National Collaborating Centre for Cancer

Melanoma:

assessment and management of melanoma

Clinical Guideline

Full guideline

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Draft for Consultation

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Contents

Foreword

Cutaneous melanoma is increasing in incidence in many of the developed countries as this form of cancer occurs predominantly in pale skinned people who expose themselves to intense sunlight, especially when taking holidays in sunny places. The increased work-load for melanoma services resulting from this increase is furthermore complicated by the fact that the individuals with the most rapid rate of increase in incidence are those over the age of 60 and especially men. Male sex and age are two poor prognostic factors for melanoma and therefore the likelihood is that despite efforts to promote primary and secondary melanoma prevention, melanoma mortality is likely to increase rather than decrease. Although the incidence trends described above are of concern, for the first time in very recent years, the advent of therapies targeted to driver mutations (such as inhibitors of BRAF) and of T cell checkpoint inhibitors which both have efficacy in melanoma is in the process of rapidly changing management of this disease. Use of both classes of drugs has been the subject of NICE technology appraisals in recent years and these have been cross referenced in the text.

As a result of these changes both in incidence and treatment, the development of a NICE Clinical Melanoma Guideline is very opportune. The fact that some of the therapeutic changes are recent however means that important issues such as the approach that can be taken to imaging during follow up, are in a state of evolution and some aspects of the Guideline may need review in the near future.

Key priorities for implementation

- **To help people make decisions about their care, follow the recommendations on communication, information provision and support in NICE's guideline on improving outcomes for people with skin tumours including melanoma, in particular the following 5 recommendations:**
  - **'Improved, preferably nationally standardised, written information should be made available to all patients. Information should be appropriate to the patients' needs at that point in their diagnosis and treatment, and should be repeated over time. The information given must be specific to the histopathological type of lesion, type of treatment, local services and any choice within them, and should cover both physical and psychosocial issues.'**
  - **'Those who are directly involved in treating patients should receive specific training in communication and breaking bad news.'**
  - **'Patients should be invited to bring a companion with them to consultations.'**
  - **'Each LSMDT [local hospital skin cancer multidisciplinary team] and SSMDT [specialist skin cancer multidisciplinary team] should have at least one skin cancer clinical nurse specialist (CNS) who will play a leading role in supporting patients and carers. There should be equity of access to information and support regardless of where the care is delivered.'**
  - **'All LSMDTs and SSMDTs should have access to psychological support services for skin cancer patients.'**

- **Assess all pigmented skin lesions that are referred for further assessment, and during follow-up, using dermoscopy carried out by healthcare professionals trained in this technique.**

- **For a clinically atypical melanocytic lesion that does not need excision at first presentation:**
  - **use baseline photography (preferably dermoscopic) and**
  - **review the clinical appearance of the lesion, using the baseline photographic images, 3 months after first presentation to identify early signs of melanoma.**

- **If targeted systemic therapy is a treatment option for stage 4 disease, offer genetic testing using:**
  - **a secondary melanoma tissue sample if there is adequate cellularity or**
  - **a primary melanoma tissue sample if a secondary sample is not available or is of inadequate cellularity.**

- **Measure vitamin D levels at diagnosis in all people with melanoma.**

- **Consider sentinel lymph node biopsy as a staging rather than a therapeutic procedure for people with stage 1B-2C melanoma with a Breslow thickness of 1 mm or more, and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.**

Possible advantages of sentinel lymph node biopsy	Possible disadvantages of sentinel lymph node biopsy
The operation helps to find out whether the cancer has spread to the lymph nodes. It is better than ultrasound scans at finding very small cancers in the lymph nodes	The purpose of the operation is not to cure the cancer. There is no good evidence that people who have the operation live longer than people who do not have it
The operation can help predict what might happen in the future. For example, in people with a primary melanoma that is between 1 and 4 mm thick: • around 1 out of 10 die within 10 years if the sentinel lymph node biopsy is negative • around 3 out of 10 die within 10 years if the sentinel lymph node biopsy is positive.	The result needs to be interpreted with caution. Of every 100 people who have a negative sentinel lymph node biopsy, around 3 will subsequently develop a recurrence in the same group of lymph nodes.
People who have had the operation may be able to take part in clinical trials of new treatments for melanoma. These trials often cannot accept people who haven't had this operation.	A general anaesthetic is needed and this causes complications for 4-10 out of every 100 people who have the operation.

- **Consider completion lymphadenectomy for people with a positive sentinel lymph node biopsy (stage 3A melanoma) and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.**

Possible advantages of completion lymphadenectomy	Possible disadvantages of completion lymphadenectomy
Removing the rest of the lymph nodes before cancer develops in them reduces the chance of the cancer returning in the same part of the body.	Lymphoedema (long-term swelling) may develop, and is more likely if the operation is in the groin than in other parts of the body.
The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them.	In 4 out of 5 people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily.
People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. These trials often cannot accept people who have not had this operation.	There is no evidence that people who have this operation live longer than people who do not have it.
	Having any operation can cause complications.

- **Consider surveillance imaging as part of follow-up for people who have had stage 2C melanoma with no sentinel lymph node biopsy or stage 3 melanoma and who would become eligible for systemic therapy as a result of early detection of metastatic disease if:**
  - **the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging is identified or**
  - **there is a clinical trial of the value of regular imaging.**

Key research recommendations

- **In people with reported atypical spitzoid melanocytic lesions, how effective are fluorescence *in situ* hybridization (FISH), comparative genomic hybridization (CGH) and tests to detect driver mutations compared with histopathological examination alone in predicting disease-specific survival? This should be investigated in a prospective diagnostic study. Secondary outcomes should include sensitivity, specificity, accuracy, positive predictive value, disease-specific survival and progression-free survival.**

- **For people with lentigo maligna (stage 0 in sun-damaged skin, usually on the face) how effective is Mohs micrographic surgery, compared with excision with a 0.5 cm clinical margin, in preventing biopsy-proven local recurrence at 5 years? This should be investigated in a randomised controlled trial. Secondary outcomes should include cosmetic and functional outcomes**

- **In people treated for high-risk stage 2 and 3 melanoma, does regular surveillance imaging improve melanoma-specific survival compared with routine clinical follow-up alone? This should be investigated in a randomised controlled trial. Secondary outcomes should include time to recurrence, site of recurrence, proportion of people receiving active therapy at recurrence, cost effectiveness and quality of life.**

- **In people with stage 1–3 melanoma does vitamin D supplementation improve overall survival? This should be investigated in a placebo-controlled randomised trial. Secondary outcomes should include disease-specific survival and toxicity, including the development of renal stones and hypercalcaemia.**

- **In people diagnosed with melanoma what is the effect of drug therapy to treat concurrent conditions on disease-specific survival? This should be investigated in a national prospective cohort study. Secondary outcomes should include overall survival and quality of life.**

Methodology

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the assessment and management of melanoma. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing clinical evidence based questions'.

This guideline is relevant to all healthcare professionals who come into contact with people with melanoma, as well as to the people with melanoma themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of people.

The remit of the guideline

Involvement of Stakeholders

Key to the development of all NICE guidelines are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2012). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the melanoma guideline can be found in Appendix F.

The guideline development process – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix F), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG
- developing clinical questions

- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

The scope

The scope was drafted by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategies

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a three week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix E. During the consultation period, the scope was posted on the NICE website. Comments were invited from registered stakeholder organisations and NICE staff. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed and signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The melanoma GDG was recruited in line with the 'NICE guidelines manual' (NICE 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed in person prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix F). Individual GDG members were selected for telephone interview by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix F).

Guideline Development Group meetings

Thirteen GDG meetings were held between 21-22 May 2013 and 8-9 April 2015. During each GDG meeting (held over either 1 or 2 days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG. These recommendations were then discussed and agreed by the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/carer representatives

Individuals with direct experience of melanoma services gave an important user focus to the GDG and the guideline development process. The GDG included two patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Expert advisers

During the development of the guideline the GDG identified staging of melanoma using sentinel lymph node biopsy as a topic that required additional expert input. Two experts were identified by the NCC-C and GDG (Appendix F) and invited to advise the GDG on drafting their recommendations for that clinical question.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as ‘evidence-based textbooks’ or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope, the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study), I – the interventions (what is being done), C – the comparison (other main treatment options), O – the outcomes (the measures of how effective the interventions have been).

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: NHS Evidence, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), Health Economic Evaluations Database (HEED), Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (Table 1) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the evidence review.

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG
Rationale	An explanation of why the clinical question is important. For example, is the topic contentious? Is there variation in practice across the UK?
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The method that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards
- Web of Science [specifically Science Citation Index Expanded

- (SCI-EXPANDED) 1899 onwards and Social SciencesCitation Index (SSCI) 1956 onwards]

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards
- Psychinfo 1806 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6-8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, September 2014 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using GRADE (NICE 2012; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE ‘evidence profile’. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each outcome was examined for the quality elements defined in Table 2 and subsequently graded using the quality levels listed in Table 3. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table 2: Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and clinical question
Imprecision	Results are imprecise when studies include relatively few events and when the confidence interval around the effect estimate includes both no effect and appreciable benefit or harm

Quality element	Description
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	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	Any estimate of effect is very uncertain

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2012). In general, no formal contact was made with authors.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was provided. The quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting et al., 2011).

Needs Assessment

As part of the guideline development process the NCC-C undertook a needs assessment (see Appendix G). This aims to describe the burden of disease and current service provision for people with melanoma in England and Wales, and informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented early in the stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to melanoma. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2012):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

A review of the economic literature was conducted at scoping. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies of 'cost of illness' studies are generally excluded from the reviews (NICE 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012; Appendix H). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 4).

Table 4: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 5).

Table 5: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should

	usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There are several published technology appraisals (TAs) which are relevant to this guideline (TA268, 269, 319 and 321 - see www.nice.org.uk/TA/published). In line with NICE methodology, the recommendations from these TAs have either been cross referenced (TA319 and 321) or incorporated (TA268 and 269).

Agreeing the recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicitly in the accompanying LETR statement (see below).

Wording of the recommendations

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations are based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm
- ‘Do not offer’ – the intervention will not be of benefit for most patients

- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Children and young people

For every clinical question in this guideline the population always included children and young people as specified in the scope (see Appendix E). For clarity, children are defined as 'from birth to 15 years' and young people 'aged 16-24 years'. Where recommendations in this guideline refer to 'people' this will include children, young adults and adults. However where the evidence allows, specific recommendations have been made for children and young adults and an explanation for these has been provided in the accompanying linking evidence to recommendations section (LETR).

In clinical practice in the UK, patients over the age of 16 years are treated as autonomous adults. They are permitted to give their consent to or to refuse treatment without parental involvement. Children under 16 can consent to medical treatment if they understand what is being proposed. It is up to the doctor to decide whether the child has the maturity and intelligence to fully understand the nature of the treatment, the options, the risks involved and the benefits. A child who has such understanding is considered Gillick competent. The parents cannot overrule the child's consent when the child is judged to be Gillick competent. Children under 16 who are not Gillick competent and very young children cannot either give or withhold consent. Those with parental responsibility need to make the decision on their behalf. In an emergency situation, when a person with parental responsibility is not available to consent, the doctor has to consider what the child's best interests are and then act appropriately. The treatment should be limited to what is reasonably required to deal with the particular emergency.

LETR (Linking evidence to recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost effectiveness of an intervention
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed.

Guideline implementation

This guideline was selected by NICE to be part of a pilot exercise to replace the current implementation section within guidelines with a more meaningful summary which at publication will highlight for users:

- the three most important and challenging areas in practice and likely key areas for attention;
- the barriers and facilitators to achieving this;
- resource implications;
- resources produced by NICE or partners that can help;
- potential examples from practice

The methods used by the GDG and NICE to achieve this were as follows:

- The GDG agreed 3 areas which they considered to be the most important and most significantly challenging to changes in practice
- An implementation section (see section 2 of the NICE version) for the guideline was prepared by the GDG and NICE and was included as part of the draft consultation documents to obtain the views of Stakeholders.
- Comments from stakeholders were used to inform the needs analysis and development of the final implementation section.

Consultation and validation of the guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix F) had one opportunity to comment on the draft guideline which was posted on the NICE website between 30 January 2015 and 13 March 2015 in line with NICE methodology (NICE 2012).

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders who have signed a confidentiality form to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2012).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the melanoma guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- NICE pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP)', which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were repeated for all of the clinical questions at the end of the guideline development process, allowing any relevant papers published before 1 October 2014 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer (NCC-C) was commissioned by NICE to develop this guideline.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

National Institute for Health and Clinical Excellence (2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

Whiting P, Rutjes A. Reitsma J, Bossuyt P & Kleijnen J (2003) The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Medical Research Methodology, 3: 25.

Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM, Group Q-2 (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine, 155: 529-536.

Staging system

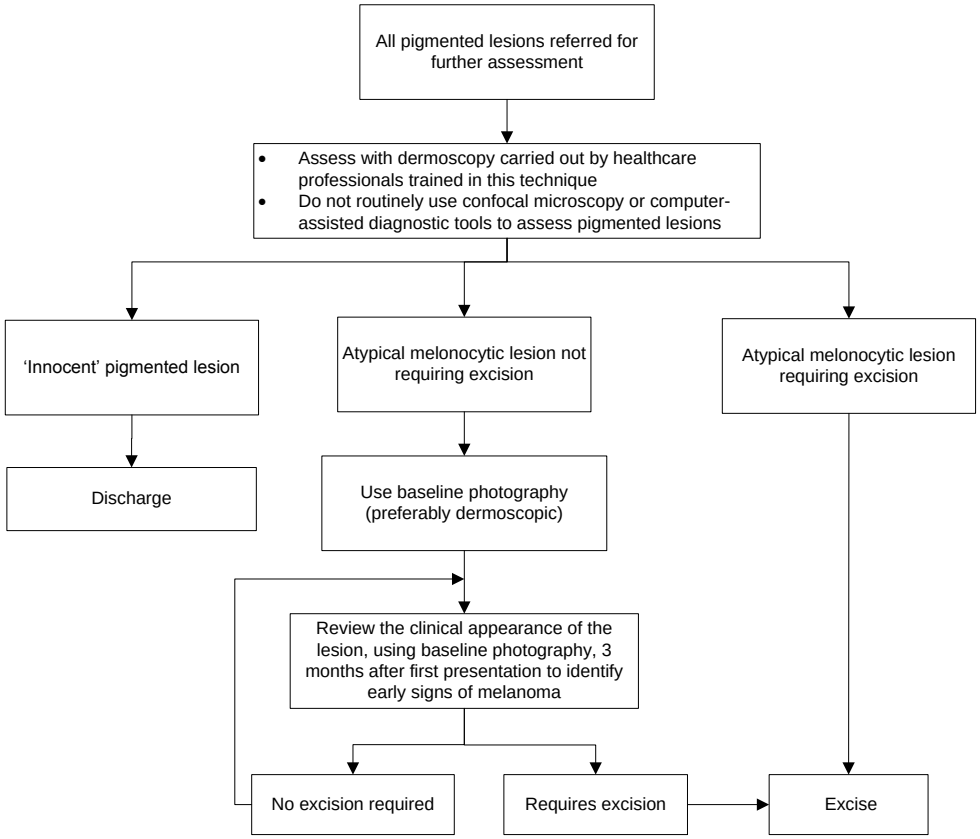
Staging of primary melanoma is carried out in two steps. The initial staging is based upon the histopathological features reported by the pathologist looking at the microscopic sections of the tumour. Based upon factors such as the thickness of the tumour and the presence or absence of ulceration, the disease will be staged as Stage 0 to 2C. In many hospitals (but not all) in the UK, this first step is followed by the option of a second, which is a sampling of the lymph nodes most likely to contain secondary melanoma cells (sentinel lymph node biopsy or SLNB). If a SLNB is performed and microscopic disease is detected then the patient's stage becomes stage 3. If no microscopic disease is detected then the initial stage is used.

