
Embase	3283 – 575 sifted	56	08/06/2015

Cochrane Library	162 – 65 sifted	4	08/06/2015
Web of Science (SCI & SSCI)	982 – 96 sifted	16	08/06/2015
AMED, Psycinfo, Cinahl	Nothing new	Nothing new	08/06/2015

Total References retrieved (after de-duplication): 66

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 10 – Preventing and managing complications - Managing fatigue — Literature search summary

Which interventions are most effective in reducing fatigue in patients being treated for myeloma?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	898	130	06/05/2014
Premedline	6 May 2014	39	5	07/05/2014
Embase	1974 -	2182	198	08/05/2014
Cochrane Library	As per database	126	47	07/05/2014
Web of Science (SCI & SSCI)	1970 -	1051	232	08/05/2014
Psychinfo	1806 -	24	11	07/05/2014
AMED	1985 -	24	5	07/05/2014
Cinahl	1937 -	68	23	08/05/2014

Total References retrieved (after de-duplication): 379

Medline search strategy *(This search strategy is adapted to each database)*
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Fatigue/
9 fatigu$.ti,ab.

10 (exhaust$ or tired$ or weary or weariness).ti,ab.
11 (low adj energy).ti,ab.
12 ((astenia or asthenic) and syndrome).tw.
13 ((lack or loss or lost) adj3 (energy or vigo?r)).tw.
14 (feel$ adj3 (drained or sleep$ or sluggish)).tw.
15 vitality.tw.
16 (apath$ or lassitude or letharg$).tw.
17 or/8-16
18 7 and 17
19 exp Exercise Therapy/ or exp Exercise Movement Techniques/ or exp Exercise/
20 exercis$.ti,ab.
21 (physical adj activit$).tw.
22 (pacing adj schedule$).tw.
23 (psychostimulan$ or stimulant$).tw.
24 exp Methylphenidate/
25 exp Methamphetamine/
26 (methylphenid$ or modafinil or methamphetamine).tw.
27 (Concerta or Metadate or Methylin or Quillivant or Ritalin or Provigil).tw.
28 207ZZ9QZ49.rn.
29 R3UK8X3U3D.rn.
30 44RAL3456C.rn.
31 exp Sleep/
32 sleep$.tw.
33 exp Complementary Therapies/
34 exp Diet/
35 exp Erythropoietin/
36 (Epogen or Eprex or Procrit or EPO or Erythropoietin or rHuEPO or rhEPO).tw
37 11096-26-7.rn.
38 (blood adj transfusion).tw.
39 or/19-38
40 7 and 39
41 18 or 40

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	971 – 88 sifted	2	08/06/2015
Premedline (5 June, 2015)	69	4	08/06/2015
Embase	2565 – 481 sifted	8	08/06/2015
Cochrane Library	183 – 54 sifted	5	08/06/2015
Cinahl	79 – 11 sifted	1	08/06/2015

Psychinfo	28 – 4 sifted	0	08/06/2015
AMED	24 – 0 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	1140 – 97 sifted	8	08/06/2015

Total References retrieved (after de-duplication): 19

1

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 11 – Monitoring Literature search summary

What is the optimal follow-up protocol for patients with myeloma (including duration, frequency, investigations and onward referral)?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 -	288	73	18/07/2014
Premedline	July 17, 2014	11	4	18/07/2014
Embase	1974 -	969	165	18/07/2014
Cochrane Library	As per database	329	13	18/07/2014
Web of Science (SCI & SSCI)	1970 -	366	87	18/07/2014
AMED	1985 -	6	0	18/07/2014
Psycinfo	1806 -	4	1	18/07/2014
Cinahl	1937 -	107	9	18/07/2014

Total References retrieved (after de-duplication): 215

Medline search strategy *(This search strategy is adapted to each database)*
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6

8 exp Aftercare/
9 (aftercare or after-care or followup or follow-up or surveillance).m_titl.
10 ((post-treatment or posttreatment) adj1 evaluation$).mp.
11 ((post-treatment or posttreatment) adj1 care).mp.
12 ((post-treatment or posttreatment) adj1 monitoring).mp.
13 or/8-12
14 *Treatment Outcome/
15 (response adj2 assessment).tw.
16 (response adj2 criteria).tw.
17 or/14-16
18 13 or 17
19 7 and 18

2. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

3. Any further comments

Basic exclusions filter only and no date limits applied. Any possibly relevant material selected.

1

4. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	305 – 48 sifted	1	08/06/2015
Premedline (5 June, 2015)	17	0	08/06/2015
Embase	1309 – 414 sifted	36	08/06/2015
Cochrane Library	374 – 45 sifted	0	08/06/2015
Web of Science (SCI & SSCI)	389 – 35 sifted	5	08/06/2015
AMED	6 – 0 sifted	0	08/06/2015
Psycinfo	5 – 1 sifted	0	08/06/2015
Cinahl	158 – 51 sifted	2	08/06/2015

Total References retrieved (after de-duplication): 38

2

NATIONAL COLLABORATING CENTRE FOR CANCER

Myeloma Clinical Guideline

Chapter 12 – Managing relapsed myeloma
Second autologous stem cell transplant

Literature search summary

- **Which patients with myeloma should be considered for allogeneic stem cell transplantation?**

5. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2000 onwards	1704	507	23/09/2014
Premedline	12 Sept, 2014	235	122	15/09/2014
Embase	2000 onwards	1556	710	02/10/2014
Cochrane Library	As per database	599	599	30/09/2014

Total References retrieved (after de-duplication): 1573

Medline search strategy *(This search strategy is adapted to each database)*
1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6
8 exp Stem Cell Transplantation/
9 exp Bone Marrow Transplantation/
10 (allograft* or autograft* or allo-graft* or auto-graft*).tw.
11 (allotransplant* or allo-transplant* or autotransplant* or auto-transplant*).tw.
12 ((allogen* or allo-gen* or autolog*) adj5 (transplant* or graft* or rescue*)).tw.
13 (homograft* or homo-graft* or homotransplant* or homo-transplant*).tw.
14 (bone marrow adj2 (transplant* or graft* or rescue*)).tw.
15 ((stem cell* or stem-cell*) adj2 (transplant* or graft* or rescue*)).tw.
16 (ASCT or ABMT or SCT or BMT or HSCT or HBMT).tw.
17 exp Transplantation, Autologous/
18 exp Transplantation, Homologous/
19 exp Transplantation Conditioning/
20 exp Hematopoietic Stem Cell Mobilization/
21 (nonmyeloablat$* or non-myeloablat* or myeloablat*).tw.
22 (reduced intens* or full intens* or high intens*).tw.
23 (mini-transplant* or minitransplant*).tw.
24 (RIC or MAC).tw.
25 (graft adj2 host).tw.

26 GVHD.tw.
27 exp Graft vs Host Disease/
28 or/8-27
29 7 and 28
30 limit 29 to yr="2000 -Current"

6. Health Economics Literature search details

This topic was not selected for health economic modelling. The health economics search undertaken across the population identified any general health economics papers on myeloma.

7. Any further comments

Systematic review, RCT and observational filters were used. Date limit of 2000 onwards applied with agreement with GDG. Any possibly relevant material selected.

8. Update Search

For the update search, the same search criteria/filters were applied as initial search, date limit of 2014 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline (and check on Pubmed)	1769 – sifted 226	29	08/06/2015
Premedline (8 June, 2015)	309	53	08/06/2015
Embase	1838 – sifted 436	78	08/06/2015
Cochrane Library	769 – sifted 143	4	08/06/2015
Web of Science (SCI & SSCI)	Topic I – 809 total Topic F & J – 1798 total	Topic I - 157 Topic F & J - 25	08/06/2015 08/06/2015

Total References retrieved (after de-duplication): 162

1

NATIONAL COLLABORATING CENTRE FOR CANCER

Multiple Myeloma Clinical Guideline **Scoping literature search**

1. Literature search details

Cochrane Library
HTA Database (2007 onwards)
Basic population search: 47 (43) on 12/09/2013
CDSR
Basic population search: 16 (13) on 12/09/2013
DARE
Basic population search: 39 (35) on 12/09/2013

Medline/PreMedline
Basic population search with guidelines search filter & systematic review filter
PreMedline (Sept 11, 2013): 29 (17) 12/09/2013
Medline: 395 (173) on 12/09/2013

NICE
5 (3 published and 2 in progress) on 12/09/2013. See details below.
Published
Multiple myeloma - bortezomib (TA129)
Multiple myeloma - lenalidomide (TA171)
Multiple myeloma (first line) - bortezomib and thalidomide (TA228)

In progress
Multiple myeloma - bortezomib (consolidation therapy) [ID529]
Multiple myeloma - bortezomib (induction therapy) [ID610]

Suspended
Multiple myeloma (newly diagnosed) - lenalidomide [ID474]
Multiple myeloma - lenalidomide (maintenance, post autologous stem cell transplantation) [ID475]
Multiple myeloma (one prior therapy) - vorinostat (with bortezomib) [ID501]

Related guidance on
Osteoporosis Fragility Fracture (CG146)
Anaemia (cancer-treatment induced) - erythropoietin (alfa and beta) and darbepoetin (TA142)
Bone metastases from solid tumours - denosumab (TA265)

NIHR
1 (already identified in search database) on 12/09/2013

DUETS
7 (already identified in search database) on 12/09/2013

CLINICAL EVIDENCE
0 on 12/09/2013

COMET
1 (already identified in search database) on 12/09/2013

TRIP Database
24 on 16/09/2013

NHS Evidence
97 (21) on 16/09/2013

NATIONAL GUIDELINE CLEARINGHOUSE
27 (6) on 16/09/2013

Website of Relevant Professional Bodies/Organisations
SIGN – no results (16/09/2013)
BCSH and NCCN searched on TRIP database.

BMJ Best Practice
http://bestpractice.bmj.com/best-practice/monograph/179.html

FINAL TOTAL: 250

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Multiple Myeloma/
2 exp Neoplasms, Plasma Cell/
3 exp Plasmacytoma/
4 (myeloma* or plasmacytoma).tw.
5 (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
6 Kahler*.tw.
7 or/1-6

2. Health Economics Literature search details

For the purposes of the health economics search, a full search was undertaken with no date limit to ensure full coverage of topics for the economic plan and for dealing with different health economic analyses from the last guideline

Database name	No of references found	Finish date of search
Medline (2011 onwards, SIGN HE filter)	98	12/09/2013
Premedline (Sept 11, 2013)	25	12/09/2013
Embase (2011 onwards, SIGN HE filter)	372	12/09/2013
Cochrane: HTA	47	12/09/2013
Cochrane: NHSEED	37	12/09/2013
HEED	144	23/09/2013

Total References retrieved (after de-duplication): 463 (plus 144 from HEED)

Database name	No of references found	Finish date of search
Medline (2011 onwards, SIGN HE filter)	127 - 42 new refs	02/06/2015
Premedline (June 1, 2015)	25 - 14 new refs	02/06/2015
Pubmed	149 - 35 new refs	02/06/2015
Embase (2011 onwards, SIGN HE filter)	608 - 305 new refs	02/06/2015
Cochrane: HTA	53 - 10 new refs	02/06/2015

Cochrane: NHSEED	48 - 8 new refs	02/06/2015

Total References retrieved (after de-duplication): 362 (no access to HEED this year)

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2

Review protocols

Topic	**The specific information and support needs of patients with myeloma and their families and carers at diagnosis and treatment planning, and during and after treatment (including end of life care).**
Review question	What are the specific information and support needs of patients with myeloma and their families and carers?
Topic Subgroup	**Lead**: Lesley Roberts **Subgroup**: Monica Morris, Nicola Montacute, Sam Ahmedzai
Economic Priority	low

Background

Myeloma is a rarer cancer, and most people have not heard of it at the point of diagnosis so high quality, appropriate and clear individualised information, at different points in the patient pathway is essential. A clear care plan, changed as necessary, is crucial to allow as smooth a journey as possible.

As Myeloma is treatable but not curable, and it requires multiple lines of treatment, some patients, carers and their families may want to know all the information available, while others may wish to know little or nothing.

It is a complex, cancer with many different treatments, perhaps involving chemotherapy and /or stem cell treatment. It mainly afflicts the older age group, and not all will be internet confident, so the presentation of the information needs to differ too.

This is a long term condition, so the care plan should include the assessment of the "patient in the round", including the family conditions as well. To ensure this happens the sharing of information between secondary and primary care and the various community teams is essential.

Palliative care needs are variable from symptom control at all stages of pathway, to end of life care, but these should be explained clearly and carefully to alleviate the psychological impact of the prognosis.

There are many differences in the experiences of myeloma patients and their families in relation to the information and support received during diagnosis, treatment, follow-up and into end of life care. Patients and carers report either too little or too much information leading to poor patient experience. While it is important to understand the information needs at an individual level, it is also important that there is consensus across all centres on the minimum information given, by whom and when, to ensure that informed consent, and patient understanding, is achieved at each stage. It is hoped that these recommendations will provide guidance here.

PICO Table

Population	Themes	Outcomes
Adults) with myeloma and their carers: • At diagnosis and treatment planning • During treatment • During follow up • During end of life care	Information and support needs of patients with myeloma and their families and carers, e.g., • Patient and carer perceived support and information needs • Perceived problems with the number of specialists/sites involved in care • Education • Pregnancy prevention/fertility issues • Involvement of clinical nurse specialists in all aspects of patient/carer support • Advance care planning	• Patient and/or carer satisfaction (with communication, information support and treatment received) • Health-related quality of life • Holistic needs assessment • Achievement of advance care planning • Understanding/knowledge of disease and treatment • Psychological factors (e.g. depression, distress, coping) • Referral to support groups/networks

	• Use of online resources	

Additional comments on PICO		
All information and support needs identified in the literature will be reviewed and presented - it will not be limited to those examples in the PICO. Extend to all haematological malignancies?		
	Details	**Additional Comments**
Type of review	Qualitative – information and support	Any relevant quantitative data will also be included
Language	English language only	
Study design	qualitative studies survey data case studies RCTs	
Status	n/a	
Other criteria for inclusion / exclusion of studies	n/a	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Depression Anxiety coping strategies holistic needs assessment	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	NICE. Improving Outcomes in Haematological cancers manual 2003. NICE cancer service guidance 2004. Improving supportive and palliative care for adults with cancer. NICE quality standard 13 (2011). End of life care for adults. Snowden, J. A., Ahmedzai, S. H., Ashcroft, J., D'Sa, S., Littlewood, T., Low, E., Lucraft, H., Maclean, R., Feyler, S., Pratt, G., Bird, J. M. & Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. (2011) Guidelines for supportive care in multiple myeloma 2011. [Review]. *British Journal of Haematology,* 154: 76-103. Oerlemans S, Husson O, Mols F, Poortmans P, Roerdink H, Daniels LA, Creutzberg CL, van de Poll-Franse LV. (2012) Perceived information provision and satisfaction among lymphoma and multiple myeloma survivors - results from a Dutch population-based study. Ann Hematol. 91(10):1587-95.	
Amendments		

1

2

Topic	**The role of specialist diagnostic investigations, including trephine biopsy, immunophenotyping, cytogenetics and molecular technologies, in diagnosing MGUS and standard and high-risk myeloma.**
Review question	What is the optimal laboratory testing strategy for suspected myeloma?
Topic Subgroup	**Lead:** Matthew Jenner **Subgroup:** Matthew Streetly, Lesley Roberts
Economic Priority	medium

Background

A diagnosis of myeloma may be suspected as a result of a wide range of clinical features and laboratory abnormalities, in some cases incidental laboratory findings. The key question in diagnosis is to establish whether the individual has symptomatic myeloma requiring treatment, smouldering (asymptomatic) myeloma or the precursor condition monoclonal gammopathy of undetermined significance (MGUS). The latter two conditions can remain asymptomatic for many years and may not ever progress to symptomatic myeloma requiring treatment. MGUS has an approximately 1% per year risk of progression to symptomatic myeloma (or occasionally to non-Hodgkins lymphoma) whereas smouldering myeloma has an approximately 10% risk per year risk of progressing to symptomatic disease during the first five years from diagnosis.

Unlike other haematological malignancies, the diagnosis of myeloma is not based on a single test such as a bone marrow or lymph node biopsy but on a combination of clinical features, radiological findings and laboratory tests. Imaging tests are addressed in topic D, whilst this question focuses on laboratory testing methods. The gold standard is the examination of bone marrow showing plasma cell infiltration and also detection and quantification of monoclonal protein in the serum or urine. Along with evidence of related organ or tissue impairment (ROTI) including hypercalcaemia, renal impairment, anaemia and lytic bone disease or osteoporosis in addition to other features such as recurrent infection or hyper viscosity symptoms, these tests can help to provide a diagnosis of symptomatic myeloma. But there are a number of other tests that are also useful including specialist diagnostic investigations such as trephine biopsy, immunophenotyping, cytogenetics and molecular technologies that can be used to differentiate between the type and stage of myeloma.

A bone marrow biopsy is a potentially painful invasive test and therefore it is important to establish which groups of patients a bone marrow biopsy should be considered in. Other diagnostic tests may help to stratify the patients more or less likely to have symptomatic myeloma. In addition it is preferable to avoid repeating the bone marrow biopsy to determine prognostic information if a diagnosis of symptomatic myeloma is confirmed therefore it is important to consider what tests to undertake on the initial sample to provide the maximum information. These additional tests such as cytogenetics or immunophenotyping do have a cost implication but generally have to be undertaken on fresh bone marrow therefore retrospective testing once a diagnosis has been made is rarely an option. The prognostic value of such tests will be considered in greater detail in question C2.

From this evidence review it is hoped guidelines can be developed to define the laboratory testing strategy to stratify those more or less likely to have symptomatic myeloma.

PICO Table

Population	Index tests	Reference standard	Outcomes
People referred to secondary care with suspected myeloma, including those with MGUS	• Bone marrow trephine biopsy and immunochemistry • Bone marrow aspirate biopsy • Bone marrow immunophenotyping • Protein electrophoresis • Immunofixation • Urinary Bence Jones protein/urinary free light chains • Serum free light chains •Different sequences of the above tests	Note what reported by studies	• Diagnostic accuracy • Rate of confirmed diagnosis • Delay in diagnosis • Test related adverse events • Patient awareness of diagnosis • Cost effectiveness

Additional Comments on PICO			
Conditions in the differential diagnosis: Plasma cell dyscrasia Plasma cell leukaemia Plasmacytoma Amyloidosis Waldenstrom's macroglobulinaemia POEMS syndrome Paraproteinamia Smoldering myeloma Light chain deposition disease B cell lymphoid disorders Potential reference standards: Beta2 microglobulin/ Serum albumin			
	Details	**Additional Comments**	

Type of review	Diagnostic	
Language	English language only	
Study design	Systematic reviews Randomised controlled trials Diagnostic accuracy studies If insufficient evidence is identified, will also include cohort studies	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	2000 date limit	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	None identified	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	NICE. Improving Outcomes in Haematological cancers manual 2003 BCSH and UKMF guidelines for diagnosis and management of multiple myeloma 2013 Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, Fonseca R, Stewart AK, Harousseau JL, Dimopoulos M, Jagannath S, Hajek R, Sezer O, Kyle R, Sonneveld P, Cavo M, Rajkumar SV, San Miguel J, Crowley J, Avet-Loiseau H; International Myeloma Workshop Consensus Panel 2. (2011) Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. Blood. 2011 May 5;117(18):4696-700. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, Ludwig H, Joshua D, Mehta J, Gertz M, Avet-Loiseau H, Beksaç M, Anderson KC, Moreau P, Singhal S, Goldschmidt H, Boccadoro M, Kumar S, Giralt S, Munshi NC, Jagannath S; International Myeloma Workshop Consensus Panel 3. (2011) Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood. 2011 May 5;117(18):4701-5.	
Amendments		

1

2

Topic	**The role of specialist diagnostic investigations, including trephine biopsy, immunophenotyping, cytogenetics and molecular technologies, in diagnosing MGUS and standard and high-risk myeloma.**
Review question	Can investigations done at the diagnosis of myeloma, including trephine biopsy, immunophenotyping and cytogenetic and molecular genetic tests accurately predict treatment outcomes (for example, can they identify patients with a poor prognosis for whom an alternative treatment approach may be preferable)?
Topic Subgroup	**Lead:** Matthew Jenner **Subgroup:** Matthew Streetly, Lesley Roberts, Hamdi Sati
Economic Priority	Medium/high

Background

Multiple myeloma is a heterogeneous disease with a wide range of clinical outcomes. Advances in treatments over the last decade have improved median overall survival in younger patients with myeloma to around 7 to 10 years from diagnosis. However there remains a group of patients with significantly worse outlook, loosely defined as having high risk myeloma. A wide range of techniques performed on the diagnostic bone marrow sample have been used to provide prognostic information in both newly diagnosed and relapsed myeloma cases. These can be broadly separated in to immunological techniques (immunophentotyping and immunohistochemistry) and genetic techniques (including cytogenetics, fluorescent in situ hybridisation, polymerase chain reaction techniques, sequencing and microarray technologies).

Immunological techniques are typically used to identify surface or cellular proteins that can be used to both define and quantify the presence of normal or abnormal plasma cell populations. Immunohistochemistry is performed on bone marrow trephine histology sections. This can be performed retrospectively. Immunophenotyping is performed on fresh bone marrow aspirated samples and must be undertaken prospectively.

The majority of genetic techniques are performed on fresh bone marrow aspirated samples although a limited number of tests can be performed on trephine sections. Conventional cytogenetic techniques have largely been abandoned because of the low diagnostic yield. The majority of tests are now undertaken on selected plasma cells from bone marrow aspirated samples. Selection is undertaken to obtain a pure population of plasma cells without contaminating normal bone marrow cells. A range of techniques have been utilised to examine either chromosomal abnormalities (FISH, copy number array and sequencing techniques) or at a gene expression level to determine genes over or under expressed in the myeloma cells (PCR techniques and gene expression arrays). Gene signatures have been devised to attempt to define patterns of expressed genes that may define particular clinical characteristics including those with a poor prognosis.

The different prognostic tests have variation in cost, accessibility and applicability. Given the multitude of techniques available it is important to evaluate the most effective tests to determine prognosis.

A large number of new drugs are currently available with clinical data indicating that some may be able to overcome particular high risk genetic features. Where possible within the scope of the guidelines it would be helpful to evaluate whether there are particular patients who may benefit from a different treatment approach (without specifying specific drugs).

Following this evidence review it is hoped a guideline will be developed to outline what tests should be used to define high risk myeloma. This would potentially include a core panel of antibodies for either immunohistochemistry and/or immunophenotyping to define high risk MGUS and smouldering myeloma as well as symptomatic myeloma. Secondly it is envisaged that a recommendation will be made regarding the use of FISH or other genetic techniques (including a core panel of tests) to determine high risk myeloma. Thirdly, where possible within the scope there is expected to be some comment about potential therapeutic strategies for high risk cases. At present this may simply relate to identifying those cases to enable prognostic discussion with the patients and potentially consideration of clinical trials.

PICO Table

Population	Factors	Outcomes
People referred to	• Bone marrow trephine biopsy and	• Response to treatment

secondary care with probable myeloma	immunohistochemistry • FISH • Serum free light chains • heavy/light chain ratio • Bone marrow immunophenotyping/FACS/flow cytometry	• Adverse events • Overall survival • Progression-free survival • Time to next treatment (for asymptomatic patients)

Additional comments on PICO		
None		
	Details	**Additional Comments**
Type of review	prognostic	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	2005 date limit Patient number at least 100	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Hevylite chain freelite chain	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Chng WJ, Dispenzieri A2, Chim CS3, Fonseca R4, Goldschmidt H5, Lentzsch S6, Munshi N7, Palumbo A8, Miguel JS9, Sonneveld P10, Cavo M11, Usmani S12, Durie BG13, Avet-Loiseau H14; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014 Feb;28(2):269-77. Broyl A, Hose D, Lokhorst H, de Knegt Y, Peeters J, Jauch A, Bertsch U, Buijs A, Stevens-Kroef M, Beverloo HB, Vellenga E, Zweegman S, Kersten MJ, van der Holt B, el Jarari L, Mulligan G, Goldschmidt H, van Duin M, Sonneveld P. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. Blood. 2010 Oct 7;116(14):2543-53. Paiva B, Vidriales MB, Pérez JJ, Mateo G, Montalbán MA, Mateos MV, Bladé J, Lahuerta JJ, Orfao A, San Miguel JF; GEM (Grupo Español de MM) cooperative study group; PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) cooperative study group. Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. Haematologica. 2009 Nov;94(11):1599-602. Rawstron AC, Orfao A, Beksac M, Bezdickova L, Brooimans RA, Bumbea H, Dalva K, Fuhler G, Gratama J, Hose D, Kovarova L, Lioznov M, Mateo G, Morilla R, Mylin AK, Omedé P, Pellat-Deceunynck C, Perez Andres M, Petrucci M, Ruggeri M, Rymkiewicz G, Schmitz A, Schreder M, Seynaeve C, Spacek M, de Tute RM, Van Valckenborgh E, Weston-Bell N, Owen RG, San Miguel JF, Sonneveld P, Johnsen HE; European Myeloma Network. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders. Haematologica. 2008 Mar;93(3):431-8. Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro-Coy N, Drayson MT, Feyler S, Ross FM, Cook G, Jackson GH, Morgan GJ, Owen RG. Minimal residual	

	disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol. 2013 Jul 10;31(20):2540-7.
Amendments	Changes made to review protocol at 9th GDG meeting 10 march 2015 due to vast amont of evidence: 1. Date limit changed from 2000 to 2005 2. Only include studies with a sample size of at least 100 3. Exclude following tests: - Conventional cytogenetics - ISS (serum B2 microglobulin/albumin) - Gene expression 4. For molecular technologies only include tests that give the same result as FISH

1

2

Topic	**Imaging investigations at diagnosis.**
Review question	What is the optimal imaging strategy for patients with suspected myeloma?
Topic Subgroup	**Lead:** Nicola Mulholland **Subgroup:** Matthew Streetly, Jane Woodward
Economic Priority	high

Background

Patients with suspected myeloma undergo imaging to identify anatomical lesions caused by myeloma. The bones are commonly involved in myeloma, although soft tissue lesions could also be present. Plain radiographs are the primary imaging investigation used in UK.

The skeletal survey is a combination of plain radiographs which includes commonly affected sites (e.g., head, spine, chest, humeri, femora). It is widely accepted that this test is available, low cost and relatively low radiation. However, it is also known that this form of imaging is less sensitive than newer techniques available. It is possible some patients who have a normal skeletal survey do have lesions that just cannot be seen on plain films. Some patients will have a diffuse pattern of osteopaenia (loss of bone density), which is difficult to tell apart from other causes. In some centres if there is high suspicion of myeloma or symptoms, patients will have further imaging commonly with MRI spine.

More modern techniques include computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography CT (PET-CT). These are more sensitive and specific than the skeletal survey. However, they are more costly and may increase radiation burden (especially PET CT and CT).

CT scanning can be performed in minutes, can identify soft tissue lesions and is very sensitive. With improvements in dose reduction techniques, it may come to replace skeletal survey.