AJCC stage	Characteristics of the disease (Breslow thickness of the primary, microscopic ulceration status of the primary, tumour metastatic to the locoregional soft tissues (microsatellites or in transit metastases), a node or other metastases)
0	*In situ* melanoma: melanoma that is not invasive into the dermis
1A	<1 mm thickness, no nodal or distant metastases
1B	<1 mm thickness with ulceration or 1 or more mitoses, but no nodal or distant metastases
	1.01-2.0 mm thickness, no ulceration, nodal or distant metastases
2A	1.01-2.0 mm thickness, with ulceration, but no nodal or distant metastases
	2.01-4.0 mm thickness, no ulceration, nodal or distant metastases
2B	2.01-4.0 mm thickness, with ulceration but no nodal or distant metastases
	>4 mm thickness, no ulceration, nodal or distant metastases
2C	>4 mm thickness, with ulceration but no nodal or distant metastases
3A	Any tumour thickness, no ulceration but micrometastases in 1 node at sentinel node biopsy
	Any tumour thickness, but no ulceration and micrometastases in 2 or 3 nodes at sentinel node biopsy
3B	Any tumour thickness and ulceration with micrometastases in 1 to 3 nodes at sentinel node biopsy. No distant metastases.
	Any tumour thickness but no ulceration and palpable metastasis to nodes confirmed to be 1 to 3 in number histologically
	Any tumour thickness and in transit metastases/microsatellites, but no ulceration, nodal or distant metastases
3C	Any tumour thickness and ulceration with palpable nodal metastases in up to 3 nodes or an in transit/satellite lesion without palpable nodal metastases
	Any tumour thickness, and any ulceration status with palpable metastases to >4 nodes, matted nodes or in transit metastases/satellite lesions and a palpable nodal metastasis.
4	Distant metastases in any organ e.g. skin, nodes, internal organs or brain