PICO Table

Population	Index tests	Reference standard	Outcomes
Patients with suspected myeloma	• MRI (spinal and whole body) • Multiparametric MRI • Diffusion weighted MRI • Dynamic contrast MRI • CT (including low dose) • FDG-PET-CT • Skeletal survey • DEXA • ***Tc-99 MDP*** bone ***scintigraphy*** +/- SPECT +/- CT • Tc-99 MIBI	• Histo-pathologically confirmed myeloma related lesions or clinical radiological follow-up	• diagnostic accuracy (specificity and sensitivity) • lesion detection rate • radiation exposure • patient acceptability (e.g. claustrophobia, anxiety over procedure, clinical exclusions) • cost effectiveness

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	Diagnostic	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Exclude studies just on FDG PET without PET CT (ie pre 2004). Exclude CT studies prior to 2003 (ie include only multidetector CT).	
Search	The core databases as listed in the NICE Guidelines	

strategies	Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	None identified	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	NICE. Improving Outcomes in Haematological cancers manual 2003. Lu, Y. Y., Chen, J. H., Lin, W. Y., Liang, J. A., Wang, H. Y., Tsai, S. C. & Kao, C. H. (2012) FDG PET or PET/CT for detecting intramedullary and extramedullary lesions in multiple Myeloma: a systematic review and meta-analysis. [Review]. *Clinical Nuclear Medicine,* 37: 833-837. Regelink, J. C., Minnema, M. C., Terpos, E., Kamphuis, M. H., Raijmakers, P. G., Pieters-van den Bos IC, Heggelman, B. G., Nievelstein, R. J., Otten, R. H., van Lammeren-Venema, D., Zijlstra, J. M., Arens, A. I., de Rooy, J. W., Hoekstra, O. S., Raymakers, R., Sonneveld, P., Ostelo, R. W. & Zweegman, S. (2013) Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. *British Journal of Haematology,* 162: 50-61. Dimopoulos, M., Terpos, E., Comenzo, R. L., Tosi, P., Beksac, M., Sezer, O., Siegel, D., Lokhorst, H., Kumar, S., Rajkumar, S. V., Niesvizky, R., Moulopoulos, L. A., Durie, B. G. & IMWG. (2009) International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. [Review] [123 refs]. *Leukemia,* 23: 1545-1556 D'Sa S, Abildgaard N, Tighe J, Shaw P, Hall-Craggs M. (2007) Guidelines for the use of imaging in the management of myeloma. Br J Haematol.;137(1):49-63. Caers J, Withofs N, Hillengass J, Simoni P, Zamagni E, Hustinx R, Beguin Y. (2014) The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. Haematologica. 99(4): 629-637.	
Amendments		

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3

Topic	**Imaging investigations at diagnosis.**
Review question	What is the most effective imaging to guide treatment decisions in patients with newly diagnosed myeloma?
Topic Subgroup	**Lead:** Nicola Mulholland **Subgroup:** Matthew Streetly, Jane Woodward
Economic Priority	medium

Background

Once myeloma has been diagnosed, it is important to establish whether the patient requires treatment. Some patients may be asymptomatic and specialists may adopt a watch and wait approach. At this stage, imaging is required to distinguish between patients who remain asymptomatic and those who show signs of progressing to symptomatic myeloma. Patients would be considered symptomatic if there are signs of end organ damage, and imaging would be used to look for bony lesions (as a sign of end organ damage). The currently used skeletal survey is known to lack sensitivity for this and some centres would add in MRI looking at spine usually. This question is important to evaluate other forms of modern imaging which are available to define anatomy including CT and MRI. Also, functional imaging can be used to detect changes in the body which occur before anatomical imaging shows a problem e.g., PETCT and MRI with dwi, and their role in myeloma is not yet established. Finally, each test can be used to look at differing parts of the body, and it is not fully agreed which are the optimum areas to be imaged e.g., whole body imaging vs spine only.

Each method has varying success in defining disease outside the bones/ bone marrow called extramedullary disease (or soft tissue disease). It would be useful to evaluate which imaging method is optimum for this and how it would impact on management.

Finally, the majority of myeloma patients can be followed up with laboratory indices, and imaging would be a secondary means of response assessment. A minority termed as non secretory are much harder to follow up as there is no laboratory marker to use. Follow up with imaging may be particularly useful in these patients, with MRI and PET CT showing most promise.

Although there is relatively limited access to complex MRI and PET-CT which maybe performed at larger centres, both are available in cancer networks and are standard tertiary investigations in UK.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with newly diagnosed myeloma including the following subgroups: - Non-secretory - Asymptomatic - Symptomatic - Extra-medullary plasmacytoma - Multiple plasmacytomas	• MRI (spinal and whole body) • Multiparametric MRI • Diffusion weighted MRI • Dynamic contrast MRI • CT (including low dose) • FDG-PET-CT • Skeletal survey	Each other	• Patient acceptability (e.g. claustrophobia, anxiety over procedure, clinical exclusions) • Diagnostic yield • Incremental upstaging • Radiation exposure/risk of second primary cancers • Prognostic accuracy for PFS and OS • Reduction of SREs

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	

Other criteria for inclusion / exclusion of studies	Exclude studies just on FDG PET without PET CT (ie pre 2004). Exclude CT studies prior to multidetector CT (2004) Date limit of 2000 for all other interventions	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Dose reduction Iterative reconstruction	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Caers J, Withofs N, Hillengass J, Simoni P, Zamagni E, Hustinx R, Beguin Y. (2014) The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. Haematologica. 99(4): 629-637.	
Amendments		

1

2

Topic	The management of asymptomatic myeloma
Review question	What are the most effective primary management strategies (including observation) for patients with asymptomatic myeloma?
Topic Subgroup	**Lead**: Matthew Streetly **Subgroup**: John Snowden, Hamdi Sati, Jane Woodward
Economic Priority	medium

Background

Myeloma is a malignant disorder of a type of cell called a plasma cell that affects the bone marrow. Myeloma is diagnosed on the basis an increased number of abnormal bone marrow plasma cells and/or a raised myeloma specific protein in the blood. The myeloma can cause a variety of problems that include anaemia, kidney damage, recurrent infections and bone pains. At diagnosis most patients will require some form of treatment, usually chemotherapy, as a result of the effects that the myeloma cells have. However, 10-15% of patients when diagnosed will have no evidence of myeloma related organ or tissue injury. These patients have what is called asymptomatic or smouldering myeloma. It is known that most of these patients will develop myeloma requiring treatment (symptomatic) at some time in the future.

Historically it has been thought that patients with asymptomatic myeloma do not require specific treatments as this has not improved the long term consequences of the myeloma. More recently with the introduction of newer more effective and better tolerated therapies for symptomatic myeloma it is being suggested that some patients with asymptomatic myeloma may benefit from earlier treatment. It has also been suggested that the availability of more sensitive ways of assessing the myeloma may identify specific groups of patients with asymptomatic myeloma who may benefit from earlier treatment with the same chemotherapy used to treat myeloma patients or specific treatments for asymptomatic myeloma. In addition newer tests may make predicting how soon patients are likely to require treatment more accurate.

It is important to be able to accurately predict which patients may benefit from earlier therapy or more intensive monitoring as there are a range of potential adverse effects that could occur (both physical and psychological) if treatment occurs too early.

The guideline would recommend whether there are investigations that can accurately identify patients who should receive symptomatic myeloma directed treatment earlier and if there are any settings or treatments that should be offered to any of the specific risk groups of patients with asymptomatic myeloma. Such treatments could consist of chemotherapy and/or supportive treatments such as bisphosphonates.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients diagnosed asymptomatic myeloma	• Treatment intervention immediately - Chemotherapy - Thalidomide based regimens - Bortezomib based regimes - Lenalidomide based regimens - bisphosphonates	• observation (deferred treatment until progression of the disease)	• disease-related mortality • Overall survival • Progression free survival • Progression to symptomatic myeloma • Prevention of renal failure • HRQOL • Patient acceptability • Adverse events • Skeletal related events

Additional comments on PICO

Note how patients were selected for treatment.

Report data on fixed duration versus continuous treatment if available.

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	Randomised trials Systematic review of randomised trials	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	n/a	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Asymptomatic Smouldering stage I myeloma	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	He, Y., Wheatley, K., Glasmacher, A., Ross, H. & Djulbegovic, B. (2003) Early versus deferred treatment for early stage multiple myeloma. *Cochrane Database of Systematic Reviews.* Dhodapkar Blood 2014 Predictors of progression in aMM Kastritis Leukemia 2013 Predictors of progression in aMM Witzig Leukemia 2013 ThalZom v Zom 4 aMM Rago Cancer 2013 Predictors of progression in aMM D'Arena Leuk Lymphoma 2011 Pamidronate v no treatment Mateos NEJM 2013 Treatment of high risk smoldering myeloma Dispenzieri Blood 2013 – Review of definitions of smoldering myeloma and treatment Terpos E, Sezer O, Croucher PI, García-Sanz R, Boccadoro M, San Miguel J, Ashcroft J, Bladé J, Cavo M, Delforge M, Dimopoulos MA, Facon T, Macro M, Waage A, Sonneveld P; European Myeloma Network. (2009) The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol. 2009 Aug;20(8):1303-17.	
Amendments		

1

Topic	**The local and regional service provision needed for adequate disease management and equity of access**
Review question	What is the optimal configuration of local and regional haematology services for management of myeloma (including access to specialised radiological imaging, radiotherapy services, the management of renal disease, spinal disease and bone disease, clinical trials and supportive & palliative care)?
Topic Subgroup	**Lead**: Hamdi Sati **Subgroup**: Sam Ahmedzai, Alan Chant, John Snowden, Matthew Jenner, Andrea Guy, Nicola Mullholand
Economic Priority	low

Background

The myeloma journey is complex, with many complications and side effects and so it is not uncommon for a patient to be seen by many different specialists. There is variation across the UK in terms of access to specialist services and patients may have to travel long distances to receive access to specialised treatments that are not available locally. Travelling may be problematic for myeloma patients in considerable pain.

Patients with myeloma should be managed by a multidisciplinary team with appropriate input from all relevant specialist professionals. Renal failure, bone pain and fractures and spinal cord compression are frequent complications of myeloma. Patients should have equal and timely access to relevant specialised services such as haemodialysis, radiotherapy, pain and palliative care, spinal and orthopaedic surgery, specialist restorative dentistry and oral surgery. In addition, eligible patients should also have equal access to stem cell transplantation service.

National and international clinical trials offer an opportunity to access treatment options that are still not available to patients on the national health service. Clinical trials also offer other treatment options in patients with relapsed disease when all standard care treatments have been exhausted. Patients with myeloma should have the opportunity to access relevant well designed clinical trials.

Current configurations of local and regional haematology services (as well as other relevant specialised services for the management of myeloma and its complications) across the UK will be reviewed to determine the optimal configuration for quality disease management, including timely access to relevant specialised services.

PICO Table

Population	Intervention	Comparator	Outcomes
Myeloma patients (Analyse data by centre volume)	Access to an MDT, specialised radiological imaging, radiotherapy services, the management of renal disease, spinal disease and bone disease, clinical trials, transplant services, dental clinic, and supportive & palliative care in one network	Any other service configuration	• Patient-reported outcomes (patient experience) • Travel times • HRQOL • Overall survival • Progression-free survival

Additional comments on PICO

Expand search to all haematological malignancies

	Details	Additional Comments

Type of review		
Language	English language only	
Study design	No restrictions	
Status	n/a	
Other criteria for inclusion / exclusion of studies	Date limit 2003	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	None identified	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	None identified	
Amendments		

1

2

Topic	**Primary disease management for newly diagnosed myeloma, including autologous stem cell transplantation.**
Review question	Which patients with newly diagnosed myeloma should be considered for autologous stem cell transplantation?
Topic Subgroup	**Lead**: John Snowden **Subgroup**: Hamdi Sati, Andrea Guy, Alan Chant
Economic Priority	High

Background

Autologous stem cell transplantation (ASCT) is a medical procedure in which blood-forming stem cells are removed from the patient prior to intense chemotherapy and later given back to the same patient. The chemotherapy is aimed at killing tumour cells (the higher the dose the more tumour cells are killed) but also affects normal blood-forming cells that are needed to fight infections, transport oxygen and control bleeding. By giving the patient back his or her own blood-forming cells, the recovery from the chemotherapy is notably faster and predictable.

ASCT has become the first line standard of care in those myeloma patients deemed biologically fit enough for this option mainly because of the low transplant-related mortality (TRM) and prolongation of event-free survival (EFS) resulting in improved quality of life. But not all patients with myeloma are candidates for a stem cell transplant. Many factors must be considered to determine whether a patient is a candidate for ASCT. These include: how the cancer responded to prior treatment, patient age and general physical condition, and important considerations such as myeloma related renal failure and need for dialysis.

In the past, transplants were limited to younger patients in good physical condition. However, they are now performed in a more diverse group of patients. In general, patients in overall good physical condition with adequate kidney, lung, and heart function are eligible. In addition, recent studies have shown that ASCT may even be possible in patients who have reduced kidney function or kidney failure, with proper precautions and somewhat lower doses of chemotherapy.

Transplant may not be feasible in patients who have received: certain types of chemotherapy, especially melphalan, radiation therapy to the spine or pelvis. These treatments may impact the ability to obtain the stem cells needed for the transplantation.

Although it seems counter-intuitive, some experts do not recommend ASCT for patients who have some types of high risk disease, which accounts for approximately 25% of myeloma patients. High-risk patients include those with certain types of DNA abnormalities (e.g. chromosome 13 deletion, chromosome 17 translocation). These patients tend to have shorter periods of remission.

At the moment there is no clear consensus on what makes a patient a suitable candidate for transplant and different centres use different criteria. It is hoped that the evidence reviewed here will provide guidelines for selecting patients who will benefit the most from ASCT over alternatives including no further treatment and less intensive treatments such as novel agents. The dose and type of cytotoxic therapy (chemotherapy/radiotherapy) used in the preparative 'conditioning' for ASCT, and the role of tandem (or planned double) ASCT will be a consideration, at least for subsets of patients.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with newly diagnosed myeloma grouped according to - Age - Fragility/weakness - Comorbidities (charlson score, ACE-27, FACT-BMT) - Renal impairment - Genetic abnormalities - Response depth	Autologous stem cell transplant	no further treatment comparator treatment (e.g. lesser intensity)	• Health related quality of life • Overall survival • Progression free survival • Treatment related mortality • Treatment related morbidity • Patient/carer/family acceptability • Later effects • TWiST

Additional comments on PICO

Include studies that look at prognostic factors

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Case series of 100+	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	time without symptoms of disease or toxicity of treatment (TWiST)	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma 2013 Koreth J, Cutler CS, Djulbegovic B, et al. (2007) High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant 13: 183–196. Levy V, Katsahian S, Fermand JP, Mary JY, Chevret S. (2005) A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. Medicine (Baltimore) 84: 250–260. Naumann-Winter F, Greb A, Borchmann P, Bohlius J, Engert A, Schnell R. (2012) First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. Cochrane Database Syst Rev. 2012 Oct 17;10:CD004626. Jantunen, E. (2006) Autologous stem cell transplantation beyond 60 years of age. Bone Marrow Transplantation, 38, 715-720. Reece, D.E., Bredeson, C., Perez, W.S., Jagannath, S., Zhang, M.J., Ballen, K.K., Elfenbein, G.J.,Freytes, C.O., Gale, R.P., Gertz, M.A., Gibson, J., Giralt, S.A., Keating, A., Kyle, R.A., Maharaj, D., Marcellus, D., McCarthy, P.L., Milone, G.A., Nimer, S.D., Pavlovsky, S., To, L.B., Weisdorf, D.J., Wiernik, P.H., Wingard, J.R. & Vesole, D.H. (2003) Autologous stem cell transplantation in multiple myeloma patients <60 vs >/=60 years of age. Bone Marrow Transplantation, 32, 1135-1143. Kumar, S., Lacy, M.Q., Dispenzieri, A., Rajkumar, S.V., Fonseca, R., Geyer, S., Allmer, C., Witzig, T.E., Lust, J.A., Greipp, P.R., Kyle, R.A., Litzow, M.R. & Gertz, M.A. (2004) High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. Bone Marrow Transplantation, 34, 161-167. Kumar, S.K., Dingli, D., Lacy, M.Q., Dispenzieri, A., Hayman, S.R., Buadi, F.K., Rajkumar, S.V., Litzow, M.R. & Gertz, M.A. (2008b) Autologous stem cell transplantation in patients of 70 years and older with multiple myeloma: Results from a matched pair analysis. American Journal of Hematology, 83, 614-617.	

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Amendments	

1

Topic	**The role of allogeneic stem cell transplantation in both primary treatment and treatment of relapsed myeloma (salvage therapy).**
Review question	Which patients with myeloma should be considered for allogeneic stem cell transplantation?
Topic Subgroup	**Lead**: John Snowden **Subgroup**: Andie Guy, Jane Woodward, Matthew Streetly, Matthew Jenner
Economic Priority	High

Background

Allogeneic stem cell transplantation (SCT) is a complex procedure involving administration of high dose cytotoxic therapy (chemotherapy +/- radiotherapy) followed by transplant of peripheral blood or bone marrow stem cells from a sibling or unrelated donor (and rarely cord blood). The risks are significantly higher than autologous transplantation (which is more commonly performed in myeloma patients) and include a long-term tendency to infection and graft versus host disease (GVHD). These toxicities can significantly compromise both short term and long term quality of life and amount to a treatment related mortality risk of over 10-30% depending on the type of transplant and the status of the donor. However, allogeneic transplant has the potential of very-long term disease control, and what some have termed 'operational cure'. Nevertheless, allogeneic SCT is not universally curative and, despite a successful SCT, relapse occurs in a substantial proportion of patients. In summary, allogeneic SCT offers the possibility of long-term disease control but this needs to be balanced against the potential toxicities and risk of relapse.

Allogeneic SCT works through a combination of high dose chemotherapy and immune attack against the myeloma i.e. a graft-versus-myeloma effect, which is closely associated with GVHD. If GVHD does not occur, and, there is evidence of residual or relapsing myeloma, additional treatment with donor lymphocyte infusions (DLI) is sometimes useful to produce GVHD and thereby boost the GVM effect. However, severe GVHD impacts significantly on quality of life and is an important cause of late mortality after allogeneic SCT.

Outcomes of allogeneic HSCT have improved with the use of reduced intensity transplant (often combined with an autologous SCT). Despite this, a decision to proceed with allogeneic transplantation is increasingly challenging with the advent of new therapies in myeloma, which, although not curative, may offer prolonged periods of disease control, and have significantly extended the life expectancy in patients with MM. Thus, amongst the modern treatment of myeloma, the optimum timing for allogeneic SCT is unclear. From a biological point of view, allogeneic SCT is probably most effective at killing the myeloma cells if performed early in the course of myeloma i.e. in the first remission or second remission, when the myeloma is most sensitive to therapy. Potentially, at this early stage, patients may be the least compromised by myeloma and its treatments and have the best chance of surviving the procedure. However, if major complications occur post SCT, there is a risk of substantially reducing quality of life and shortening otherwise reasonable life expectancy. On the other hand, deferring the risks of SCT to a later stage of disease run the chance of outcomes being compromised by progressive disease resistance and the patient being increasingly less fit for transplant. Understandably, there is a wide variation in practice of allogeneic SCT within the UK due to all of these factors, as well as individual patient and physician preference.

In summary, proceeding with allogeneic SCT in myeloma is very much an individualized decision treatment and one of the most challenging for both doctors and patients in the field of myeloma. The decision to offer allogeneic SCT depends on availability of matched siblings or matched unrelated donors, along with the age, general fitness and personal preference of patients and the prognosis of their myeloma. Patients need to be fully informed and involved in the decision making process. Allogeneic SCT for patients with myeloma should only be considered for very carefully selected groups because of the risk of significant transplant-related morbidity and mortality in a disease where survival can now be increasingly prolonged with other therapies with better safety profiles. It is hoped that the evidence reviewed here will provide guidelines for selecting patients who will benefit the most from allogeneic stem cell transplantation.

It would be of great clinical and health economic value to address the risk-benefit ratio between allogeneic SCT compared with standard of care at various points in the treatment pathways for various age and prognostic groups.

A Markov life modeling analysis could help to define which sub-groups of myeloma potentially benefit from allogeneic SCT in first response, second response or later stage disease compared with standard pathway. Given the considerable cost of allogeneic SCT and other myeloma treatments, economic aspects could also be usefully addressed with this model.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with newly diagnosed myeloma grouped according to - Age - Performance status - Comorbidities (charlson score, ACE-27) - Renal impairment - Genetic abnormalities (FISH) - ISS - Beta-2 microglobulin Patients with relapsed myeloma grouped according to - Age - Performance status - Comorbidities (charlson score, ACE-27) - Renal impairment - Genetic abnormalities (FISH) - Time to relapse - Number of relapses - Disease responsiveness (disease that responded or is stable after re-induction therapy)	Allogeneic stem cell transplant - Myeloablative conditioning (MAC) - Non-Myeloablative conditioning (NMA) or reduced intensity conditioned (RIC including auto/allo RIC)	• Chemotherapy • First (in newly diagnosed patients) or second (in relapsed patients) autologous stem cell transplant • no treatment	• Health related quality of life • Overall survival • Progression free survival • Treatment related mortality • Treatment related morbidity • Adverse events • Patient/carer/family acceptability • PROMs

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	Comparative studies only Sample size of at least 20	Include studies of a single intervention of they look at predictive factors
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Studies published after 2000	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL,	

	HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Allograft Mini allograft Full intensity transplant Reduced intensity conditioning RIC Myeloablative conditioning MAC Auto/allo Graft versus host disease (GVHD)	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Cavo, M., Benni, M., Cirio, T. M., Gozzetti, A. & Tura, S. (1995) Allogeneic bone marrow transplantation for the treatment of multiple myeloma. An overview of published reports. [Review] [25 refs]. *Stem Cells,* 13 Suppl 2: 126-131. BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma Sept 2010 Lokhorst H, Einsele H, Vesole D, Bruno B, San Miguel J, Pérez-Simon JA, Kröger N, Moreau P, Gahrton G, Gasparetto C, Giralt S, Bensinger W; International Myeloma Working Group. (2010) International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. J Clin Oncol. 28(29):4521-30. Bruno, B., Rotta, M., Patriarca, F., Mordini, N., Allione, B., Carnevale-Schianca, F., Giaccone, L., Sorasio, R., Omede, P., Baldi, I., Bringhen, S., Massaia, M., Aglietta, M., Levis, A., Gallamini, A., Fanin, R., Palumbo, A., Storb, R., Ciccone, G. & Boccadoro, M. (2007) A comparison of allografting with autografting for newly diagnosed myeloma. *New England Journal of Medicine,* 356, 1110-1120. Barlogie, B., Tricot, G., Anaissie, E., Shaughnessy, J., Rasmussen, E., van Rhee, F., Fassas, A., Zangari, M., Hollmig, K., Pineda-Roman, M., Lee, C., Talamo, G., Thertulien, R., Kiwan, E., Krishna, S., Fox, M. & Crowley, J. (2006b) Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *New England Journal of Medicine,* 354, 1021-1030. Bjorkstrand, B., Lacobelli, S. & Hegenbart, A. (2009) Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning (RIC) allogeneic SCT with identical sibling donor in previously untreated multiple myeloma (MM): a prospective controlled trial by the EBMT. *Bone Marrow Transplantation (abstract),* 43, 223. Crawley, C., Iacobelli, S., Bjorkstrand, B., Apperley, J.F., Niederwieser, D. & Gahrton, G. (2007) Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood,* 109, 3588-3594. Crawley, C., Lalancette, M., Szydlo, R., Gilleece, M., Peggs, K., Mackinnon, S., Juliusson, G., Ahlberg, L., Nagler, A., Shimoni, A., Sureda, A., Boiron, J.M., Einsele, H., Chopra, R., Carella, A., Cavenagh, J., Gratwohl, A., Garban, F., Zander, A., Bjorkstrand, B., Niederwieser, D., Gahrton, G. & Apperley, J.F. (2005) Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. *Blood,* 105, 4532-4539. Gahrton, G., Tura, S., Ljungman, P., Belanger, C., Brandt, L., Cavo, M., Facon, T., Granena, A., Gore, M., Gratwohl, A., Löwenberg, B., Nikoskelainen, J., Reiffers, J.J., Samson, D., Verdonck, L. & Volin, L. for the European Group for Bone Marrow Transplantation (1991) Allogeneic bone	

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Amendments	

Topic	**The management of primary plasma cell leukaemia**
Review question	What are the most effective treatments for patients with primary plasma cell leukaemia?
Topic Subgroup	**Lead**: Hamdi Sati **Subgroup**: Matthew Jenner, Monica Morris
Economic Priority	low

Background

Plasma cell leukaemia (PCL) is an aggressive type of myeloma characterised by the presence of large number of malignant plasma cells in the peripheral blood. It is further classified into primary PCL, when it occurs at 1st diagnosis or secondary PCL when it develops as a terminal phase of relapsed refractory myeloma. Primary PCL runs a more aggressive course than myeloma with poor response to conventional chemotherapy and a significantly shorter lifespan with a median survival of only 7 months. In view of the rarity of primary PCL, no large scale clinical trials have been conducted and most information about its management comes from case reports or small series from retrospective studies. Consequently, the clinical approach to the management of patients with primary plasma cell leukaemia remains variable.

These guidelines will evaluate the efficacy of treatment options including novel agents, high dose chemotherapy and stem cell transplantation and make recommendations regarding the best clinical approach for patients with primary PCL.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients diagnosed with primary plasma cell leukaemia	• Chemotherapy regimes - Proteosome inhibitor based regimens Bortezomib - Imid based regimens Thalidomide Lenalidomide pomalidomide - Combination regimens VTD-PACE DT-PACE VRD-PACE ESHAP DCEP PACE PAD VRD • Maintenance • Consolidation • autologous stem cell transplantation • allogeneic stem cell transplantation	• Each other • observation	• Overall survival • Progression free survival • HRQOL • Adverse events (e.g. graft-versus-host disease, sepsis)

Additional comments on PICO

No additional comments

	Details	Additional Comments

Type of review	intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Case series of 5 or more	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Primary plasma cell leukaemia Autologous stem cell transplantation Allogeneic stem cell transplantation	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Fernández de Larrea C, Kyle RA, Durie BG, Ludwig H, Usmani S, Vesole DH, Hajek R, San Miguel JF, Sezer O, Sonneveld P, Kumar SK, Mahindra A, Comenzo R, Palumbo A, Mazumber A, Anderson KC, Richardson PG, Badros AZ, Caers J, Cavo M, LeLeu X, Dimopoulos MA, Chim CS, Schots R, Noeul A, Fantl D, Mellqvist UH, Landgren O, Chanan-Khan A, Moreau P, Fonseca R, Merlini G, Lahuerta JJ, Bladé J, Orlowski RZ, Shah JJ; International Myeloma Working Group. (2013) Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. Leukemia. 27(4), 780-91. Niels W. C. J. van de Donk, Henk M. Lokhorst, Kenneth C. Anderson, and Paul G. Richardson. (2012) How I treat plasma cell leukemia. Blood. 120 (12), 2376-89. Katodritou E, Terpos E, Kelaidi C, Kotsopoulou M, Delimpasi S, Kyrtsonis MC, Symeonidis A, Giannakoulas N, Stefanoudaki A, Christoulas D, Chatziaggelidou C, Gastari V, Spyridis N, Verrou E, Konstantinidou P, Zervas K, Dimopoulos MA. (2014) Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group. Am J Hematol. 89 (2), 145-50. D'Arena G, Valentini CG, Pietrantuono G, Guariglia R, Martorelli MC, Mansueto G, Villani O, Onofrillo D, Falcone A, Specchia G, Semenzato G, Di Renzo N, Mastrullo L, Venditti A, Ferrara F, Palumbo A, Pagano L, Musto P. Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party. (2012) Ann Oncol. 23(6), 1499-502. Pagano L, Valentini CG, De Stefano V, Venditti A, Visani G, Petrucci MT, Candoni A, Specchia G, Visco C, Pogliani EM, Ferrara F, Galieni P, Gozzetti A, Fianchi L, De Muro M, Leone G, Musto P, Pulsoni A; GIMEMA-ALWP (Gruppo Italiano Malattie EMatologiche dell'Adulto, Acute Leukemia	

	Working Party: coordinator Sergio Amadori). (2011), Primary plasma cell leukemia: a retrospective multicenter study of 73 patients. Ann Oncol. 22(7), 1628-35.
Amendments	

1

Topic	**The management of renal disease for patients with myeloma**
Review question	**What is the optimal management of acute renal disease in patients with myeloma?**
Topic Subgroup	**Lead: Matthew Streetly** **Subgroup: Monica Morris, Hamdi Sati, Matthew Jenner**
Economic Priority	**high**

Background

Myeloma is a malignancy that can commonly be associated with renal disease. It causes renal problems in a range of ways that includes deposits of myeloma associated proteins in the kidney (cast nephropathy, amyloid or light chain deposition), high calcium levels, infection and drug associated toxicity. It is reported that up to 40% of myeloma patients will have a degree of renal dysfunction at diagnosis and up to 10% of patients will require renal replacement therapy (dialysis).