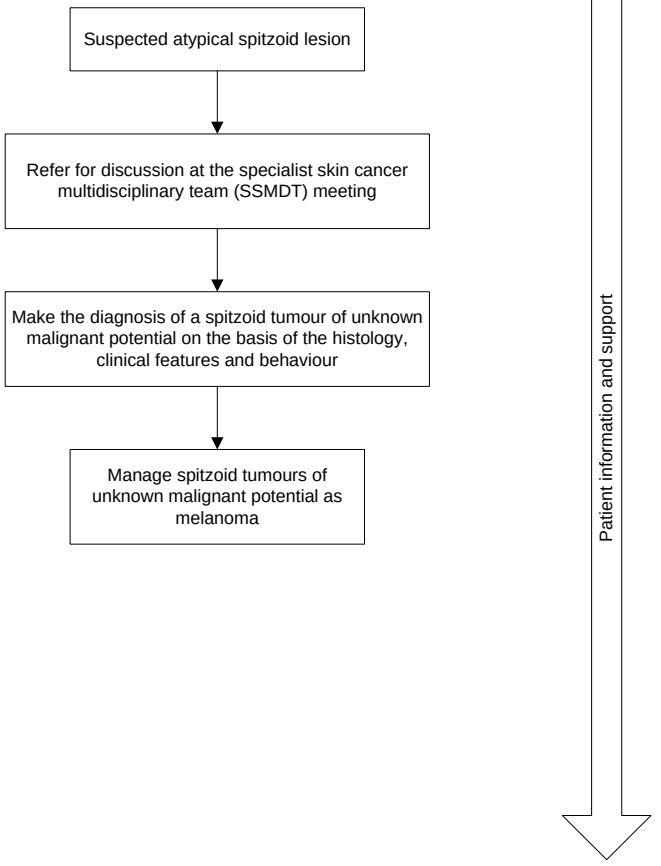
1 Algorithms

2 Diagnosing melanoma

3 *Dermoscopic evaluation of pigmented lesions*



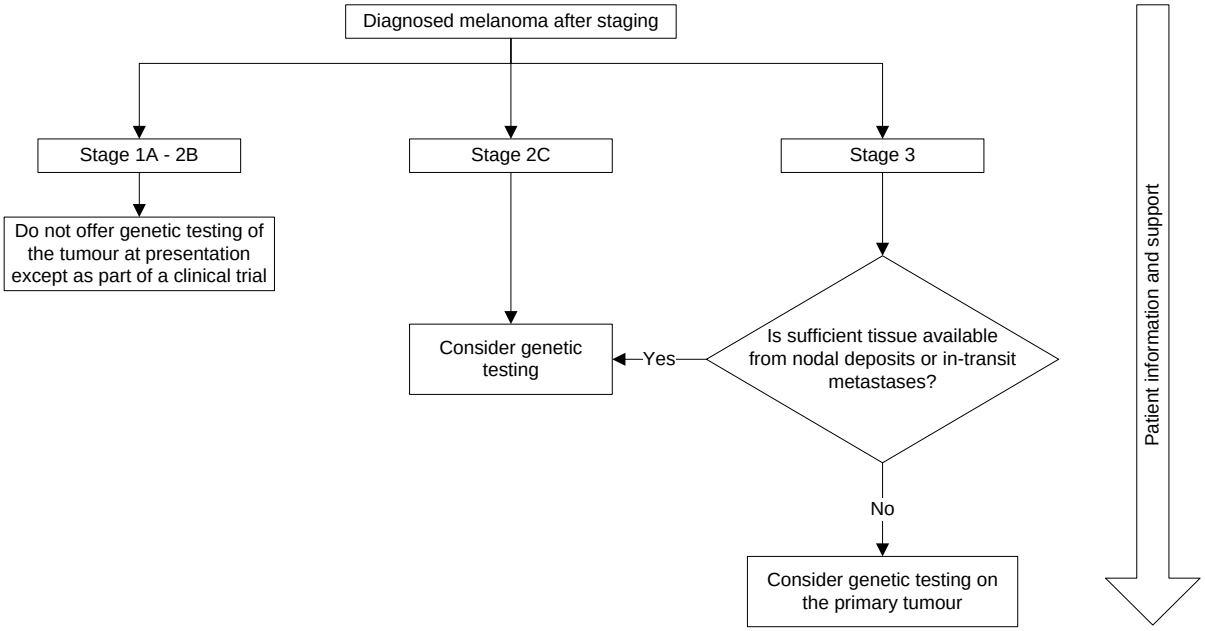
Assessment of atypical spitzoid lesions



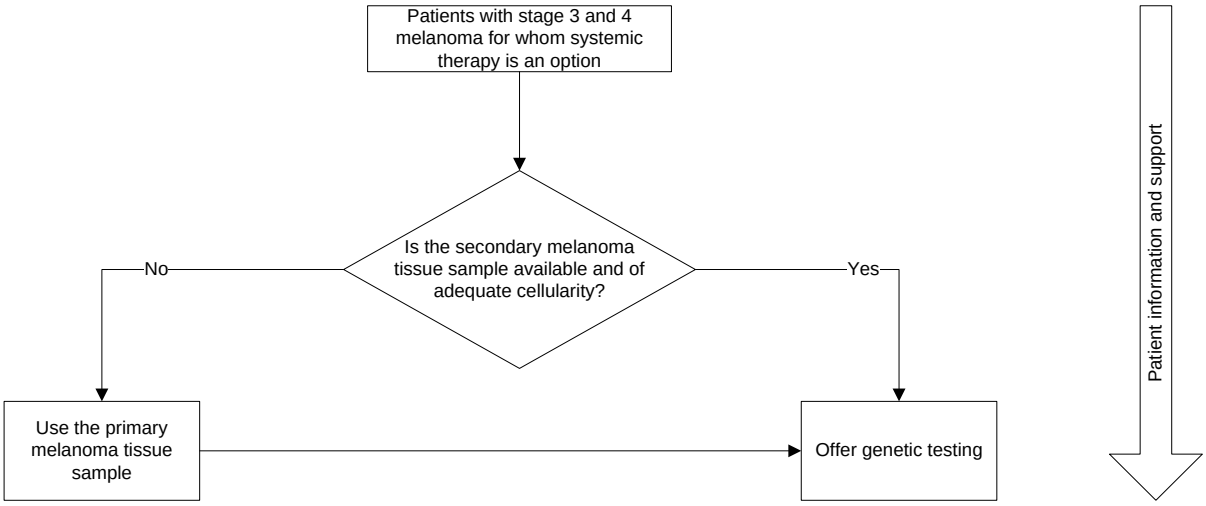
4

Genetic testing of stored tumour samples

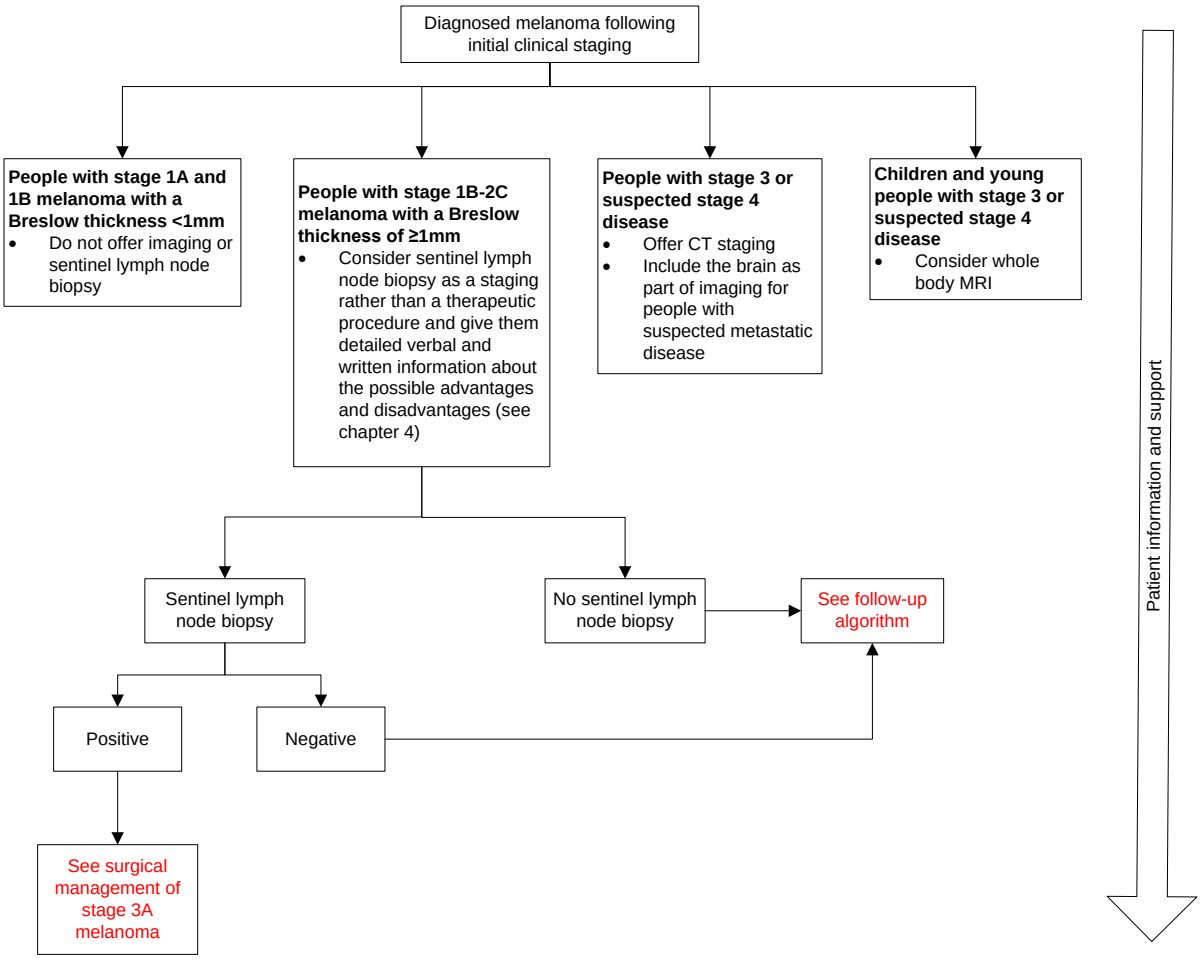
Stage 1A-2B, stage 2C and stage 3



Unresectable stage 3 and stage 4

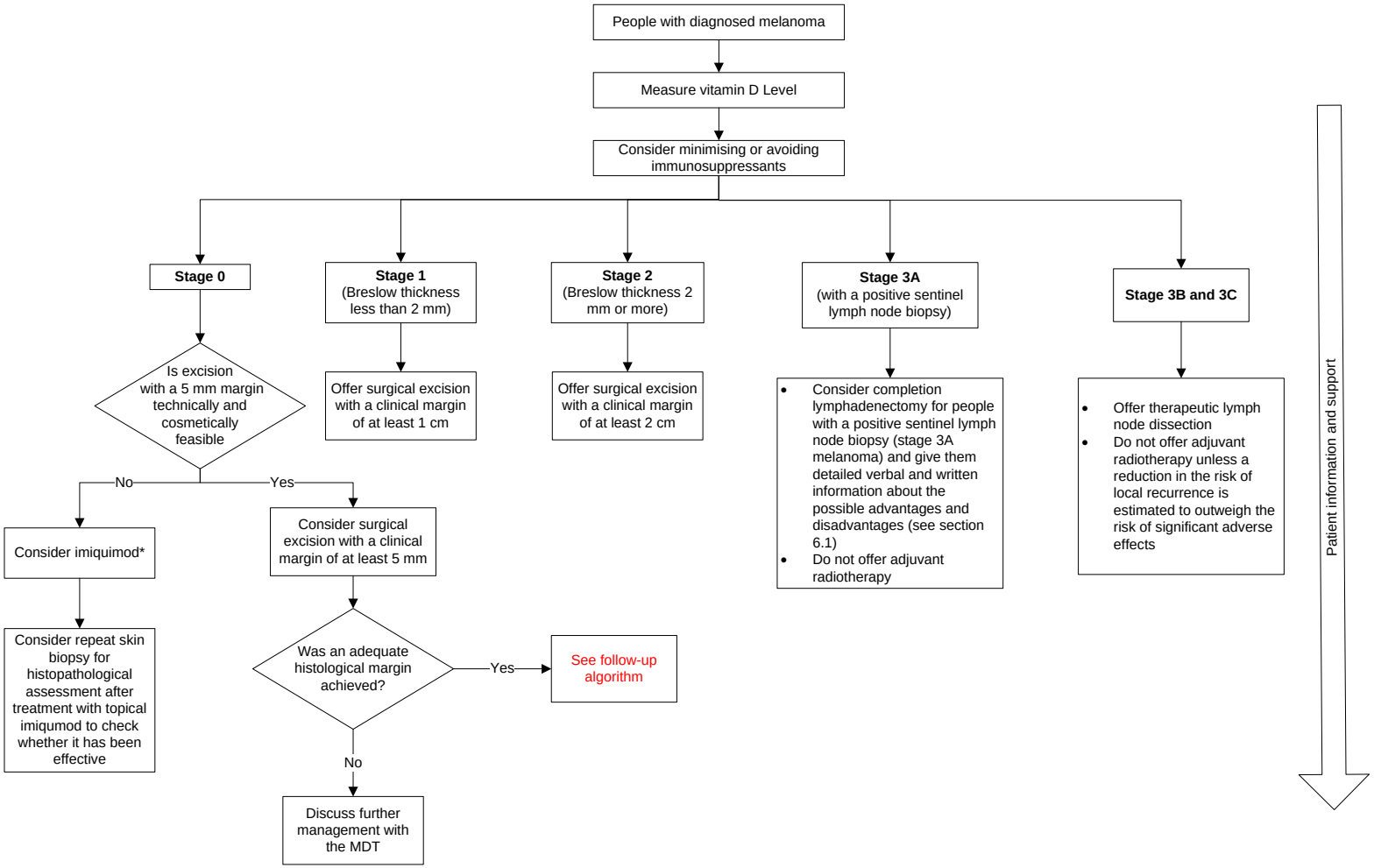


1 Staging



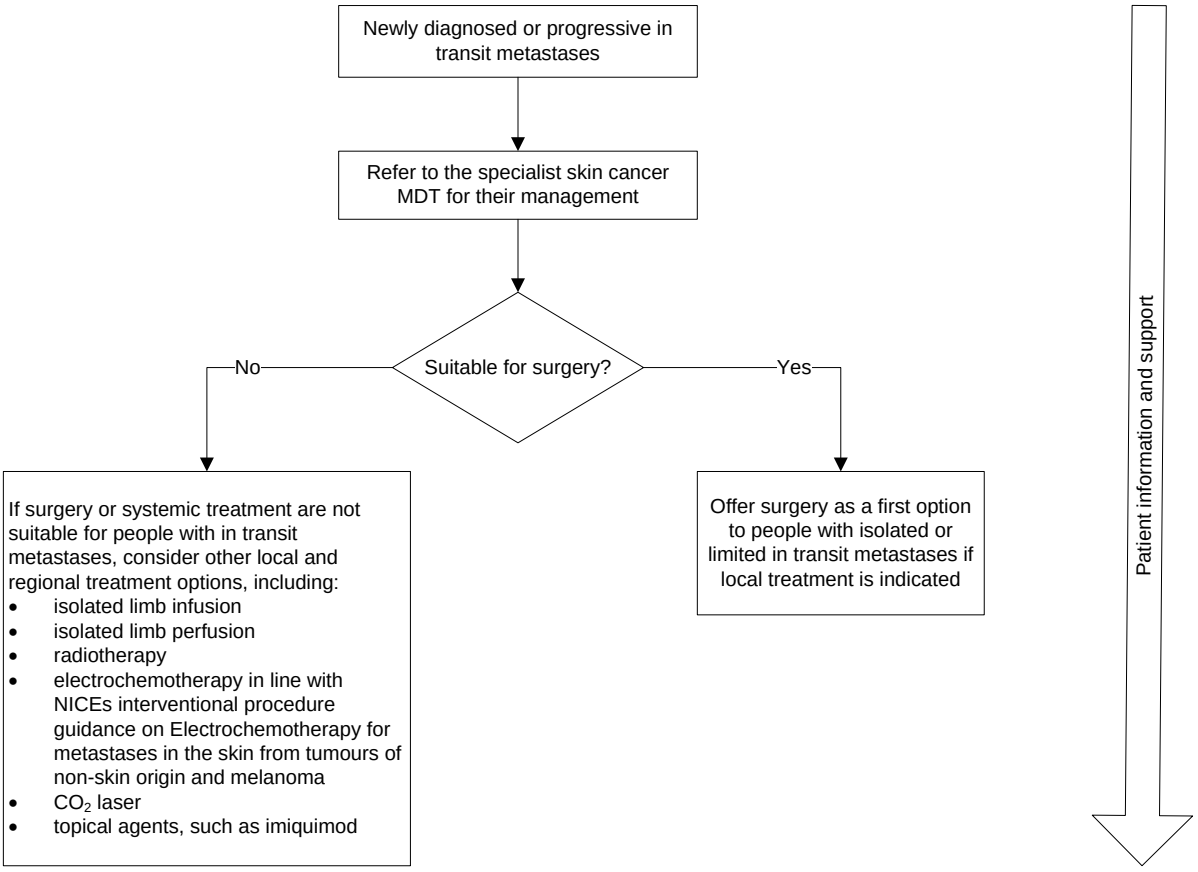
2
3
4

1 Management of stage 0-3 melanoma

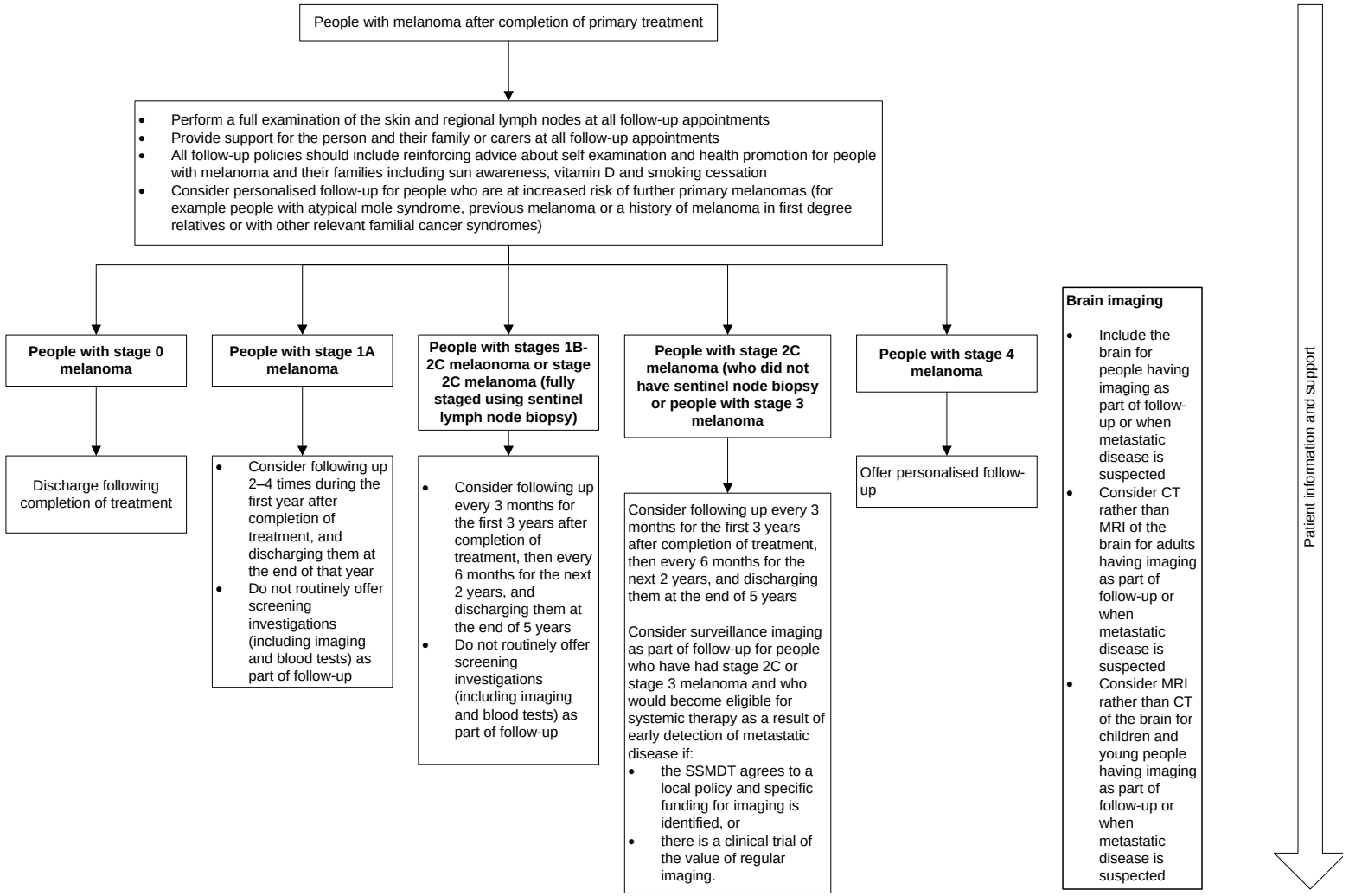


* At the time of consultation (January 2015) topical imiquimod did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's prescribing guidance: prescribing unlicensed medicines for further information

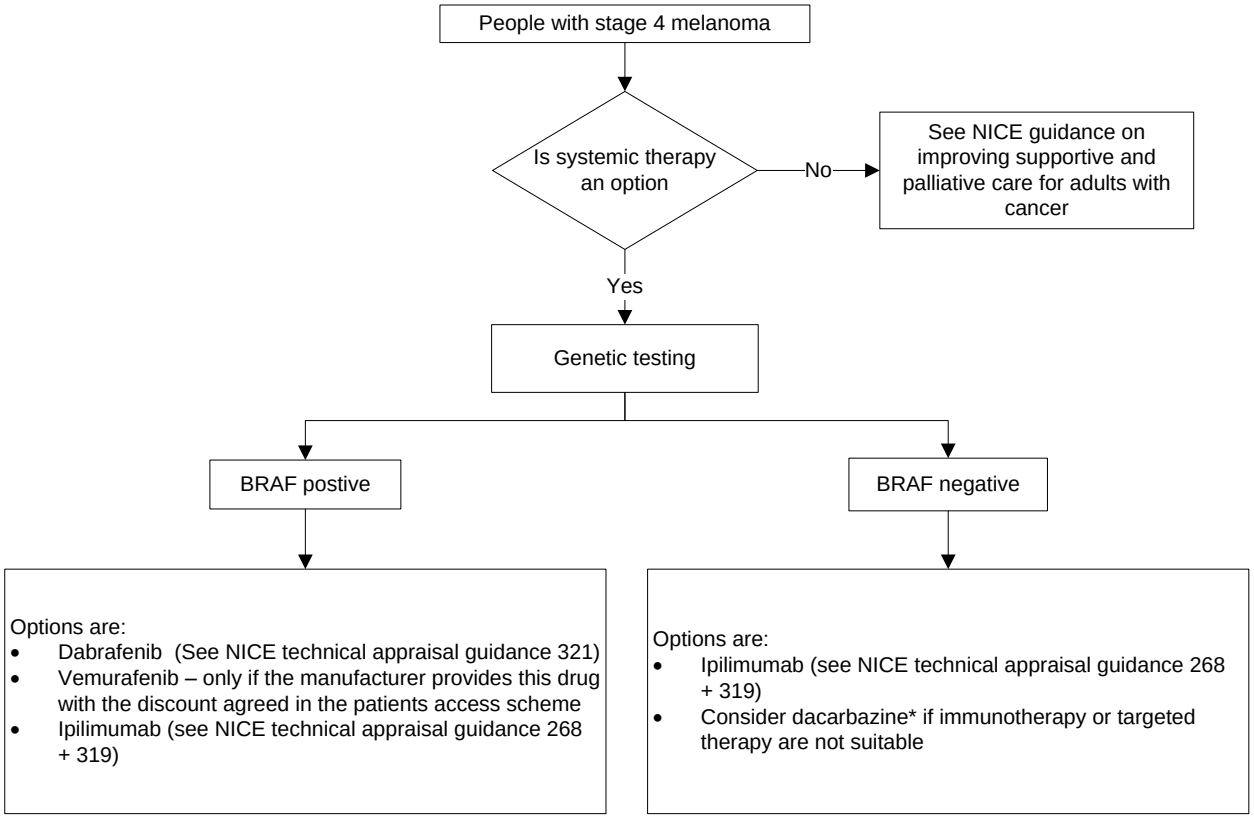
1 In transit melanoma



1 Follow-up



Management of stage 4 melanoma



*Do not offer further chemotherapy to people previously treated with dacarbazine except in the context of a clinical trail

1 Epidemiology

1.1 Introduction

Melanoma is the fifth most common cancer in the UK, with 13,348 cases diagnosed in the UK in 2011 (CRUK, 2013a). In males and females separately, melanoma is the 6th most common cancer (4% each of the male and female total). The age-standardised incidence rate of melanoma in the UK in 2012 was higher for men (25.0 melanomas per 100,000 men) than for women (22.1 melanomas per 100,000 women).

In 2012 there were 2,148 deaths from melanoma in the UK making it the eighteenth most common cause of cancer death (CRUK, 2013b).

The incidence of melanoma has increased at all anatomical locations in the last decade. In males, the most common sites are the trunk, particularly the back and on the head and neck. In women melanoma is more common on the limbs, especially the legs.

There are a number of well-known risk factors for melanoma, including ultraviolet radiation from sun exposure and sun beds. This risk is more strongly linked to intermittent exposure to high-intensity sunlight rather than to chronic or continuous sunlight exposure. Intermittent exposure of high intensity sunlight is associated with sunburn, and a history of sunburn increases the risk of melanoma. There are other risk factors in developing melanoma including the number of naevi (moles) present, and the presence of atypical naevi which are larger or more unusually shaped than normal.

Having a family history malignant melanoma doubles the risk of developing the condition and having had an organ transplant also doubles the risk. A previous history of having had a melanoma increases the risk of a second melanoma by approximately a factor of 10 and this risk is higher in women. Also having a past history of one of a wide range of other cancers, for example, thyroid cancer or some lymphomas also increases the risk of developing melanoma.

1.2 Methods

This chapter consists of two parts. The first provides an up to date report on the epidemiology of melanoma in England looking a trends in incidence, mortality, survival and prevalence. The effects of sex, age, anatomical location and income deprivation have been investigated and reported (sections 1.3 to 1.6). The second part presents the results of a survey of skin cancer multidisciplinary teams (MDTs) in England and Wales, planned in collaboration with the Guideline Development Group (GDG), investigating aspects of current service provision of relevance to the guideline. The topics included systemic therapy use, advice on vitamin D, genetic testing of tumour samples, advice on sentinel lymph node biopsy and the provision of patient information and support (section 1.7).