Renal disease can occur at any time throughout the disease course and it is estimated that up to 50% of patients will be affected during their disease course. The presence of renal dysfunction has a significant negative impact on the ability to effectively treat myeloma as chemotherapy drugs often require dose changes or are associated with increased toxicity in the presence of renal disease. It also significantly affects patient survival with studies demonstrating that renal disease and in particular dialysis dependence is associated with a particularly poor overall survival for myeloma patients.

A number of approaches have been developed to try to reverse renal dysfunction and/or protect the kidneys from further damage. These approaches include mechanical methods to remove damaging myeloma proteins (plasmapheresis, high cut-off dialysis), chemotherapy approaches and supportive treatments.

These guidelines will make recommendations on the appropriate use of renal disease assessment tools, supportive approaches for myeloma patients with renal impairment, the use of mechanical methods to reverse renal disease as well as best evidence chemotherapy approaches.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with myeloma who have myeloma-induced acute renal disease Subgroups: • castnephropathy • amyloid • other causes	• plasmapheresis • hemodialysis (including wide pore membrane dialysis), haemofiltration, CAPD, renal replacement therapy • systemic therapies/chemotherapy regimens: - lenalidomide based regimens - thalidomide based regimens - proteasome based regimens - dexamethasone - bendamustine - VAD - Melphalan & prednisolone	• each other • hydration and supportive management	• improvement in renal function • recovery from dialysis • rate of dialysis • overall survival • progression-free survival • health related quality of life • adverse events

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	Intervention	

Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Date limit – last 20 years Patient number >10	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	myeloma kidney, cast nephropathy, plasma exchange, plasmapheresis, haemofiltration, haemodialysis, peritoneal dialysis, CAPD, renal impairment, renal failure, acute renal failure	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Gupta D, Bachegowda L, Phadke G, Boren S, Johnson D, Misra M. (2010) Role of plasmapheresis in the management of myeloma kidney: a systematic review. Hemodial Int. 14(4):355-63. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, Niesvizky R, Giralt S, Fermand JP, Bladé J, Comenzo RL, Sezer O, Palumbo A, Harousseau JL, Richardson PG, Barlogie B, Anderson KC, Sonneveld P, Tosi P, Cavo M, Rajkumar SV, Durie BG, San Miguel J. (2010) Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 28(33):4976-84. Chanan-Khan et al (2012) Novel therapeutic agents for the management of patients with multiple myeloma and renal impairment. Clin Cancer Res 18(8): 2145-63. NICE clinical guideline 169 (2013). Acute kidney Injury.	
Amendments		

1

2

Topic	**The prevention and management of bone disease, including spinal bone disease, for patients with myeloma.**
Review question	What is the most effective method of preventing bone disease in patients with myeloma?
Topic Subgroup	**Lead**: Hamdi Sati **Subgroup**: Andrea Guy, Nicola Montacute, Alan Chant, John Snowden
Economic Priority	Medium/high

Background

Bone disease remains the most common presenting feature of myeloma. The development of bone damage in myeloma is thought to be due to the stimulating effects of the tumour cells on bone tissue resulting in a shift in favour of the bone eating cells, called osteoclasts, making bones fragile and easy to fracture. Clinical features of bone disease of myeloma may take the form of bone pain, bone fractures spontaneously or following minimal trauma (pathological fractures), spinal cord compression, high calcium in the blood (hypercalcaemia) with possible consequent renal damage, and development of holes in the bones (lytic lesions). These features are usually named collectively as skeletal related events (SREs).

The primary management of patients with symptomatic myeloma usually starts with introduction of effective combination chemotherapy. However, a number of clinical trials have also examined the efficacy of other treatment measures that can specifically prevent and/or treat SREs. Bisphosphonates (BP), a class of drugs that inhibit osteoclastic activity, was the first bone directed therapy shown in randomised clinical trials to improve SREs in patients with myeloma. BPs therapy is now commonly used as part of the treatment of symptomatic patients, however some aspects of their use remain unclear. These include type of BP, treatment duration and scheduling, their use in patients with asymptomatic myeloma and alternative treatment options in patients who could not tolerate the BP therapy. Also the use of some BPs can cause complications such as osteonecrosis of the jaw (ONJ). Alternatives/adjunct to BPs include calcium supplements, vitamin D supplements, bone anabolic therapy and exercise. Biochemical markers of bone turnover are being assessed as a mean of monitoring and guiding BP therapy in patients with osteoporosis and bone metastasis. It would be interesting to examine their clinical application in patients with myeloma. However this is a new area of research in myeloma and there in unlikely to very much evidence at this time.

This guideline will review the evidence for various methods of preventing bone disease in myeloma and make recommendations on the most appropriate use of these measures, including ongoing measures/surveillance with the aim of limiting incidence of associated risks such as ONJ.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients diagnosed with symptomatic myeloma Patients diagnosed with asymptomatic myeloma Patients diagnosed with myeloma who have renal disease Patients with relapsed myeloma	• Bisphosphonates (including type of bisphosphonate, treatment duration and scheduling) • Calcium supplements • Vitamin D supplements • Osteoclast inhibition (RANKL INHIBITORS eg DENOSUMAB) • Bone anabolic therapy • exercise	• placebo • no treatment • each other	• skeletal related events • Adverse events (e.g., ONJ, hypocalcaemia, renal impairment) • Quality of life • Overall survival • Progression-free survival • Pain • Need for radiotherapy • Hypercalcaemia

Additional comments on PICO

For papers on BPs note if they report the use of bone turnover markers such as urinary NTX and serum CTX (both markers of bone resorption) and bone specific alkaline phosphatase (BSAP) a marker of bone formation, to assess clinical application in monitoring/guiding BP therapy in patients with myeloma.

	Details	Additional Comments
Type of review	intervention	
Language	English language only	
Study design	For interventions bisphosphonates and denosumab: - Randomised Trials - Systematic reviews of randomised trials No filter for other interventions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Date limit - 1992	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Bisphosphonates Soduim Clodronate Disoduim Pamidronate Zoledronic acid Bone anabolic agents RANKL inhibitors Denosumab Ibandronate Alendronate Osteonecrosis of the jaw Lytic lesions	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Mhaskar R, Redzepovic J, Wheatley K, Clark OA, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B. (2012) Bisphosphonates in multiple myeloma: a network meta-analysis. Cochrane Database Syst Rev. 2012 May 16;5:CD003188. Bloomfield, D. J. (1998) Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. [Review] [42 refs]. *Journal of Clinical Oncology,* 16: 1218-1225 Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N, Sezer O, García-Sanz R, Shimizu K, Turesson I, Reiman T, Jurczyszyn A, Merlini G, Spencer A, Leleu X, Cavo M, Munshi N, Rajkumar SV, Durie BG, Roodman GD. (2013) International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol. 31(18):2347-57.	

	Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Journal of Clinical Oncology, 29(9); 1125-32. Larocca A, Child J A, Cook G et al, (2013) The impact of response on bone-directed therapy in patients with multiple myeloma. Blood, 122(17) 2974-77. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. (1992) Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Lancet, 340(8827); 1049-52. Laakso M, Lahtinen R, Virkkunen P, Elomaa I.(1994) Subgroup and cost-benefit analysis of the Finnish multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Br J Haematol. 87(4); 725-9. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, Lipton A, Keller A, Ballester O, Kovacs MJ, Blacklock HA, Bell R, Simeone J, Reitsma DJ, Heffernan M, Seaman J, Knight RD. (1996) Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N ENGl J Med 334980; 488-93. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, Lipton A, Keller A, Ballester O, Kovacs M, Blacklock H, Bell R, Simeone JF, Reitsma DJ, Heffernan M, Seaman J, Knight RD. (1998) Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol 16(2); 593-602. Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, Dreicer R, Kuross SA, Lipton A, Seaman JJ. (2001) Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. Cancer; 91(7); 1191-200. Morgan GJ, Child JA, Gregory WM, Szubert AJ, Cocks K, Bell SE, Navarro-Coy N, Drayson MT, Owen RG, Feyler S, Ashcroft AJ, Ross FM, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Wu P, Davies FE; National Cancer Research Institute Haematological Oncology Clinical Studies Group. 211) Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): secondary outcomes from a randomised controlled trial. Lancet Oncol 12(8); 743-52.
Amendments	

1

2

Topic	**The prevention and management of bone disease, including spinal bone disease, for patients with myeloma.**
Review question	What are the most effective treatments (other than chemotherapy) for non-spinal bone disease in patients with myeloma (including radiotherapy and surgical intervention)?
Topic Subgroup	**Lead**: Hamdi Sati **Subgroup**: Sam Ahmedzai, Nicola Montacute, Andrea Guy, Jane Woodward *(invite clinical oncologist and orthopaedic surgeon as expert advisors)*
Economic Priority	low

Background

Bone disease remains the most common presenting feature of myeloma. The development of bone damage in myeloma is thought to be due to the stimulating effects of the tumour cells on bone tissue resulting in a shift in favour of the bone eating cells, called osteoclasts, making bones fragile and easy to fracture. Bone pain, pathological fractures, lytic bone lesions and hypercalcaemia are the main skeletal related events (SREs) in non-spinal bone disease due to myeloma. The management of these SREs is multidimensional and depends on several factors including site and extent of involvement, symptoms, performance status, co-morbidities, life expectancy in addition to patient circumstances and preferences.

Decisions of treatment involve multidisciplinary professionals including clinical haematologist, clinical oncologist, radiologist, orthopaedic surgeon, pain control and palliative care specialist, physiotherapist and clinical nurse specialist. One or more modalities of treatment, in addition to combination chemotherapy, are usually required. These may include radiotherapy, osteoclast inhibitors such as bisphosphonates and orthopaedic surgical intervention.

These guidelines will review the evidence and make recommendations on the most appropriate treatment modality for non-spinal bone disease in patients with myeloma including the sequencing of localised therapy such as radiotherapy and prophylactic surgical intervention.

PICO Table

Population	Intervention	Comparator	Outcomes
myeloma patients with non-spinal bone disease	• orthopaedic surgery (pinning, plating, bone grafting. prophylactic vs therapeutic intervention) • Radiotherapy (including dose) • Interventional pain management • Bisphosphonates • Denosumab • Supportive care	• Each other • Conservative management	• Health related quality of life • Progression free survival • Overall survival • Adverse events (e.g., ONJ) • pain control • Mobility/dependency • Patient expectation

Additional comments on PICO

Look for whether rehabilitation reported in studies.
Look at early and late effects - some interventions may be effective early on but become less effective over time?

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	No study design filter	
Status	Published studies only	
Other criteria for inclusion /	Date limit 1992 Exclude chemotherapy as an intervention.	

exclusion of studies		
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Lytic lesions Bisphosphonate related osteonecrosis of the jaw BRONJ AREDIA ZOMETA BONEFOS Bisphosphonates Soduim Clodronate Disoduim Pamidronate Zoledronic acid Bone anabolic agents RANKL inhibitors Denosumab Ibandronate Alendronate Interventional pain management - Neurolytic blockade, regional blockade, cordotomy, intrathecal drug management	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N, Sezer O, García-Sanz R, Shimizu K, Turesson I, Reiman T, Jurczyszyn A, Merlini G, Spencer A, Leleu X, Cavo M, Munshi N, Rajkumar SV, Durie BG, Roodman GD. (2013) International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol. 31(18):2347-57. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. Journal of Clinical Oncology, 29(9); 1125-32. Larocca A, Child J A, Cook G et al, (2013) The impact of response on bone-directed therapy in patients with multiple myeloma. Blood, 122(17) 2974-77. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. (1992) Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Lancet, 340(8827); 1049-52. Laakso M, Lahtinen R, Virkkunen P, Elomaa I.(1994) Subgroup and cost-benefit analysis of the Finnish multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. Br J	

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Amendments	

1

2

Topic	**The prevention and management of bone disease, including spinal bone disease, for patients with myeloma.**
Review question	Excluding chemotherapy, which treatments are effective for spinal bone disease in patients with myeloma, and in which circumstances and order should they be offered?
Topic Subgroup	**Lead**: Nicola Montacute **Subgroup**: Nicola Mulholland, Sam Ahmedzai,, Alan Chant, Hamdi Sati, Andrea Guy, Matthew Streetly *(include a spinal/relevant orthopaedic surgical and an intervention radiologist as expert advisors)*
Economic Priority	medium

Background

Bone disease remains the most common presenting feature of myeloma. The development of bone damage in myeloma is thought to be due to the stimulating effects of the tumour cells on bone tissue resulting in increased activity of the bone eating cells (osteoclasts), making bones fragile and easy to fracture. When myeloma affects the vertebral spine, it causes severe pain usually affecting the back and that often spreads around the chest or abdomen in the distribution of spinal nerves. Myeloma in the neck vertebrae can lead to pain going down the shoulders and arms, whereas disease affecting the lowest segments of the spine (lumbar and sacral levels) causes pain affecting the legs.

Spinal bone disease can sometimes lead to collapse of one or more vertebrae, which causes very serious consequences including acute severe pain and if there is spinal cord compression, weakness or paralysis of the lower limbs and loss of bladder and bowel control which can rapidly become permanent without urgent treatment, with devastating consequences. Metastatic spinal cord compression is covered in NICE clinical guideline 75 (2008) so the management of this condition will not be covered by this new guideline.