This report was prepared on behalf of the GDG and the National Collaborating Centre for Cancer by the South West Knowledge and Intelligence Team at Public Health England.

1.2.1 Epidemiological data

Epidemiological data for this report were obtained from the National Cancer Information Service and the Office for National Statistics (ONS).

Incident cases were extracted from the National Cancer Registration Service (NCRS) in England. The following code was used to identify cases:

- C43 ‘Malignant melanoma of skin’

All deaths in England and Wales are certified by a medical professional and then processed by the Office for National Statistics (ONS). The ONS derive a single underlying cause of death which is used to identify melanoma deaths.

Deprivation in England has been measured using the income deprivation component of the English Indices of Deprivation (DCLG, 2012).

Melanoma incidence and mortality are reported as age-standardised rates (per 100,000 population) using the 2013 European Standard Population (http://www.ons.gov.uk/ons/guide-method/user-guidance/health-and-life-events/revised-european-standard-population-2013--2013-esp-/index.html). Analysis of trends in age-standardised incidence and mortality rates was carried out using variance-weighted log-linear regression.

Survival figures are reported as age-standardised net survival using the Pohar Perme estimator (Pohar Perme et al., 2012). Analysis of trends in age-standardised net survival was carried out using variance-weighted linear regression, with time split into four periods: 2001-2003; 2004-2006; 2007-2009; and 2010-2012.

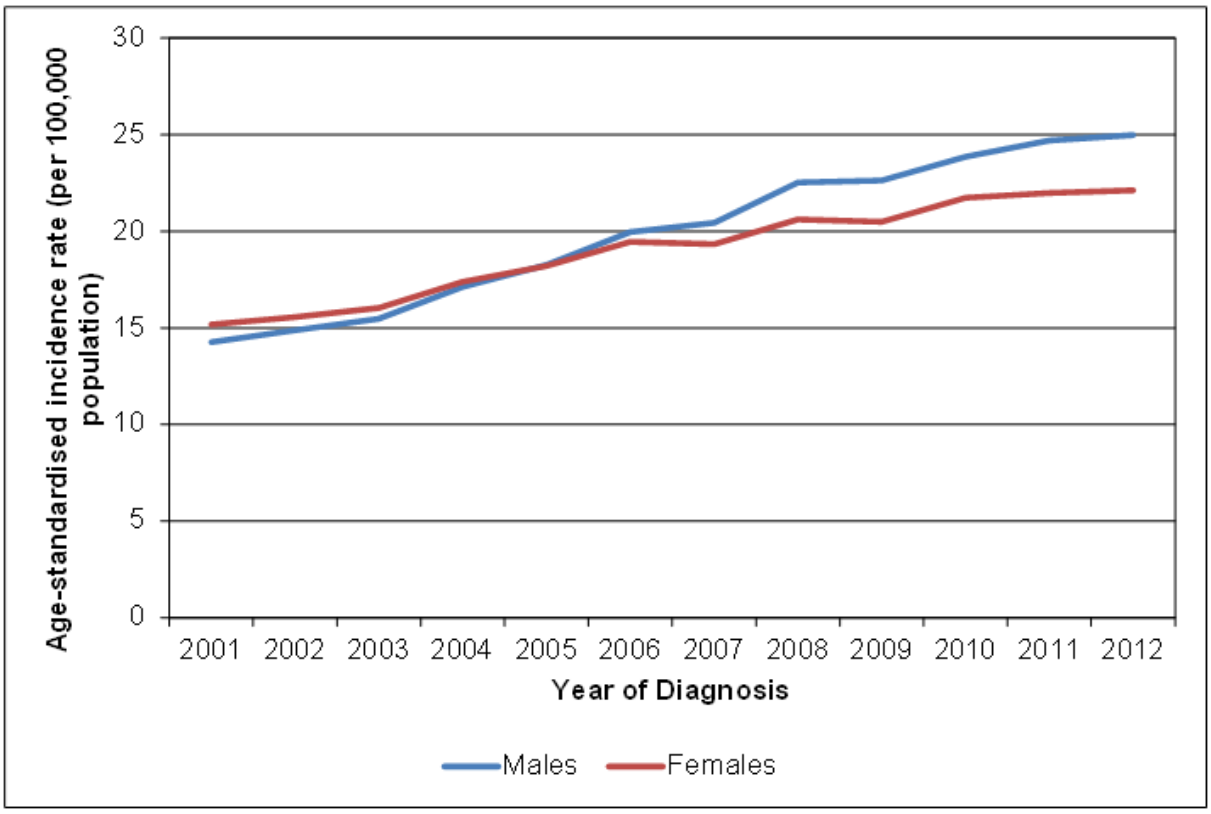
Prevalence (or survivorship) represents the number of people living with a cancer diagnosis within the last ‘n’ years. Here, the number of melanomas diagnosed between 2008 and 2012 in people alive at the end of 2012 are reported. The number of melanomas is used rather than the number of patients, in order that the information can be separated by tumour-level variables such as Breslow thickness and stage, even for patients who have more than one tumour.

1.3 Incidence

1.3.1 Sex

The age-standardised incidence rate for melanoma in England has increased for both sexes over the last decade (Figure 1). The average annual increase was significantly higher for men (5.5%) than for women (3.7%).

Figure 1: Age-standardised incidence rates (per 100,000 population) of melanoma by sex, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

1.3.2 Age

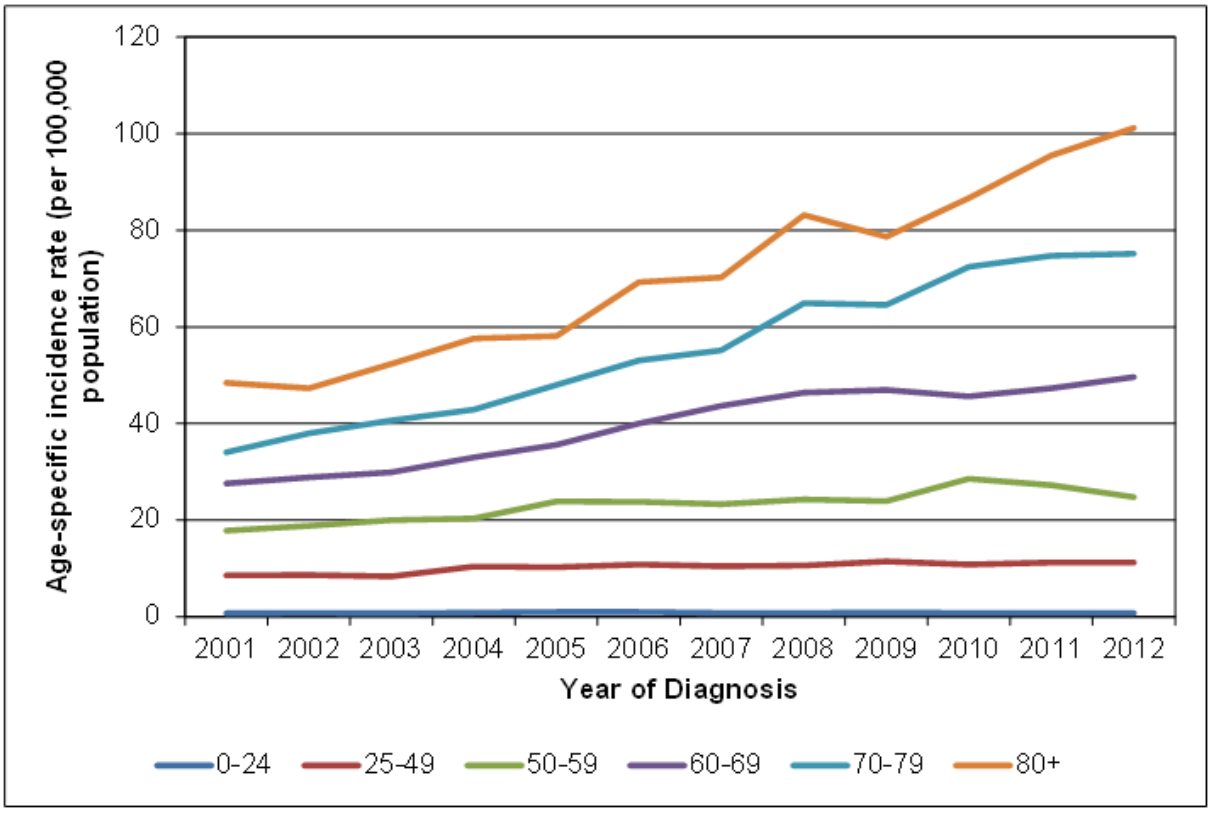
The increasing incidence of melanoma between 2001 and 2012 was especially marked in those over the age of 60 and that increase was greater in men than in women (Table 6 and Figures 2 and 3). Melanoma has generally been more common in women but recent data suggest that this may be changing. In 2012, the age-specific incidence rates for men (over 60 were higher than for older women (Figure 4).

Table 6: Annual percentage change in incidence rates by age group, 2001-2012

Age Groups (years)	Male AAPC	Female AAPC
0-24	0	-0.4
25-49	2.6*	2.9*
50-59	3.6*	2.3*
60-69	5.6*	5.0*
70-79	7.8*	4.9*
80+	7.4*	4.7*

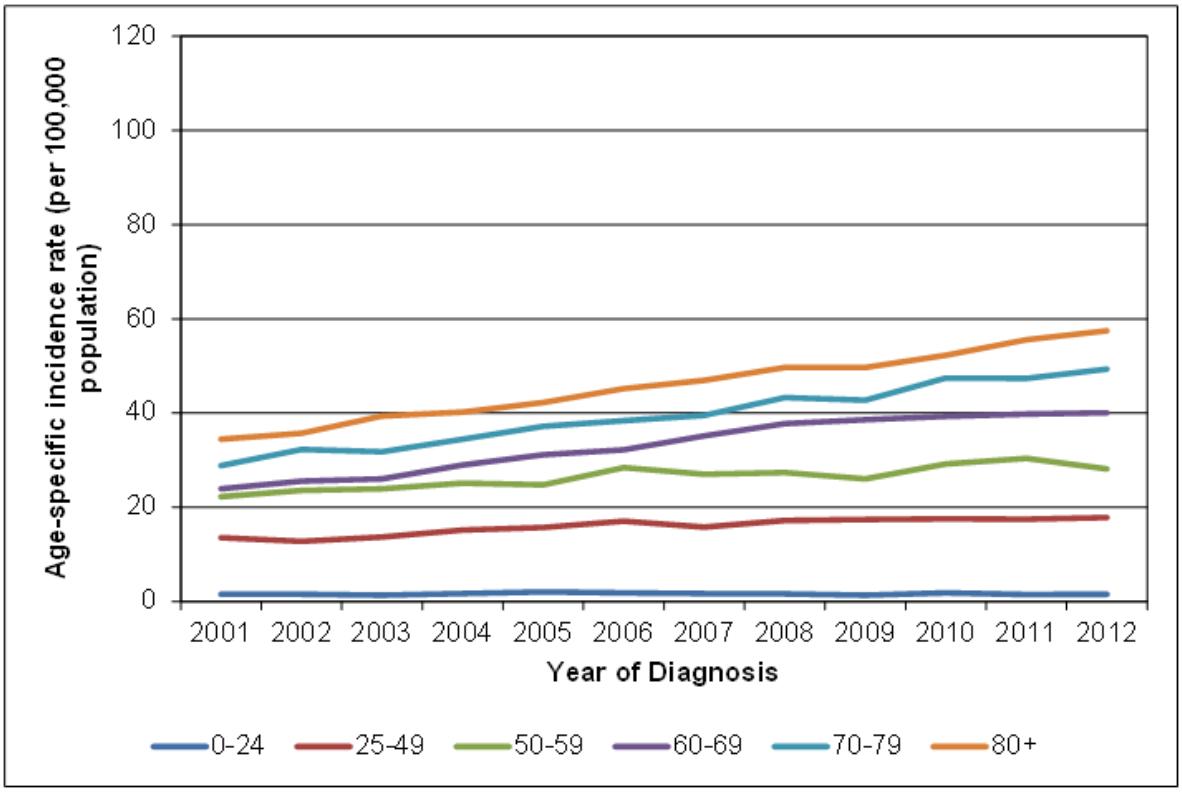
*AAPC = Average Annual Percentage Change; * = $p < 0.05$*

Figure 2: Age-specific melanoma incidence rates for males (per 100,000 men) by age group, England, 2001-2012



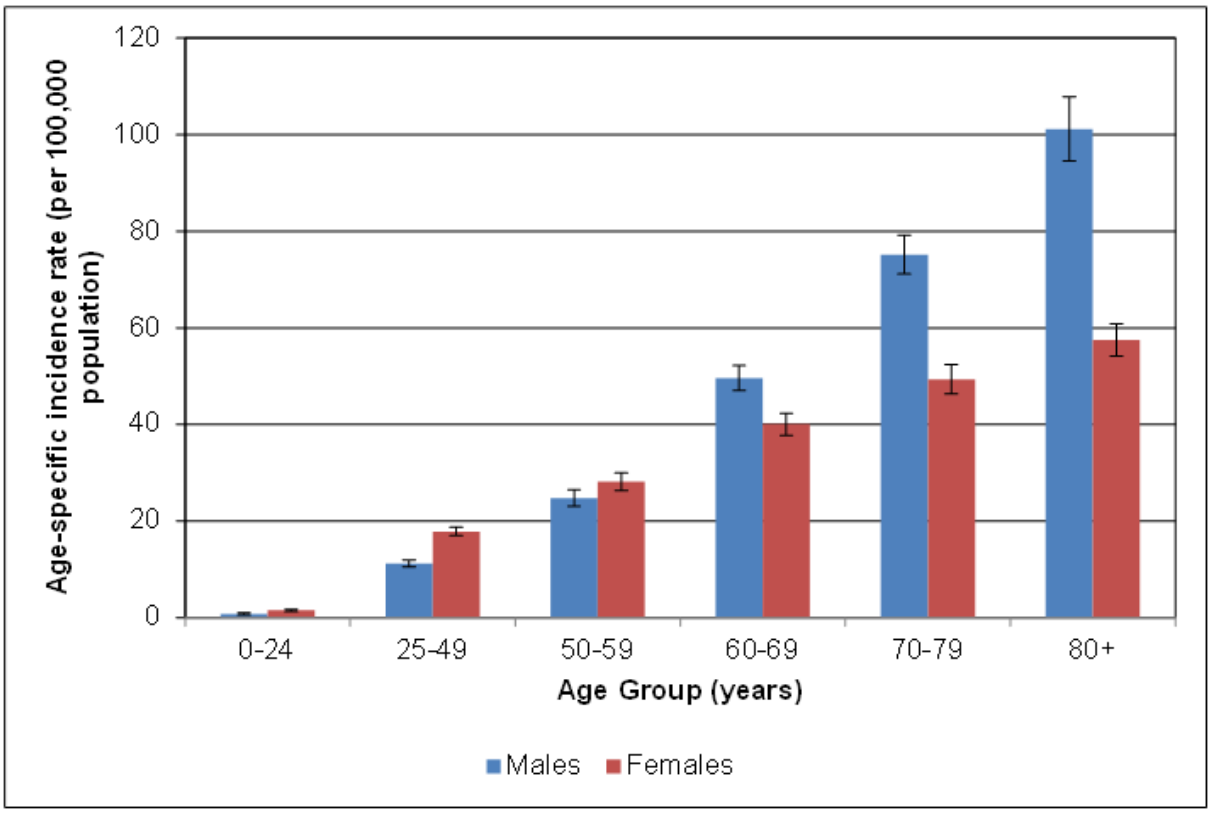
Source: National Cancer Registration Service; Office for National Statistics

Figure 3: Age-specific melanoma incidence rates for females (per 100,000 women) by age group, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 4: Age-specific melanoma incidence (per 100,000 people) by sex and age group, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

1.3.3 Anatomical site

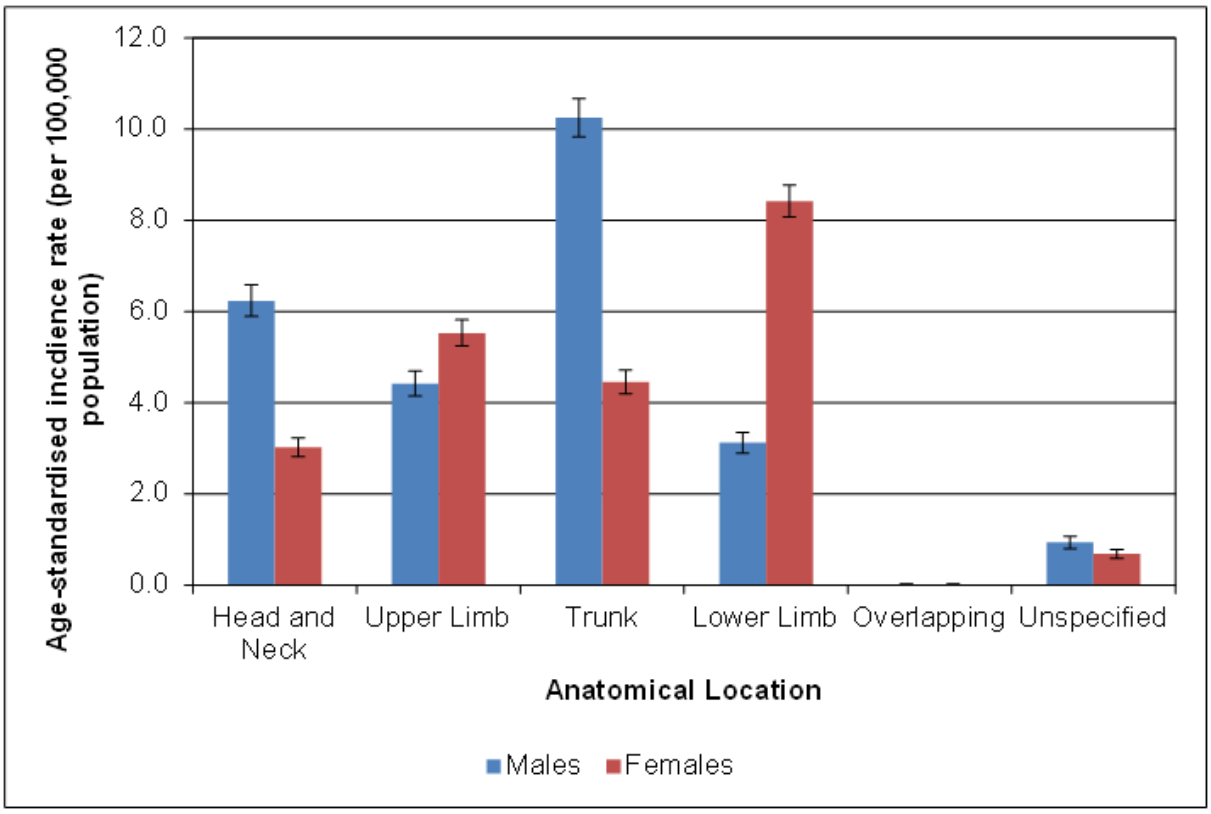
The incidence of melanoma has increased between 2001 and 2012 at all anatomical sites (Table 7). In men, the most common sites are the trunk, particularly the back, and on the head and neck but in women it is more common on the limbs, especially the legs. The number of melanomas with an unspecified location has decreased, suggesting better recording; this will contribute to the apparent increase at other anatomical sites (Figure 5).

Table 7: Annual percentage change in incidence rates by anatomical location, 2001-2012

Anatomical Location	Male AAPC	Female AAPC
Head and Neck	5.7*	3.1*
Lower Limb	4.6*	2.9*
Overlapping	n/a	n/a
Trunk	6.4*	5.6*
Unspecified	-2.9*	-3.7*
Upper Limb	6.6*	5.4*

*AAPC = Average Annual Percentage Change; * = p < 0.05; There were too few cases of melanomas at overlapping regions to ascertain a trend.*

Figure 5: Age-standardised melanoma incidence (per 100,000 people) by sex and anatomical location, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

1.3.45 Income deprivation

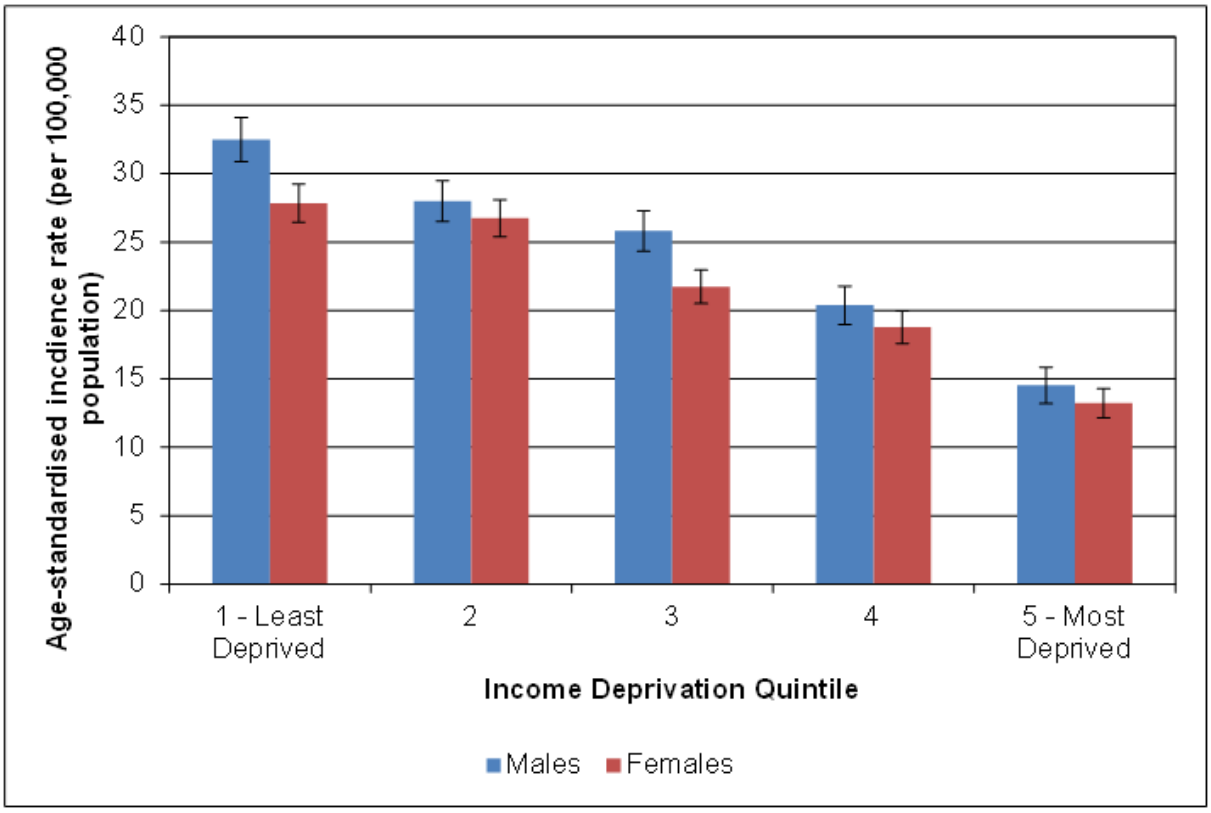
Melanoma incidence in 2012 was highest in the least deprived quintile of the population (Figure 6). Melanoma is unusual in showing an inverse relationship between incidence and deprivation, for both men and women. During 2001-2012 the incidence increased at a similar rate in all income deprivation quintiles and so the effect of deprivation was similar throughout this period (Table 8).

Table 8: Annual percentage change in melanoma incidence rates by income deprivation quintile, 2001-2012

Deprivation Quintile	Male AAPC	Female AAPC
1 - Least Deprived	5.6*	3.7*
2	5.3*	3.5*
3	5.1*	3.7*
4	5.6*	3.7*
5 - Most Deprived	5.5*	3.1*

*AAPC = Average Annual Percentage Change; * = $p < 0.05$*

Figure 6: Age-standardised melanoma incidence (per 100,000 people) by sex and income deprivation, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

1.3.5 Projected incidence of melanoma

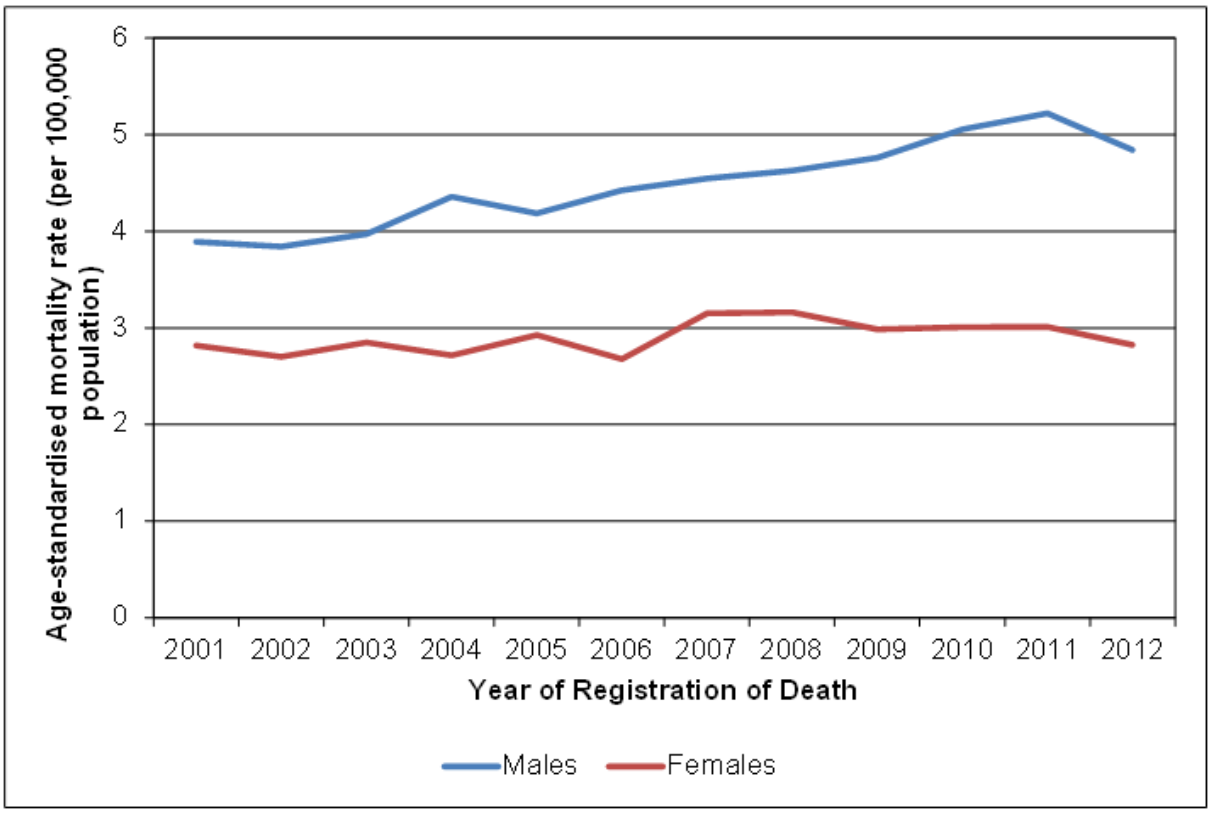
The age-standardised rates of melanoma are projected to increase by > 1% per year from 14.6 per 100,000 for men and 15.4 per 100,000 for women in 2007 to 22.3 and 23.4 respectively in 2030 (Mistry et al 2011). Melanoma was the 14th most common cancer in men in 1984 (1% of all male cancers) and is predicted to become the fourth most common accounting for almost 5% of cases by 2030 (Mistry et al 2011).

1.4 Mortality

1.4.1 Sex

The age-standardised mortality rate for melanoma in England has significantly increased for men but not women between 2001 and 2012 (Figure 7). The average annual increase was 2.7% for men and 0.8% for women. In 2012 the age-standardised mortality rate for melanoma was higher for men (4.8 deaths per 100,000) than for women (2.8 deaths per 100,000).