Spinal bone disease may be prevented or slowed down by using drugs such as bisphosphonates or denosumab, which block the osteoclasts that cause bone destruction. However, the evidence base for their use is not as robust as it is in solid tumours which cause bone disease, such as breast or lung cancer. The use of these drugs can cause complications such as osteonecrosis of the jaw (ONJ).

The core aims of the management of spinal bone disease in myeloma are decompression, stabilization and pain control. Management consists of pain management using drugs (analgesics), radiotherapy, external bracing/orthotics and in severe cases, open spinal surgery. Radiotherapy is effective for pain relief and most patients need one or two fractions; however it may take several weeks for the full effect and some patients experience a pain 'flare' in the early days after treatment. Patients need to travel to a radiotherapy centre and will require to lie flat on a hard table for several minutes.

Faster-acting interventions include procedures such as vertebroplasty or balloon kyphoplasty, in which plastic cement is injected into the diseased vertebrae. Side-effects are usually mild and temporary but may be problematic in a few patients. Vertebral cement augmentation can be done by orthopaedic surgeons or by interventional radiologists, usually as a day case procedure. The use of these vertebral cement techniques is covered by NICE interventional procedure guidance 166 (2006) (Balloon kyphoplasty for vertebral compression fractures) and NICE interventional procedure guidance 12 (2003) (Percutaneus vertebroplasty), but the best times to use them in multiple myeloma is not known. Not all hospitals offer vertebroplasty so some patient may have to travel some distance for this procedure.

The optimum sequence of these treatments is not known in multiple myeloma. The order in which to offer patients radiotherapy or vertebroplasty will depend partly on the severity of pain, the number of vertebrae involved, the risk of spinal cord compression, local availability of specialist services and whether the patient has to travel a long distance.

When several vertebrae are affected vertebral cement augmentation may not be feasible. If there is severe spinal instability with risk of spinal cord compression, then the spine may need to be stabilised using open surgery. Metal rods have to be inserted alongside the spine and fixed using screws into the healthy vertebrae. These operations can be carried out by either orthopaedic surgeons or neurosurgeons. It is currently unclear which type of surgery is best in multiple myeloma, optimal timing of the procedure and who should carry it out. Again, it is also not known if

where spinal surgery fits in the algorithm with other management strategies such as radiotherapy, vertebroplasty or invasive drug treatments such via as intrathecal catheters and neurolytic procedures; and which are more appropriate in terms of improving the outcomes for patients with advanced disease.

There is variation across the UK in terms of access to specialist surgery for spinal surgery, including management of rehabilitation after spinal cord compression. There is also considerable variation across the UK in the access patients have to other treatments such as palliative radiotherapy. Travelling to supra-regional centres may be problematic for myeloma patients in considerable pain. These issues of locations of treatment interventions will be addressed in question E. However, this question aims to determine the effectiveness of the different treatments for the management of spinal bone disease in patients with myeloma and to make recommendations in which circumstances and order they should be considered.

PICO Table

Population	Intervention	Comparator	Outcomes
Myeloma patients with spinal bone disease grouped according to type of spinal disease: - Lytic lesions - Pathological fracture - Vertebral collapse with risk of spinal cord compression - Vertebral collapse leading to loss of height and deformity (kyphosis) - Spinal instability	• Vertebral cement augmentation • Vertebroplasty • Balloon kyphoplasty • Lordoplasty • Spinal surgery • Percutaneous fixation • External bracing • Radiotherapy • Bisphosphonates • Denosumab • Interventional pain management • Supportive care	• Each other • Conservative management	• Vertebral collapse • Spinal cord compression • Health related quality of life • Progression free survival • Overall survival • Performance status • Adverse events • Pain control • Activities of daily living/mobility • Dependency

Additional comments on PICO

Look for whether rehabilitation is reported in studies (e.g., physiotherapy and OT)

Do any studies identify treatment algorithms which help clinicians decide the order of treatments, eg radiotherapy first or vertebroplasty first?

Make notes if any of the following are also reported to affect treatment decision:
Level of pain
Location of pain
Duration of pain
Time elapsed since the fracture occurred
Number of vertebrae affected
Previous treatments
Other conditions/co-morbidities

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	No study design filter	
Status	Published studies only	Excluded studies only published as conference abstracts (JH, Aug 2014)
Other criteria for inclusion / exclusion of studies	Exclude spinal cord compression No date limit for radiotherapy 2000 date limit for other interventions 1990 date limit for bisphosphonates	Studies were excluded if majority of population included cancers other than myeloma. A recent pooled analysis of case series for vertebroplasty/kyphoplasty identified, so

		any further case series published after that search date were looked for using the same criteria (excluded n <15) Data for bisphosphonates extracted from network meta-analysis (Mhaskar 2012) which was also presented for topic L1 (JH, Aug 2014)
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Pain score / pain level Paralysis Vertebral compression fracture Vertebral cement augmentation Kyphosis Spinal surgery Spinal rehabilitation External bracing Orthotics Lordoplasty Bisphosphonates Clodronate (Bonefos®) Pamidronate (Aredia®) Zoledronic acid (Zometa®) Denosumab Bone anabolic agents RANKL inhibitors Ibandronate Alendronate Interventional pain management - Neurolytic blockade, regional blockade, cordotomy, intrathecal drug management	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	CAFÉ study. Berenson et al., The Lancet Oncology, March 2011, Vol 12, 225-235 Balloon Kyphoplasty versus non surgical fracture management for treatment of painful vertebral compression fractures in patients with cancer: a multicentre randomised controlled trial. Terpos et al., Journal of Clinical Oncology, June 20 2013, Vol 31, no.18, 2347-2357 International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma-Related Bone Disease. Van M Meirhaeghe J, Bastian L, Boonen S, et al. Spine 2013 A randomised trial of balloon kyphoplasty and non-surgical management for treating acute vertebral compression fractures: vertebral body kyphosis correction and surgical parameters. Masala S. et al., Tumori. 2004 Jan-Feb;90(1):22-6. Percutaneous kyphoplasty: indications and technique in the treatment of vertebral fractures from myeloma.	

	Tancioni F. et al, Neurol Sci. 2010 Apr;31(2):151-7. Vertebroplasty for pain relief and spinal stabilisation in muliple myeloma Masala S. et al., J Spinal Disord Tech. 2008 Jul;21(5):344-8. Percutaneous vertebroplasty in multiple myeloma vertebral involvement. Khan OA, et al., AJNR Am J Neuroradiol. 2013 Jul 18. [Epub ahead of print] Vertebral Augmentation in Patients with Multiple Myeloma: A Pooled Analysis of Published Case Series. Orgera G, et al., Cardiovasc Intervent Radiol. 2013 May 8. [Epub ahead of print] Percutaneous Vertebroplasty for Pain Management in Patients with Multiple Myeloma: Is Radiofrequency Ablation Necessary? Wilson DJ, et al., Eur Radiol. 2013 Jul;23(7):1785-90. doi: 10.1007/s00330-013-2787-0. Epub 2013 Feb 27. Coblation vertebroplasty for complex vertebral insufficiency fractures. Mendoza et al. J Pain. 2012 Jun;13(6):564-70. doi: 10.1016/j.jpain.2012.03.003. Epub 2012 Apr 28. Changes in pain and other symptoms in patients with painful multiple myeloma-related vertebral fracture treated with kyphoplasty or vertebroplasty. Köse KC, J Natl Med Assoc. 2006 Oct;98(10):1654-8. Functional results of vertebral augmentation techniques in pathological vertebral fractures of myelomatous patients. Kasperk et al., Journal of Surgical Oncology 2012; 105:679-686 Kyphoplasty in patients with Multiple Myeloma a retrospective comparative pilot study.
Amendments	

1

2

Topic	**Prophylaxis of infection for patients with myeloma**
Review question	What is the most effective prophylactic strategy for infection in patients with myeloma (including immunoglobulin, antibiotics, growth factors and vaccinations)?
Topic Subgroup	**Lead**: Matthew Streetly **Subgroup**: Andrea Guy , Hamdi Sati, Jane Woodward
Economic Priority	medium

Background

Myeloma is a malignancy of plasma cells. These are antibody producing cells and are a major component of the immune system. Patients with myeloma have an increased risk of developing all types of infections and often these infections can be more difficult to treat than in people without myeloma. In addition treatment with chemotherapy can also increase the risk of infections developing and it has been observed in clinical studies that infections are one of the commonest causes of death in the first 3 months after diagnosis. It is also known that specific treatments can be associated with specific types of infections.

There are a number of possible ways to try and reduce the risks posed by infections that include regular prophylaxis with antibiotic, antiviral or antifungal drugs, the use of pre-emptive vaccination (e.g. for flu), the use of growth factors which stimulate aspects of the immune system and regular immunoglobulin replacement therapy. The use of many of these approaches requires clarification at the different timepoints in a myeloma patient's journey as whilst there may be benefits in terms of reducing the number and severity of infections there is also a possible risk as a result of drug related side effects and the development of drug resistance due to overuse.

These guidelines will make recommendations on the use of different anti-infective approaches at the different timepoints in a myeloma patient pathway including at diagnosis / initial therapy, at relapse and post autologous stem cell transplant, for specific treatments (e.g. proteosome inhibitors) and for patients who are not currently requiring chemotherapy.

PICO Table

Population	Intervention	Comparator	Outcomes
Newly diagnosed myeloma patients relapsed myeloma patients Patients on active therapy or maintenance therapy myeloma patients currently off treatment post autologous transplant myeloma patients	• Antibiotics (including anti-mycobacterial prophylaxis) • Anti-virals • Anti-fungals • Pneumocystis prophylaxis • Immunoglobulins • Growth factors • Vaccination	• placebo • no treatment • each other (within treatment type group)	• sepsis • recorded infections • death related to infection • hospital admissions • adverse events (e.g. growth factor related bone pain) • response to vaccination • patient adherence and acceptability

Additional comments on PICO

Exclude patients who have undergone allogeneic transplant as there are already guidelines in place for these patients

Report what treatment patients are having as there is likely to be specific intervention for specific therapies that patient is on e.g. with bortezomib patient at risk of singles so get specific treatment for this.

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	Randomised Trials Systematic reviews of randomised trials Large cohorts (100+) in the last 10 years	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	n/a	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Re pneumocystis – might be useful to search Pentamidine nebuliser in addition to Co Trimoxazole	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Cheuk-Daniel, K. L., Chiang-Alan, K. S., Lee, T. L., Chan-Godfrey, C. F. & Ha, S. Y. (2011) Vaccines for prophylaxis of viral infections in patients with hematological malignancies. Cochrane Database of Systematic Reviews. Raanani, P., Gafter, G. A., Paul, M., Ben, B., I, Leibovici, L. & Shpilberg, O. (2008) Immunoglobulin prophylaxis in hematological malignancies and hematopoietic stem cell transplantation. Cochrane Database of Systematic Reviews Raanani, P., Gafter-Gvili, A., Paul, M., Ben-Bassat, I., Leibovici, L. & Shpilberg, O. (2009) Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. [Review] [20 refs]. Leukemia & Lymphoma, 50: 764-772. Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird JM; Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. (2011) Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 154(1):76-103. NICE clinical guideline 151 (2012). Neutropenic sepsis. Department of health. Clinical guideline for immunoglobulin use. 2008. (and update 2011) Augustson JCO 2005 – overview of early mortality	
Amendments		

1

Topic	**The management of neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain).**
Review question	**What is the most effective way to manage neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain)?**
Topic Subgroup	**Lead: Sam Ahmedzai** **Subgroup: Lesley Roberts, Nicola Montacute, John Snowden**
Economic Priority	**low**

Background

Neuropathy is the condition when nerves (including the spinal cord) are damaged or diseased. This can occur in multiple myeloma as a result of direct pressure on spinal nerves, when vertebral bones have been weakened by myeloma and become compressed. Neuropathy also occurs when a substance called amyloid, which is produced in myeloma patients, becomes deposited in several body tissues including in the nervous system. It also arises as a consequence of treatment for myeloma, especially when certain drugs have been used. These include thalidomide and bortezomib. It must also be remembered that other concurrent illnesses (called 'co-morbid' conditions) can cause neuropathy, eg diabetes mellitus or shingles (herpes zoster infection).

Neuropathy causes several unpleasant symptoms which can impair the patient's quality of life The main symptoms are numbness, pins and needles (paraesthesiae), pain, and in severe cases, it may cause muscle weakness. The feet, lower legs and hands are most commonly affected by drug-related neuropathy. Shingles may affect any part of the body, including the face.

The management of neuropathy and in particular of the painful symptoms can be very difficult and may require a combination of strong painkillers (analgesics), including opioids (drugs related to morphine) and drugs originally licensed for other conditions such as epilepsy or depression. All of these drugs carry potentially upsetting or even dangerous side-effects. Using these drugs in such a way as to reduce symptoms without adding undue side-effects often needs the help of specialists in pain management or palliative medicine. NICE guidance on drug management of neuropathic pain has recently been updated and so it is not necessary to repeat an evidence review for pharmacological management of neuropathic pain here.