Figure 7: Age-standardised mortality rates (per 100,000 population) for melanoma by sex, England, 2001-2012



Source: Office for National Statistics

1.4.2 Age

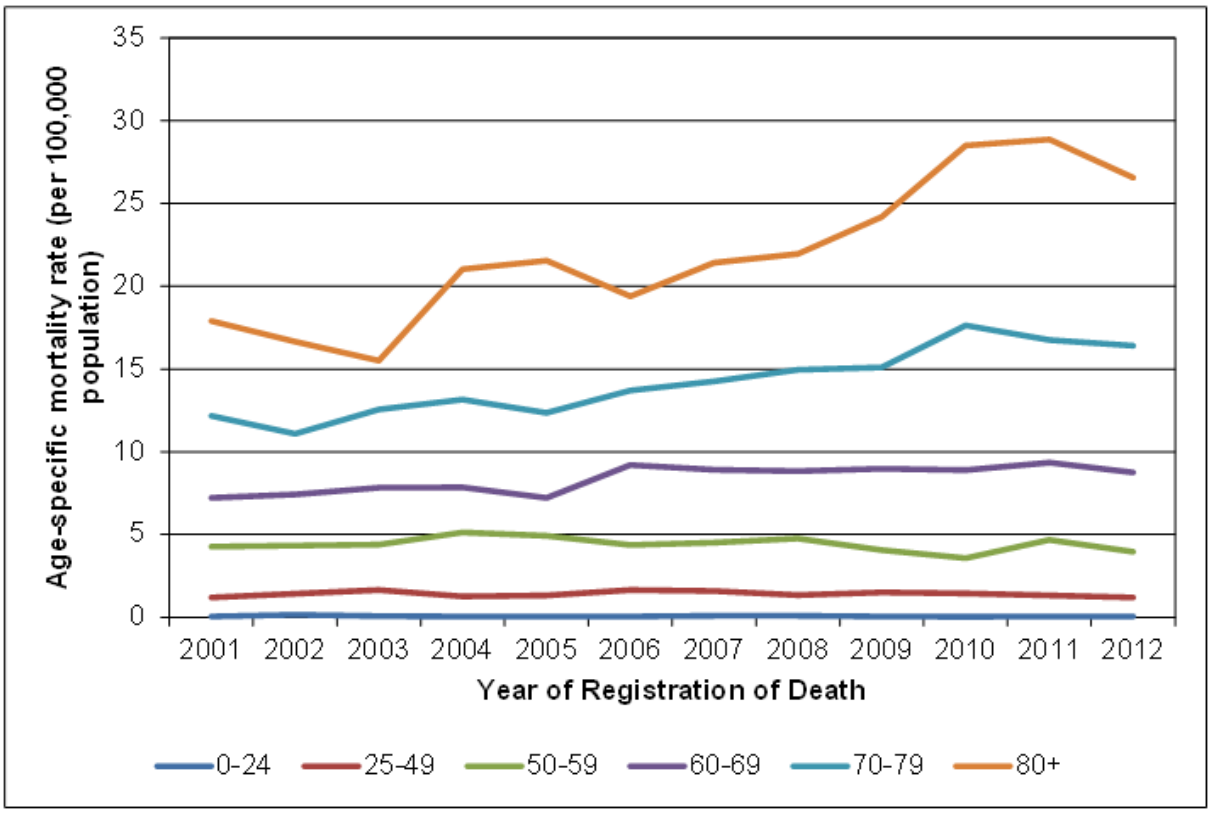
The mortality rates for melanoma have mostly increased in the older age groups and particularly for men between 2001 and 2012 (Table 9 and Figures 8 and 9). In 2012, the age-specific mortality rates for older men (60+ years old) were higher than for older women (Figure 10).

Table 9: Annual percentage change in melanoma mortality rates by age group, 2001-2012

Age Groups (years)	Male AAPC	Female AAPC
0-24	-6.4	-4.6
25-49	-0.7	-1.3
50-59	-0.8	-0.8
60-69	2.2*	1.8
70-79	3.8*	0.4
80+	5.3*	2.4*

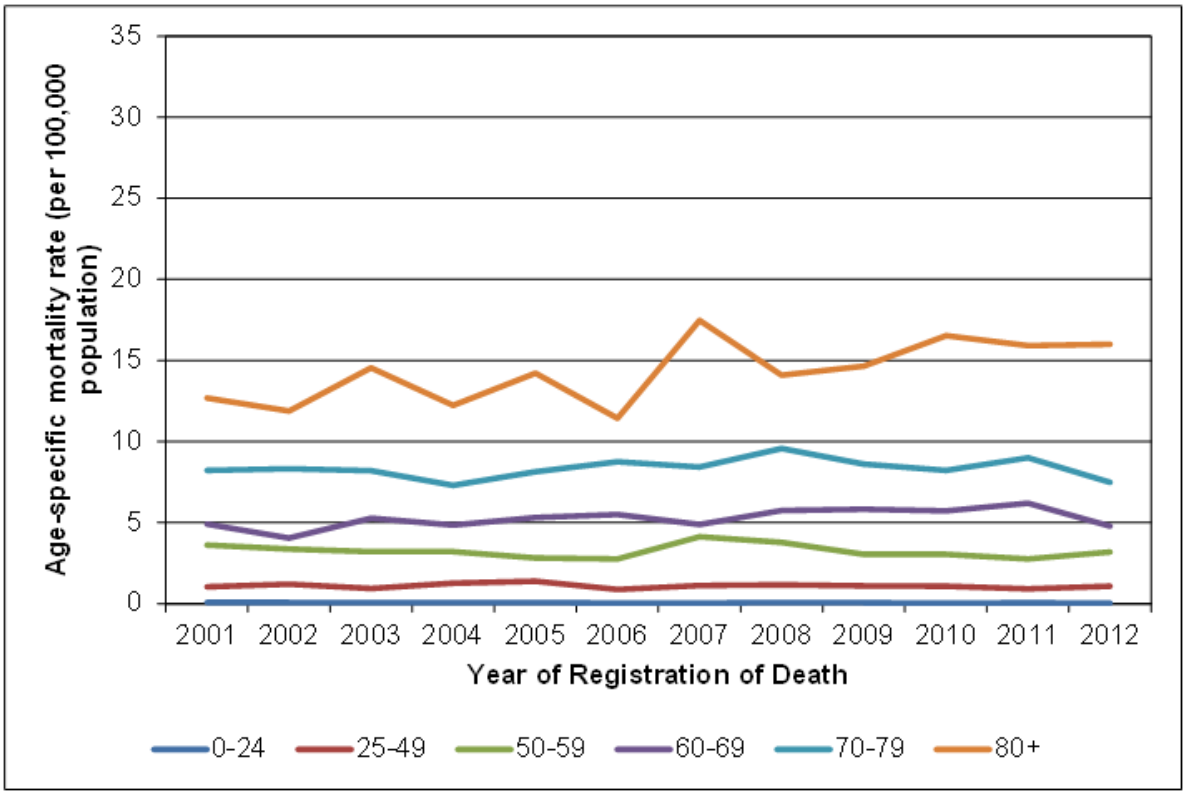
*AAPC = Average Annual Percentage Change; * = $p < 0.05$*

Figure 8: Age-specific melanoma mortality rates for males (per 100,000 men) by age group, England, 2001-2012



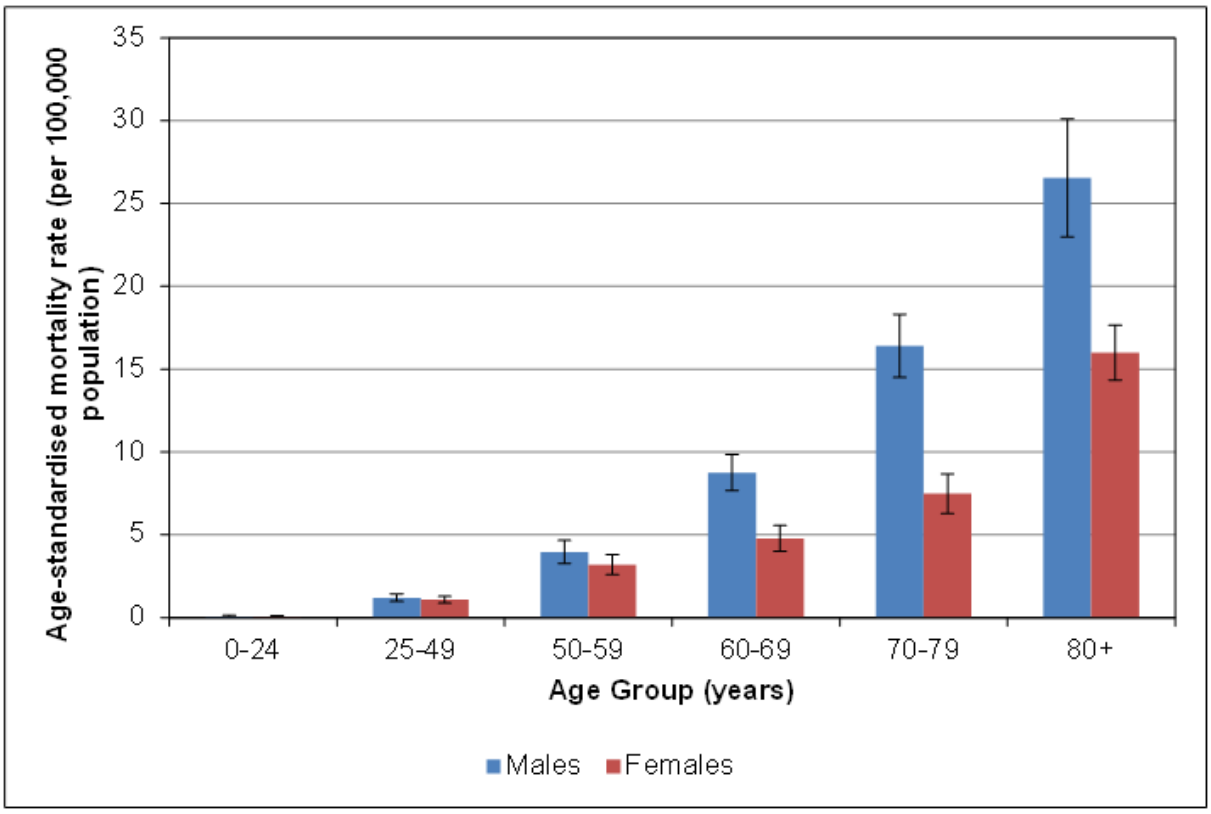
Source: Office for National Statistics

Figure 9: Age-specific melanoma mortality rates for females (per 100,000 women) by age group, England, 2001-2012



Source: Office for National Statistics

Figure 10: Age-specific melanoma mortality rates (per 100,000 people) by sex and age group, England, 2012

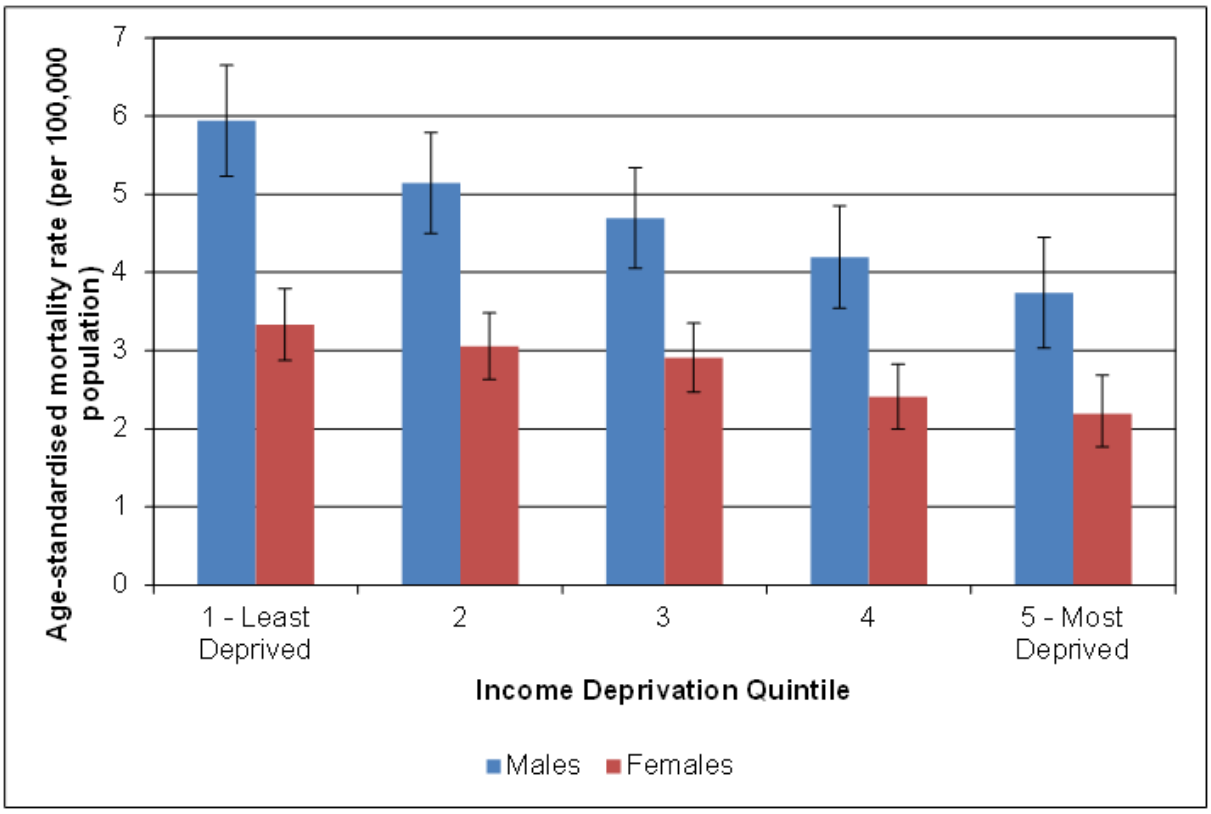


Source: Office for National Statistics

1.4.3 Income deprivation

In 2012 melanoma mortality was highest in the least deprived sections of the population (Figure 11), where the incidence is also highest.

Figure 11: Age-standardised melanoma mortality rates (per 100,000 people) by sex and income deprivation, England, 2012



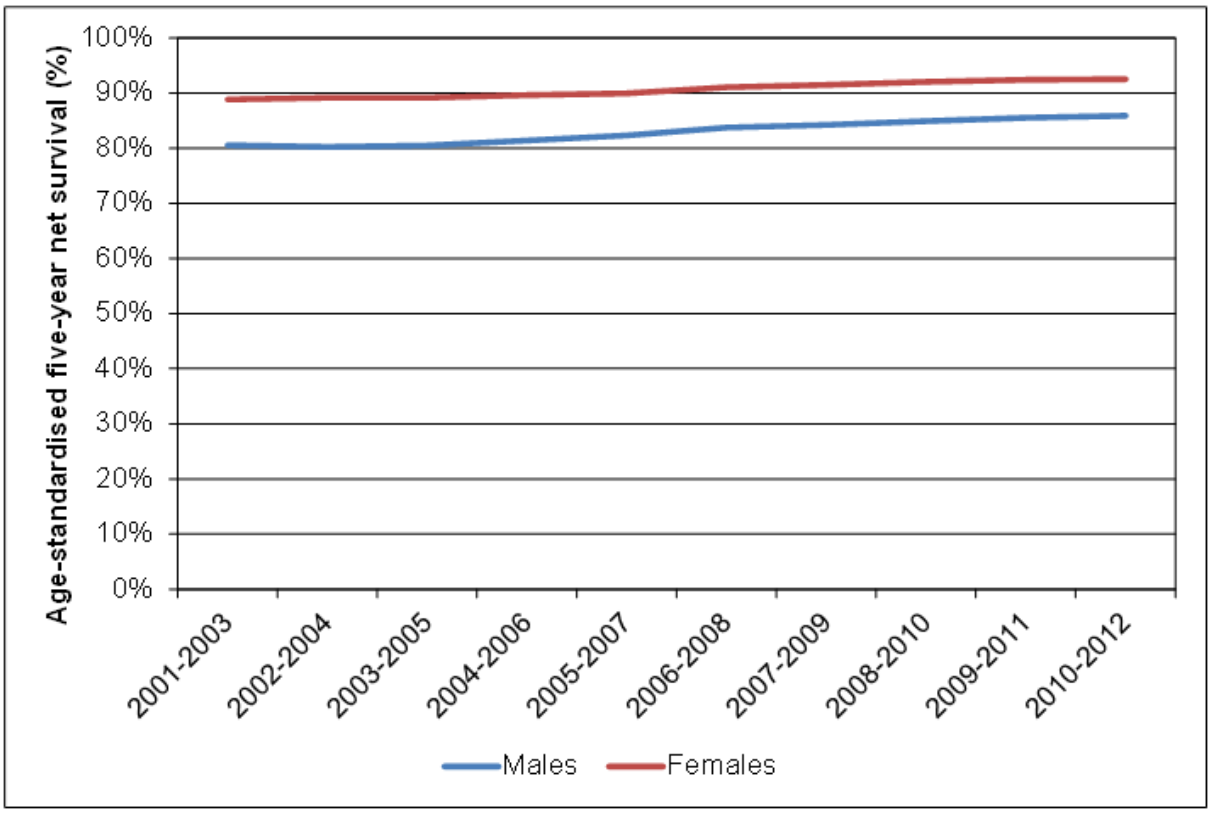
Source: National Cancer Registration Service; Office for National Statistics

1.5 Survival

1.5.1 Sex

The age-standardised five-year net survival for melanoma in England has significantly increased for both men and women between 2001 and 2012 (Figure 12). The age-standardised five-year net survival for melanoma in 2010-2012 was higher for women (93%) than for men (86%).

Figure 12: Age-standardised five-year net survival (%) for melanoma by sex, England, 2001-2012

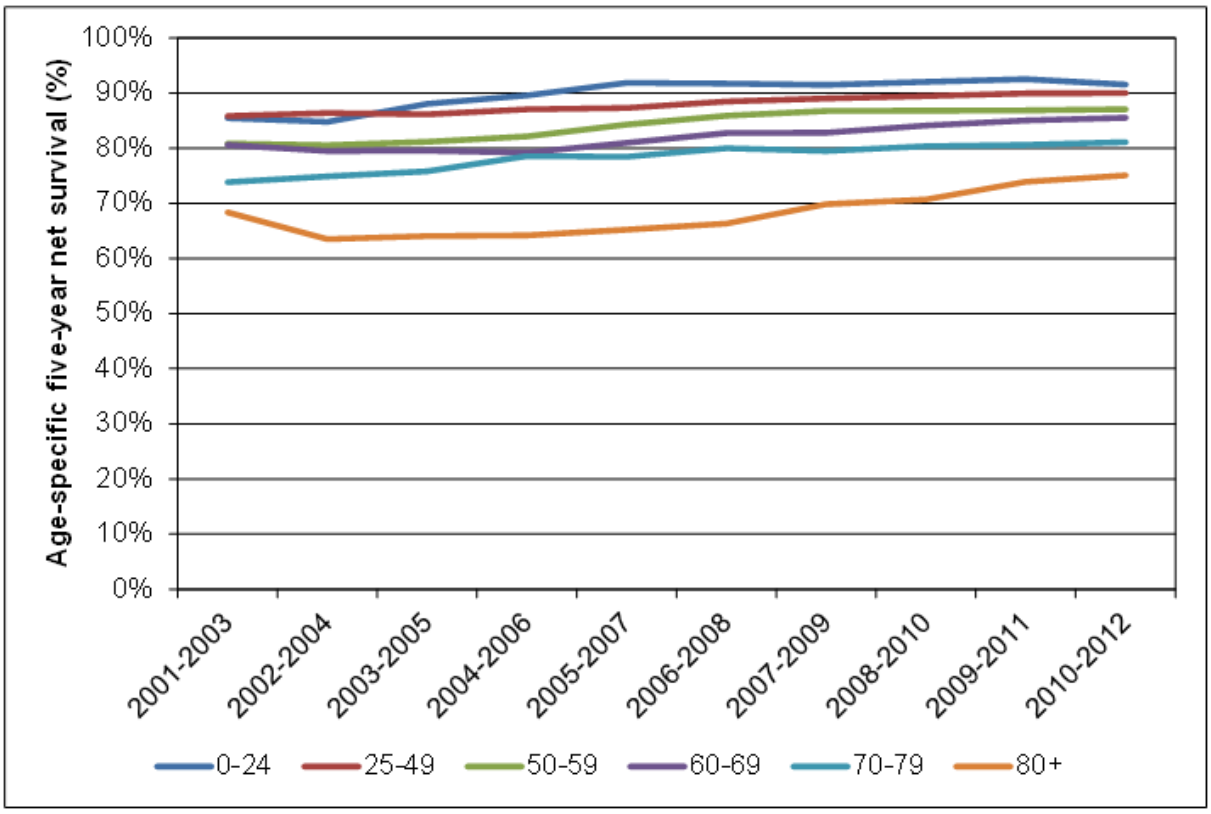


Source: National Cancer Registration Service

1.5.2 Age

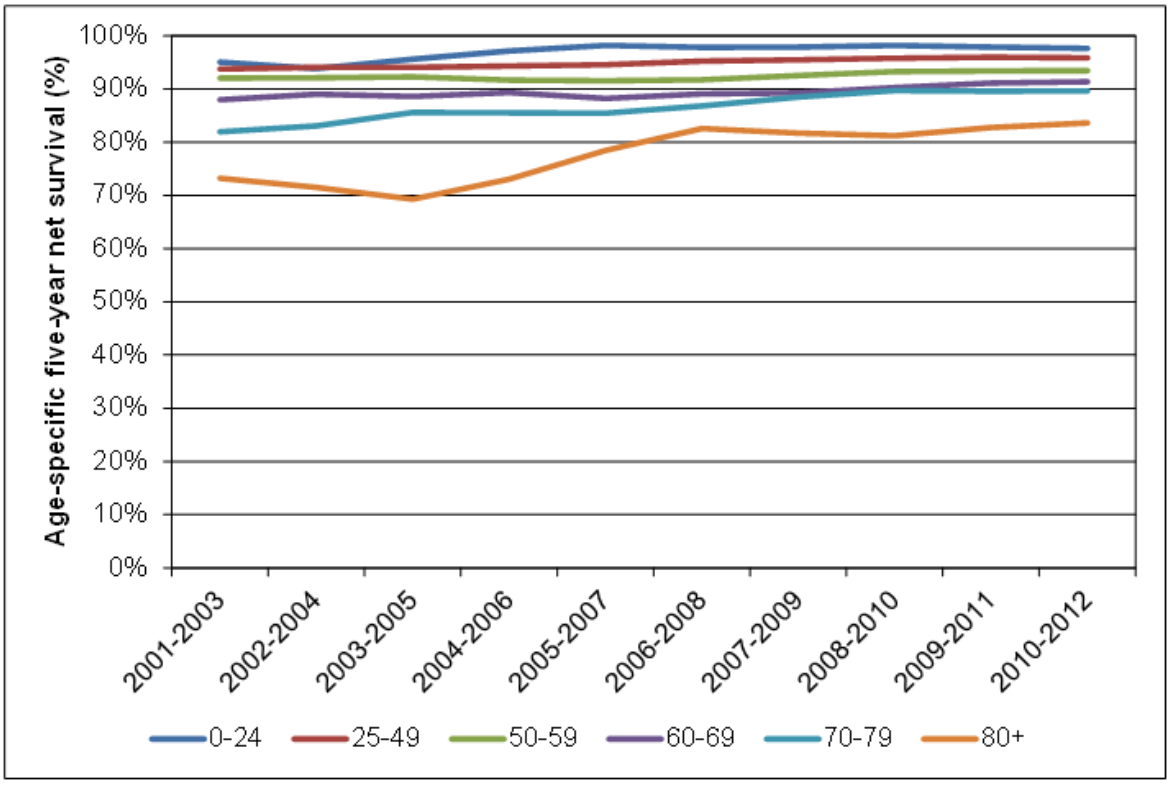
Survival from melanoma is increasing in all age groups, although this is not always statistically significant (Figures 13 and 14). The increase is greater for older age groups, with a significant interaction between age group and time period for females. In 2012, five-year net survival was significantly lower for older age groups for men (an absolute decrease in net survival of 3% with increasing age group) and for women (an absolute decrease of 2.4% with increasing age group) (Figure 15).

Figure 13: Age-specific five-year net survival for melanoma in males, by age group, England, 2001-2012



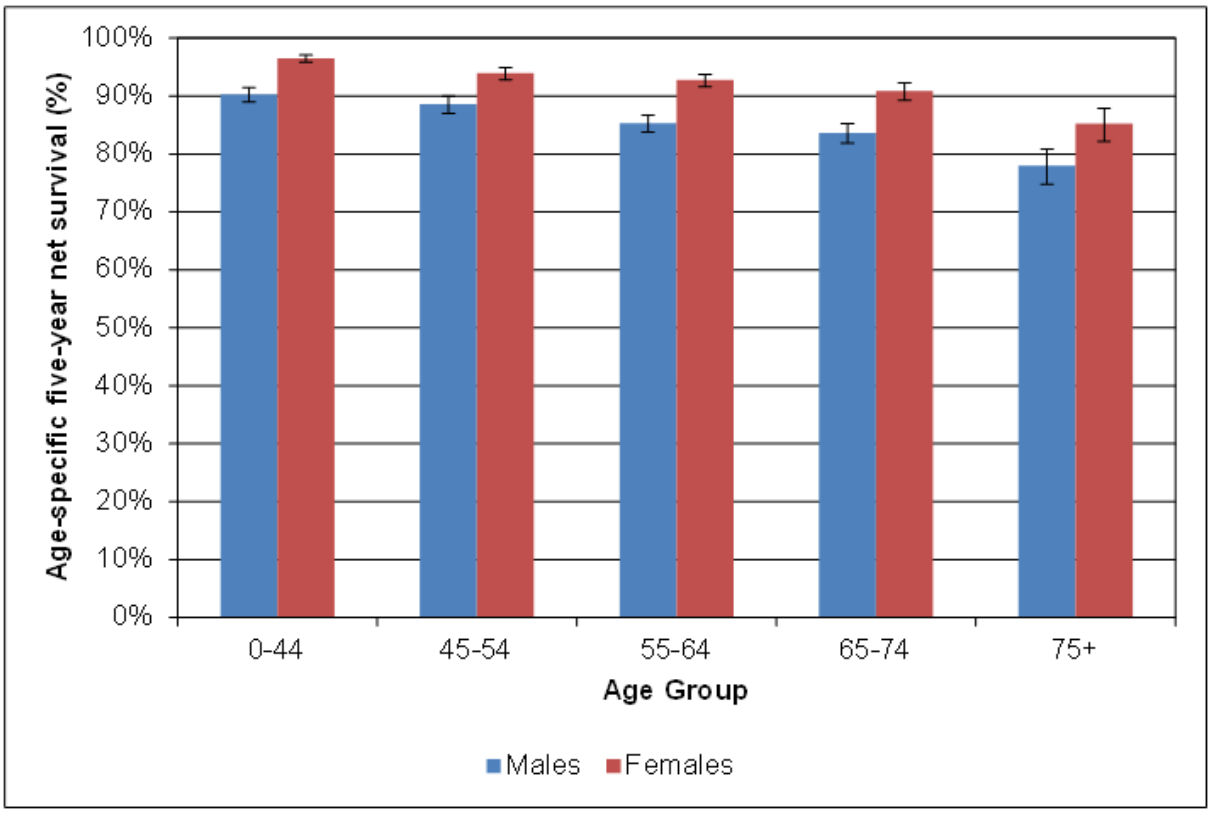
Source: National Cancer Registration Service

Figure 14: Age-specific five-year net survival for melanoma in females, by age group, England, 2001-2012



Source: National Cancer Registration Service

Figure 15: Age-specific five-year net survival for melanoma by sex and age group, England, 2010-2012