The scope of this topic, however, is non-pharmacological management of neuropathy resulting from myeloma treatment, and there is considerable uncertainty and debate surrounding this. Lowering the dose of the drug thought to be responsible, or stopping it for a period of time, may help. Although a reduction in symptoms may not happen immediately and is not guaranteed. Some patients may need to stop the treatment permanently to avoid long-term damage. Stopping treatment can be very difficult to accept if it is working well against the disease as it may lead to sub-optimal management and potentially affect survival. Other options include complementary therapies such as reflexology and acupuncture, TENS (trans-cutaneous nerve stimulation), and vitamin supplements such as vitamin B complex, folic acid, magnesium and alphalipoic acid.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with myeloma who have neuropathy resulting from myeloma treatment	• Graded dose reduction • Anti-myeloma drug withdrawal • Use of nutritional supplements, including vitamins • Complementary therapies (e.g. reflexology, acupuncture) • TENS (trans-cutaneous nerve stimulation) • active monitoring	• each other • standard care / best supportive care	• Improvement or resolution of symptoms • Quantitative sensory testing • Overall survival • HRQOL • Physical and social functioning • Adverse events • Reduction or early discontinuation of myeloma treatment

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	Exclude studies examining pharmacological Management of neuropathic pain. No date restriction	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Neuropathy Peripheral neuropathy Quantitative sensory testing Performance status Activities of daily living Treatment reduction Treatment discontinuation Vitamin supplementation trans-cutaneous nerve stimulation	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird JM; Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. (2011) Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 154(1):76-103. Richardson PG, Delforge M, Beksac M, Wen P, Jongen JL, Sezer O, Terpos E, Munshi N, Palumbo A, Rajkumar SV, Harousseau JL, Moreau P, Avet-Loiseau H, Lee JH, Cavo M, Merlini G, Voorhees P, Chng WJ, Mazumder A, Usmani S, Einsele H, Comenzo R, Orlowski R, Vesole D, Lahuerta JJ, Niesvizky R, Siegel D, Mateos MV, Dimopoulos M, Lonial S, Jagannath S, Bladé J, Miguel JS, Morgan G, Anderson KC, Durie BG, Sonneveld P. (2012) Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia 26(4):595-608. Boland E, Eiser C, Ezaydi Y, Greenfield DM, Ahmedzai SH, Snowden JA. Living with advanced but stable multiple myeloma: a study of the symptom burden and cumulative effects of disease and intensive (hematopoietic stem cell transplant-based) treatment on health-related quality of life. J Pain Symptom Manage. 2013 Nov;46(5):671-80. Zaroulis CK, Chairopoulos K, Sachanas SP, Maltezas D, Tzenou T, Pessach I, Koulieris E, Koutra E, Kilindireas K, Pangalis GA, Kyrtsonis MC. Assessment of bortezomib induced peripheral neuropathy in multiple myeloma by the reduced Total Neuropathy Score. Leuk Lymphoma. 2014 Mar 19.	
Amendments		

1

Topic	**Follow-up for patients with myeloma**
Review question	What is the optimal follow-up protocol for patients with myeloma (including duration, frequency, investigations and onward referral)?
Topic Subgroup	**Lead**: Hamdi Sati **Subgroup**: Monica Morris, Nicola Mulholland
Economic Priority	low

Background

Multiple myeloma is characterised by a remitting and relapsing clinical course. This means that most patients are not cured and will need continuing follow up as relapse can be gradual or sudden, and unpredictable. Furthermore, many patients who are diagnosed with myeloma may not have symptoms and therefore do not need immediate treatment. Appropriate monitoring of these patients is crucial to insure early detection of disease progression before the development of irreversible complications such as spinal cord compression, bone fracture or renal failure.

Disease monitoring is performed by regular clinical assessment when patients attend for their out-patient clinics and by checking various laboratory tests performed on blood and/or urine. In addition, a number of radiological imaging techniques may be used to investigate skeletal related symptoms and disease activity. The frequency of monitoring patients who are on active treatment is often dictated by the nature of their chemotherapy protocols. However, there is variation in practice in the modality and frequency of monitoring patients who are not on active anti-myeloma therapy.

These guidelines will make recommendations regarding the optimal protocols for follow-up of patients with multiple myeloma who are not on specific tumour therapy including the optimal laboratory and imaging tests required for early detection of disease progression/relapse which will allow for timely introduction of specific treatment and prevention of irreversible complications.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients diagnosed with myeloma: • Asymptomatic myeloma • Symptomatic patients not on active therapy • Symptomatic patients on long term therapies	Follow-up protocols involving combinations of: • serum and urine electrophoresis and/or free light-chain determination • β2-microglobulin • serum quantitative immunoglobulins • imaging procedures (CT, MRI, radiograph, skeletal survey, PET-CT) • **Bone marrow aspiration and biopsy** • flow cytometry	Any other protocols	• Overall survival • progression free survival • Health-related quality of life • Adverse events • PROMs • Patient experience

Additional comments on PICO

Look for any papers comparing follow-up protocols. As well as looking at the follow up procedures also look at the timings of the follow-up.

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion /	Date limit 2000	

exclusion of studies		
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Follow-up, surveillance, monitoring, relapse	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	NICE. Improving Outcomes in Haematological cancers manual 2003. Anderson et al. (2011) Multiple Myeloma. Journal of the National Comprehensive Cancer Network 9:1146-1183	
Amendments	<u>October 2014:</u> No studies were identified that investigated follow-up protocols for patients with myeloma. Studies were instead identified for individual follow up tests. These studies compared 2 tests to determine the most accurate (sensitivity/specificity) for detecting disease. However test accuracy is not listed as an outcome in the PICO. On discussion with the sub-group for this topic as well as the chair and clinical lead it was agreed that this evidence was of interest and clinical relevance to determine how accurate these tests are in follow up setting and so this data should be reviewed.	

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2

3

Topic	**The prevention of thrombosis for patients with myeloma.**
Review question	What is the most effective method for prevention of thrombosis in patients with myeloma?
Topic Subgroup	**Lead**: Matthew Jenner **Subgroup**: Monica Morris, Matthew Streetly, Jane Woodward
Economic Priority	low

Background

Venous thromboembolism (VTE) is a recognised complication of most cancers. This is particularly the case in myeloma because of the frequent combined occurrence of multiple thrombotic risk factors including age, immobility, fractures and infection in addition to the myeloma diagnosis. Newer treatment approaches involving immunomodulatory drugs (ImiDs) are well recognised to increase the risk of both venous and arterial thrombotic events. The risk of VTE is greatest during the first few months of treatment, particularly using combination chemotherapy involving ImiDs. VTE remains a significant cause of morbidity and mortality.

A range of preventative strategies have been used to reduce the risk of thrombotic events including anti platelet agents, low molecular weight heparin, vitamin K antagonists such as warfarin and the novel oral anticoagulants. All of these treatments carry with them practical advantages and disadvantages including differing routes of administration, need or not for monitoring and side effect profile. All will increase the risk of haemorrhage.

Clinical practice varies across the country and therefore there is a need to establish standard practice for prevention of thrombosis. Also there is little evidence on safety issues or adherence to treatment.

Following the evidence review guidelines will be developed for thromboprophylaxis strategies for patients with myeloma taking in to account particular clinical situations, including those with renal impairment, those with a past history of VTE and those receiving induction or relapse therapy. Recommendations will also be made on the proposed duration of prophylaxis, the optimal monitoring schedule for patients on dose-adjusted warfarin or LMWH and management strategies to promote safety and adherence to treatment (particularly in the elderly population).

PICO Table

Population	Intervention	Comparator	Outcomes
Patients diagnosed with myeloma and undergoing a potential ***thrombogenic therapy as initial treatment*** Patients diagnosed with myeloma and undergoing a potential ***thrombogenic therapy as ongoing treatment***	• low molecular weight heparin • aspirin • ***vitamin K antagonist*** • new oral anticoagulants - Dabigatran etexilate - Rivaroxaban - Apixaban • antiplatelet drugs - Clopidogrel - ***Dipyridamole*** • ***fondaparinux*** • ***defibrotide*** • ***Anti-coagulant and anti-platelet combination***	• each other • no treatment	• arterial thrombosis • venous thrombosis • bleeding events • Adverse events • Death/mortality • HRQOL • Compliance/adherence& patient acceptability

Additional comments on PICO

Stratify according to low and high risk for thrombosis

	Details	Additional Comments
Type of review	intervention	
Language	English language only	
Study design	Comparative studies	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	n/a	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	VTE	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Palumbo, A., Rajkumar, S. V., Dimopoulos, M. A., Richardson, P. G., San, M. J., Barlogie, B., Harousseau, J., Zonder, J. A., Cavo, M., Zangari, M., Attal, M., Belch, A., Knop, S., Joshua, D., Sezer, O., Ludwig, H., Vesole, D., Blade, J., Kyle, R., Westin, J., Weber, D., Bringhen, S., Niesvizky, R., Waage, A., von Lilienfeld-Toal, M., Lonial, S., Morgan, G. J., Orlowski, R. Z., Shimizu, K., Anderson, K. C., Boccadoro, M., Durie, B. G., Sonneveld, P., Hussein, M. A. & International Myeloma Working Group. (2008) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. [Review] [99 refs]. Leukemia, 22: 414-423. Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird JM; Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. (2011) Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 154(1):76-103. Rome S, Doss D, Miller K, Westphal J; IMF Nurse Leadership Board. Thromboembolic events associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs. 2008 Jun;12(3 Suppl):21-8. Kristinsson SY. (2010) Thrombosis in multiple myeloma. Hematology Am Soc Hematol Educ Program. 2010;2010:437-44. NICE clinical guideline 92. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. 2010.	
Amendments		

Topic	**The management of treatment-related fatigue for patients with myeloma**
Review question	Which interventions are most effective in reducing fatigue in patients being treated for myeloma?
Topic Subgroup	**Lead**: Sam Ahmedzai **Subgroup**: Lesley Roberts, Nicola Montacute, Monica Morris
Economic Priority	low

Background

Fatigue is described as a persistent tiredness or lethargy which affects the ability to complete activities of daily living. Fatigue related to cancer is not fully understood, however it is one of the most common effects of myeloma and may be related to physical changes caused by myeloma itself or its treatment (anti-myeloma chemotherapy and targeted biological treatments, painkillers (analgesics), radiotherapy, transplant or surgery). It may also be related to mood changes, deranged sleep patterns and treatment schedules which necessitate frequent visits to hospital. It is recognised that such fatigue is different to and more severe than normal fatigue as it tends to last longer and be exhausting and debilitating.

Fatigue takes three main forms – physical (affecting muscle strength and mobility); mental (affecting ability to concentrate and think rationally); and emotional (including motivation and desire to conduct a normal social life). There are validated scales for measuring these dimensions but they are infrequently used in multiple myeloma patients outside of clinical trials. It is not known if routine use of fatigue scales can lead to earlier diagnosis and better outcomes.

Almost all people with myeloma will experience fatigue at varying degrees at some point. Understanding the cause and adopting strategies to manage fatigue can help improve quality of life. Some causes of fatigue are easily correctable, e.g. anaemia or some biochemical or hormonal (endocrine) imbalances. However, there is no universal agreement on the levels of anaemia or biochemical/endocrine imbalance when treatment should start. The use of erythropoietin (EPO) to increase red blood cells, e.g. when transfusions are problematic or forbidden for religious reasons, is not agreed.

Drug management of fatigue is under-researched and there are few good evidence-based guidelines on this topic. Such treatments include psychostimulants including methylphenidate or modafanil; these may be helpful but carry the risk of cardiac and other harms. There is considerable variation between centres on the use of such drug treatments. Geographical variation also affects when patients are referred to other specialists, e.g. palliative care, physiotherapy or psychology. Over-the-counter stimulants and 'energy drinks' such as Red Bull are readily available but there is poor evidence on their effectiveness or use in this clinical situation.

There is increasing evidence that exercise programmes can be helpful for reducing fatigue and improving other outcomes in cancer patients. It is not known which myeloma patients would benefit most from exercise, when exercise regimes should be employed (e.g. during stem cell transplantation), the ideal settings for exercise programmes and who is best to supervise them. The harms of exercise, especially when there is actual or risk of bony disease affecting the spine or long bones in the legs are not known.

In this evidence review different methods employed with the aim of reducing fatigue will be assessed to determine which interventions are most effective in reducing fatigue in patients who are or have been treated for myeloma.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients who are or have been treated for myeloma	• Exercise/physical activity • pacing schedule • Prescription drugs (e.g. psychostimulants) • Non-prescription drugs, e.g. over-the-counter stimulant drinks • Complementary therapies • Dietary intervention	• Each other • Supportive care only	• Reduction of fatigue • Performance status • Daytime sleepiness • QOL • Exercise tolerance • Actimetry • Muscle function • Mobility – physical and social functioning

	• Spinal rehabilitation • Blood transfusion or EPO if anaemic • Rest • Sleep hygiene education		• Dependency for activities of daily living • Adverse events • PROMs

Additional comments on PICO		
	Details	**Additional Comments**
Type of review	intervention	
Language	English language only	
Study design	No restrictions	
Status	Published studies only	
Other criteria for inclusion / exclusion of studies	No date restrictions	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Fatigue Exercise Activity Actimetry Sleepiness Epworth scale Activities of daily living	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Boland E, Eiser C, Ezaydi Y, Greenfield DM, Ahmedzai SH, Snowden JA. Living with advanced but stable multiple myeloma: a study of the symptom burden and cumulative effects of disease and intensive (hematopoietic stem cell transplant-based) treatment on health-related quality of life. J Pain Symptom Manage. 2013 Nov;46(5):671-80. Greenfield DM, Boland E, Ezaydi Y, Ross RJ, Ahmedzai SH, Snowden JA; Late Effects Group. Endocrine, metabolic, nutritional and body composition abnormalities are common in advanced intensively-treated (transplanted) multiple myeloma. Bone Marrow Transplant. 2014 Apr 7. Potrata B, Cavet J, Blair S, Howe T, Molassiotis A. 'Like a sieve': an exploratory study on cognitive impairments in patients with multiple myeloma. Eur J Cancer Care (Engl). 2010 Nov;19(6):721-8. Snowden JA, Ahmedzai SH, Ashcroft J, D'Sa S, Littlewood T, Low E, Lucraft H, Maclean R, Feyler S, Pratt G, Bird JM; Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. (2011) Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 154(1):76-103. Coleman et al (2011) Fatigue sleep, mood and performance status in patients with multiple myeloma; Cancer Nursing, 34(3) 2219-227.	
Amendments		

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Topic	**The most effective salvage therapies for relapsed and/or refractory myeloma.**
Review question	In which patients with relapsed or refractory myeloma is a second autologous stem cell transplant more effective than other therapy?
Topic Subgroup	**Lead**: Matthew Jenner **Subgroup**: Matthew Streetly, Andie Guy, Jane Woodward
Economic Priority	medium

Background

Autologous stem cell transplant (ASCT) is a standard consolidation treatment following induction chemotherapy in people with newly diagnosed myeloma who are fit enough to tolerate this approach. A patient's bone marrow or peripheral blood stem cells are collected following induction chemotherapy and stored. Following "high dose" chemotherapy, typically involving melphalan, the stem cells are reinfused to rescue the bone marrow from the effects of the high dose chemotherapy and allow for more rapid recovery in blood counts than if the chemotherapy were given without the transplanted cells being returned.

Some UK centres have for many years advocated a second autologous transplant in those patients who subsequently progress following a first transplant whereas in others it has not been a standard approach and access has potentially been limited because of cost. ASCT is a potentially toxic treatment with a risk of both treatment related morbidity and mortality. It also involves a potentially lengthy inpatient admission to hospital and post-transplant recovery period that can impact on quality of life. New therapies have resulted in improved outcomes for patients with relapsed disease including those who do not have an ASCT. However, newer therapeutic agents and ASCT can both be costly interventions and therefore it is important to establish the patient groups that may benefit most from a second ASCT procedure. Factors of likely importance in determining potential benefit of a second ASCT include depth and duration of response to first ASCT, age and performance status, co-morbidities and cytogenetics.

Following the evidence review it is hoped that guidelines can be developed to recommend which groups of patients may benefit most (or indeed least) from a second ASCT. It is likely that duration of response following a first ASCT will be a key factor and therefore there may be different recommendations depending on this and other patient factors.

PICO Table

Population	Intervention	Comparator	Outcomes
Patients with relapsed or refractory myeloma grouped according to - Age - Performance status - Comorbidities (charlson score, ACE-27) - Renal impairment - Genetic abnormalities - Time from first autologous transplant to retreatment - Number of prior lines of therapy	• Second autologous stem cell transplant	• Other therapies (excluding allogeneic stem cell transplant) • No therapy	• Overall survival • Progression free survival • Health related quality of life • Adverse events • Treatment related mortality • Treatment related morbidity • PROMs • Patient/carer/family acceptability

Additional comments on PICO

No additional comments

	Details	Additional Comments
Type of review	Intervention	
Language	English language only	
Study design	RCTs Comparative studies	Include single intervention studies if they report predictive factors
Status	Published studies only	

Other criteria for inclusion / exclusion of studies	n/a	
Search strategies	The core databases as listed in the NICE Guidelines Manual will be searched as a minimum (i.e. Cochrane Library (CDSR, DARE via CRD, CENTRAL, HTA via CRD), Medline & Medline in Process and Embase). Additionally we will routinely search Web of Science. Consideration will be given to subject-specific databases and used as appropriate.	
Useful Search Terms	Autologous transplant Autologous stem cell transplant (ASCT) Autograft Stem cell transplant Stem cell rescue High dose chemotherapy High dose melphalan Melphalan 140 Melphalan 100	
Review strategies	Evidence will be identified, assessed and synthesized according to the methods outlined in the NICE guidelines manual (2012).	
Identified papers	Alvares CL, Davies FE, Horton C, Patel G, Powles R, Morgan GJ. (2006) The role of second autografts in the management of myeloma at first relapse. Haematologica. 91(1), 141-142. Olin RL, Vogl DT, Porter DL, Luger SM, Schuster SJ, Tsai DE, Siegel DL, Cook RJ, Mangan PA, Cunningham K, Stadtmauer EA. (2009) Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant. 43(5), 417-422. Cook G, Liakopoulou E, Pearce R, Cavet J, Morgan GJ, Kirkland K, Lee J, Davies FE, Hall R, Rahemtulla A, Russell N, Marks DI; British Society of Blood & Marrow Transplantation Clinical Trials Committee. (2011) Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant. 17(11), 1638-1645.	
Amendments		

Excluded health economic studies

1. Delea, T. E., El Ougari, K., Rotter, J., Wang, A., Kaura, S., & Morgan, G. J. "Cost-effectiveness of zoledronic acid versus clodronate in patients with multiple myeloma from a canadian healthcare system perspective." Blood Conference.var.pagings (2010): 21.
   Reason: Conference abstract.
2. Delea, T. E., El Ouagari, K., Rotter, J., Wang, A., Kaura, S., & Morgan, G. J. "Cost-effectiveness of zoledronic acid compared with clodronate in multiple myeloma." Current Oncology 19.6 (2012): e392-e403.
   Reason: Paper considered a Canadian healthcare perspective. An identical model was included in the review which took NHS and PSS perspective.
3. Duarte, R. F., Pérez-Simón, J. A., Martin, G., de la Rubia, J. Marin, P. Álvarez, M. A. "Cost-effectiveness of plerixafor plus gcsf for mobilization of peripheral blood stem cells in patients with myeloma and lymphoma in Spain." Value in Health Conference.var.pagings (2012): 7.
   Reason: Conference Abstract.
4. Duncan, N., Hewetson, M., Powles, R., Raje, N., & Mehta, J. "An economic evaluation of peripheral blood stem cell transplantation as an alternative to autologous bone marrow transplantation in multiple myeloma (Structured abstract)." Bone Marrow Transplantation 18.6 (1996): 1175-78.
   Reason: Not a cost utility study.
5. Durie, B. G. M. "Cost-effectiveness of treatments (TX) for newly-diagnosed multiple myeloma patients (NDMM PTS)." Clinical Lymphoma, Myeloma and Leukemia Conference.var.pagings (2013): S216.
   Reason: Conference Abstract.
6. Fragoulakis, V., Kastritis, E., Psaltopoulou, T., & Maniadakis, N. "Economic evaluation of therapies for patients suffering from relapsed-refractory multiple myeloma in Greece." Cancer management and research 5 (2013): 37-48.
   Reason: Outside the scope of the guideline.
7. García, Q. E., Azanza, P. J., & Lecumberri, V. R. “New therapeutic strategies for multiple myeloma. Efficacy and cost-effectiveness analyses.” Medicina Clinica 130(16):626-635. 2008.
   Reason: Interventions not covered by the scope of the guideline.

8. Gaultney, J. G., Redekop, W. K., Sonneveld, P., & Uyl-de Groot, C. A."Critical review of economic evaluations in multiple myeloma: an overview of the economic evidence and quality of the methodology. [Review]." European Journal of Cancer 47.10 (2011): 1458-67.
   Reason: Systematic review. Studies included individually in the economic evidence review where appropriate.
   Reason: Systematic review. Studies included individually in the economic evidence review where appropriate.

9. Gaultney, J. G., Redekop, W. K., Sonneveld, P., & Uyl-de Groot, C. A. "Novel anticancer agents for multiple myeloma: a review of the evidence for their therapeutic and economic value. [Review]." Expert Review of Anticancer Therapy 12.6 (2012): 839-54.
   Reason: Systematic review. Studies included individually in the economic evidence review where appropriate.
10. Hashmi, S., Pandya, C., Khera, N., Gertz, M., Dispenzieri, A., Hogan, W., ... & Kumar, S. "Cost effectiveness decision tree analysis of early versus late autologous stem cell transplantation

(ASCT) in multiple myeloma (MM) in the united states (US)." Blood Conference.var.pagings (2012): 21.
Reason: Conference abstract.

11. Hashmi, S., Pandya, C., Khera, N., Gertz, M., Dispenzieri, A., Hogan, W., ... & Kumar, S. "Cost effectiveness decision tree analysis of early versus late autologous stem cell transplantation (ASCT) in multiple myeloma (MM) in the United States (US)." Biology of Blood and Marrow Transplantation Conference.var.pagings (2013): 2-S131.
Reason: Conference Abstract.
12. Henon, P., Donatini, B., Eisenmann, J. C., Becker, M., & Beck-Wirth, G Comparative survival, quality of life and cost-effectiveness of intensive therapy with autologous blood cell transplantation or conventional chemotherapy in multiple myeloma. Bone Marrow Transplantation 16:19-25. 1995.
Reason: Interventions not covered by the scope of the guideline.
13. Hussein, M. A., Wildgust, M., Fastenau, J., & Piech, C. T. Cost-effectiveness of DVd vs Vad in newly diagnosed multiple myeloma (abstract 6548). Proceedings of the American Society of Clinical Oncology 23:567. 2004.
Reason: Conference Abstract.
14. Holbro, A., Ahmad, I., Cohen, S., Roy, J., Lachance, S., Chagnon, M., ... & Kiss, T. L. "Safety and cost-effectiveness of outpatient autologousstem cell transplantation in patients with multiple myeloma." Biology of Blood & Marrow Transplantation 19.4 (2013): 547-51.
Reason: Not a cost utility study.
15. Jagannath, S., Vesole, D. H., Zhang, M., Desikan, K. R., Copeland, N., Jagannath, M., ... & Barlogie, B. "Feasibility and cost-effectiveness of outpatient autotransplants in multiple myeloma (Structured abstract)." Bone Marrow Transplantation 20.6 (1997): 445-50.
Reason: Not a cost utility study.
16. Jiang, Y., Spencer, M., Gauthier, A., & Pacou, M."A cost-effectiveness analysis for second-line treatment of relapsed/refractory (RR) multiple myeloma (MM) in the United Kingdom." Value in Health Conference.var.pagings (2011): 7.
Reason: Conference abstract.
17. Kouroukis, C. T., O'brien, B. J., Benger, A., Marcellus, D., Foley, R., Garner, J., ... & Meyer, R. "Cost-effectiveness of a transplantation strategy compared to melphalan and prednisone in younger patients with multiple myeloma (Structured abstract)." Leukemia and Lymphoma 44.1 (2003): 29-37.
Reason: Not a cost utility study.
18. Lucioni, C., Cavo, M., Mazzi, S., & Palumbo, A."Economic evaluation of two therapeutic sequences in the treatment of relapsed/refractory multiple myeloma." PharmacoEconomics - Italian Research Articles 15.1 (2013): 1-8.
Reason: Interventions not covered by the scope of the guideline.
19. Nord, E., Wisøff, F., Hjorth, M., & Westin, J. "Cost-utility analysis of melphalan plus prednisone with or without interferon-alpha2b in newly diagnosed multiple myeloma: results from a randomised controlled trial (Structured abstract)." Pharmacoeconomics. 12.1 (1997): 89-103.
Reason: Interventions not covered by the scope of the guideline.
20. Perrier, L., Lefranc, A., Pérol, D., Quittet, P., Schmidt-Tanguy, A., Siani, C., ... & Sebban, C. "Cost effectiveness of pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous stem cell transplantation in patients with lymphoma and myeloma: an economic evaluation of the PALM Trial." Applied Health Economics & Health Policy 11.2 (2013): 129-38.
Reason: Interventions not covered by the scope of the guideline.
21. Porter, C. A. and R. M. Rifkin. "Clinical benefits and economic analysis of pegylated liposomaldoxorubicin/vincristine/dexamethasone versus

doxorubicin/vincristine/dexamethasone inpatients with newly diagnosed multiple myeloma (Provisional abstract)." Clinical.Lymphoma and Myeloma. 7.Supplement 4 (2007): S150-S155.
Reason: Conference Abstract.

22. Qasim, S., Saleem, U., Ahmad, B., Aziz, M. T., Qadir, M. I., Mahmood, S., & Shahzad, K. "Therapeutic efficacy and Pharmacoeconomics evaulation of pamidronate versus zoledronic acid in multiple myeloma patients." Journal of Applied Pharmacy 3.4 (2011): 438-52.
Reason: Not a cost utility study.
23. Reed, S. D., Radeva, J. I., Glendenning, G. A., Coleman, R. E., & Schulman, K. A. "Economic evaluation of zoledronic acid versus pamidronate for the prevention of skeletal-related events in metastatic breast cancer and multiple myeloma (Structured abstract)." American.Journal of Clinical.Oncology 28.1 (2005): 8-16.
Reason: Not a cost utility study.
24. Sampson, F. C., Beard, S. M., Scott, F., & Vandenberghe, E. "Cost-effectiveness of high-dose chemotherapy in first-line treatment of advanced multiple myeloma (Structured abstract)." British.Journal of Haematology. 113.4 (2001): 1015-19.
Reason: Not a cost utility study.
25. Sebban, C., Lefranc, A., Perrier, L., Moreau, P., Espinouse, D., Moles-Moreau, M. P., ... & Quittet, P."A randomized phase II study evaluating the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after high dose chemotherapy and autologous stem cell transplantation in patients with lymphoma and myeloma (PALM study)." Blood Conference.var.pagings (2010): 21.
Reason:Conference abstract.
26. Sebban, C., Lefranc, A., Perrier, L., Moreau, P., Espinouse, D., Moles-Moreau, M. P., ... & Quittet, P."A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study)." European Journal of Cancer 48.5 (2012): 713-20.
Reason: Not a cost utility study.
27. Trippoli, S., Messori, A., Becagli, P., Alterini, R., & Tendi, E. "Treatments for newly diagnosed multiple myeloma: analysis of survival data and cost-effectiveness evaluation (Structured abstract)." Oncology Reports. 5.6 (1998): 1475-82.
Reason: Interventions not covered by the scope of the guideline.
28. Tuffaha, H. W., Hussein, A. A., & Abdel-Rahman, F. A."Comparative cost utility analysis of plerixafor plus GCSF versus cyclophosphamide plus GCSF as salvage mobilization regimens in multiple myeloma patients." Biology of Blood and Marrow Transplantation Conference.var.pagings (2012): 2.
Reason: Conference abstract.
29. Tuffaha, H. W., Hussein, A. A., Sharma, S., Abu-Jazar, H., Al-Rawi, O. S., Saad, A. M., ... & Abdel-Rahman, F. A. "The effectiveness and cost effectiveness of plerixafor + GCSF versus GCSF 6 chemotherapy as salvage mobilization regimens in lymphoma and multiple myeloma patients." Biology of Blood and Marrow Transplantation Conference.var.pagings (2012): 2.
Reason:Conference abstract.
30. Vitova, V., Tichopad, A., Sturdikova, M., Kucera, Z., Lysak, D., & Koristek, Z."Cost-effectiveness of hematopoietic stem cell mobilization strategies in multiple myeloma and lymphoma patients in Czech Republic." Value in Health Conference.var.pagings (2012): 7.
Reason: Interventions not covered by the scope of the guideline.

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