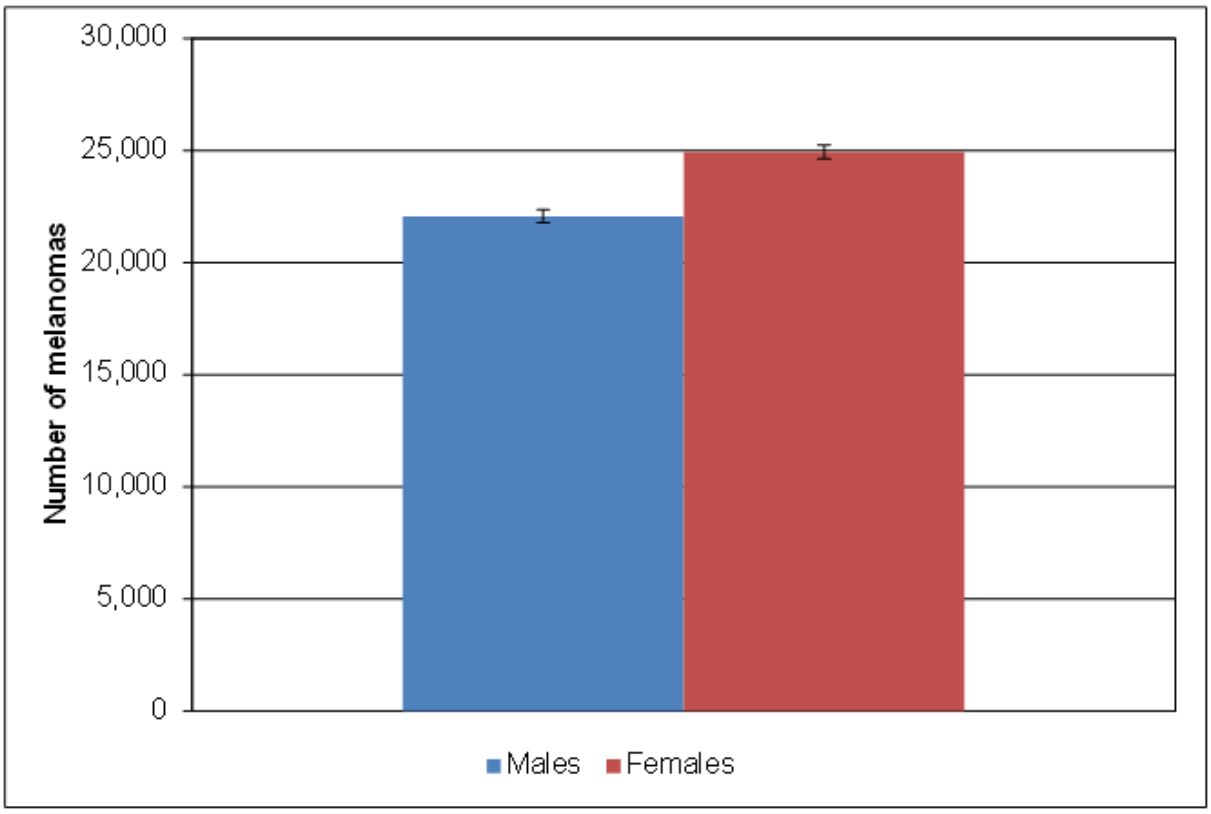


Source: National Cancer Registration Service

1.6 Prevalence (survivorship)

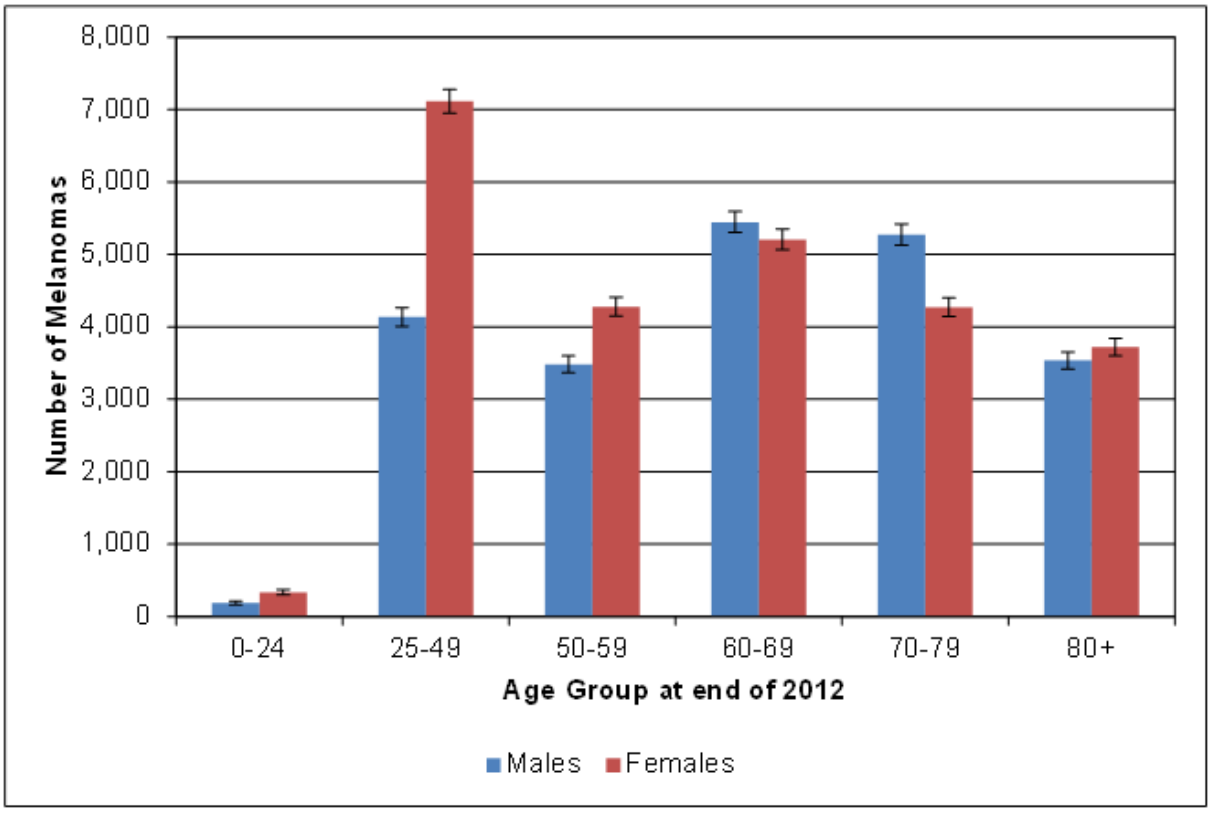
In total, there were 46,782 melanomas diagnosed between 2008 and 2012 in people who were still living at the end of 2012. Figures 16 and 17 show this prevalence information split by sex and age group. Note that these figures are counts of individual melanomas rather than rates.

Figure 16: Five-year prevalence of melanoma in England by sex, end of 2012



Source: National Cancer Registration Service

Figure 17: Five-year prevalence of melanoma in England by sex and age group, end of 2012



Source: National Cancer Registration Service

1.7 Skin cancer MDT Survey (England and Wales)

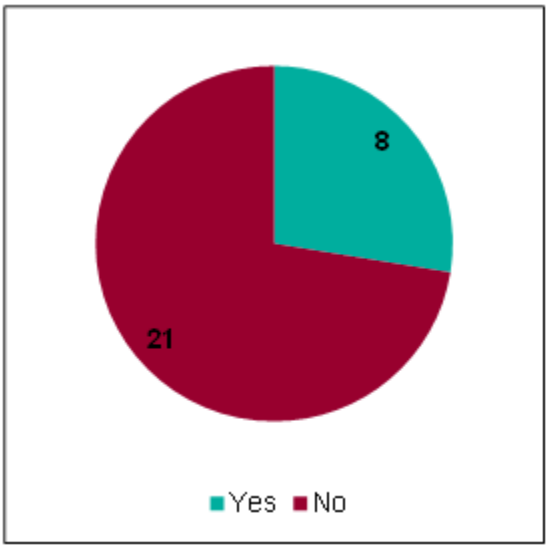
In order to better understand current clinical practice for some specific issues the GDG developed a questionnaire survey. This was sent electronically with a covering letter to all skin cancer multidisciplinary teams (MDTs) in England and Wales during July 2014 who were asked to complete the questionnaire on line. All information was treated confidentially and no hospital or healthcare professional has been identified in the final guideline or any associated report. All the data was analysed and presented by the team at the South West Knowledge and Intelligence Team at Public Health England.

A total of 77 skin cancer MDTs replied to the survey, comprising 48 local skin cancer MDTs (LSMDTs) and 29 specialist skin cancer MDTs (SSMDTs). A summary of the key findings is presented below (Figures 18-32). The full results are in the needs assessment document (Appendix G) which accompanies this guideline.

1.7.1 Vitamin D

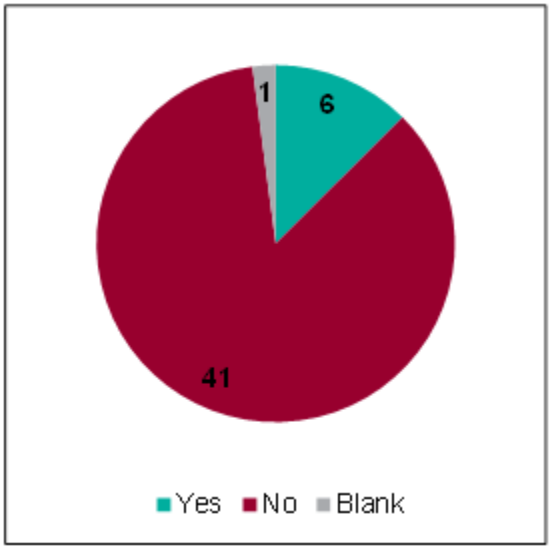
Figure 18: Does your skin cancer team give advice about avoiding depletion of vitamin D levels as a result of sun protection?

LSMDT (n = 48)

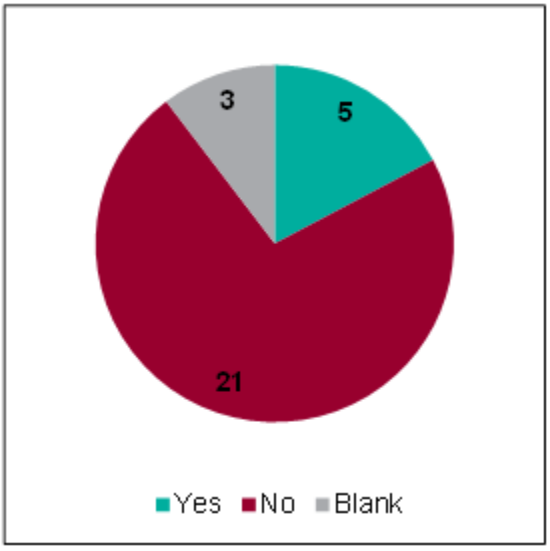


SSMDT (n = 29)

Figure 19: Are blood levels of vitamin D routinely measured in melanoma patients after diagnosis?



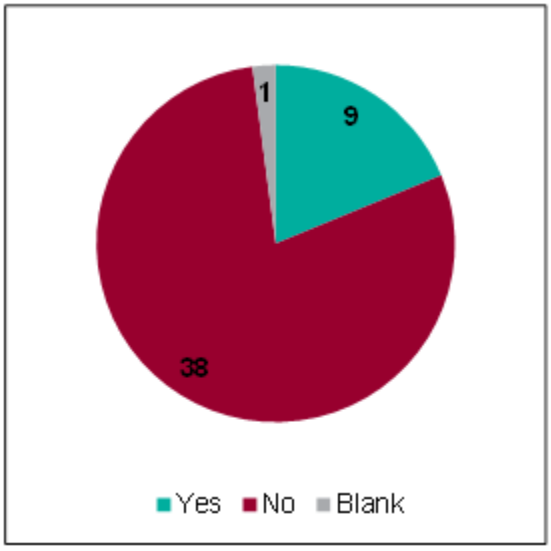
LSMDT (n = 48)



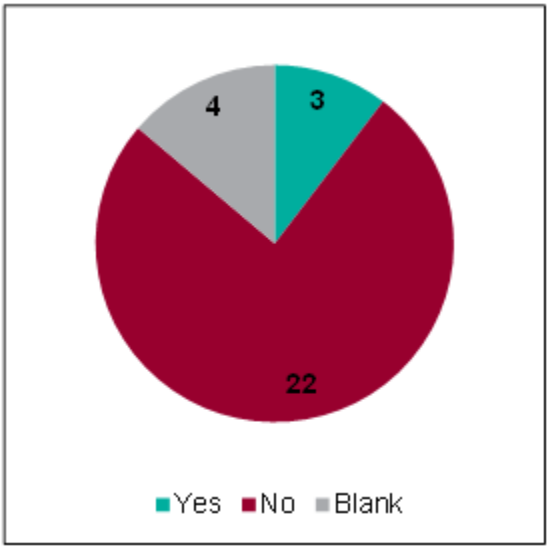
SSMDT (n = 29)

Both the LSMDTs and SSMDTs reported that levels between 50 nmol/L and 100nmol/L were the optimum blood levels suggested for melanoma patients.

Figure 20: Does the skin cancer MDT routinely recommend vitamin D supplements to melanoma patients?



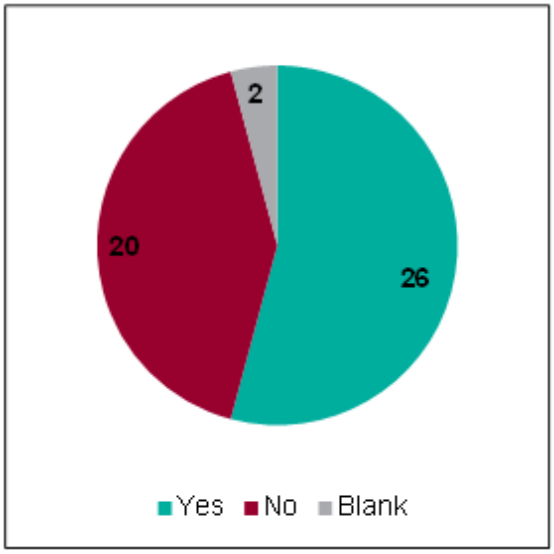
LSMDT (n = 48)

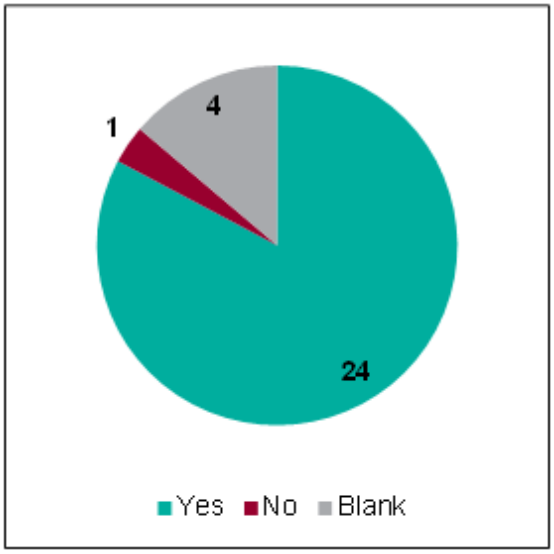


SSMDT (n = 29)

1.7.21 Genetic testing of melanoma samples within the past 2 years

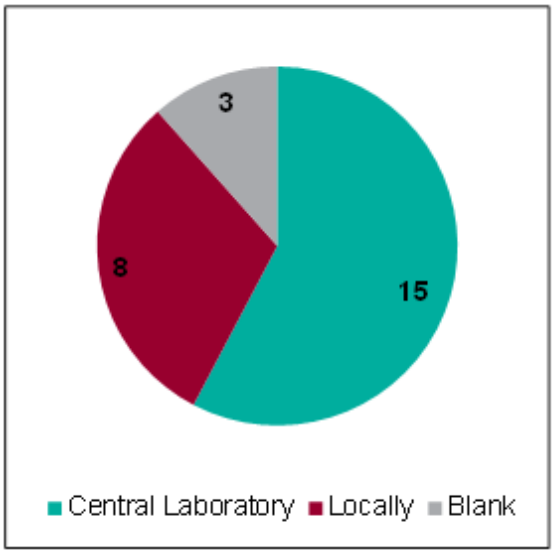
Figure 21: Have you arranged testing of tumour blocks for BRAF mutations?

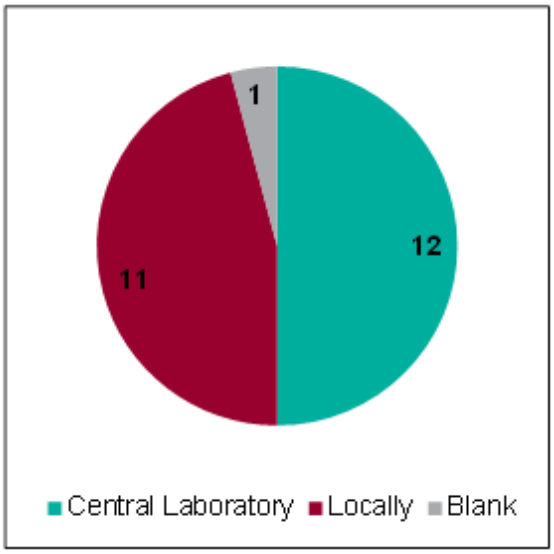




LSMDT (n = 48) *SSMDT (n = 29)*

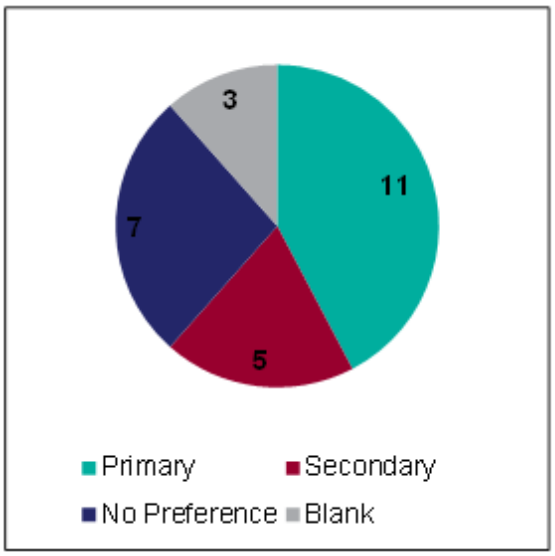
Figure 22: If yes, where was the testing carried out?

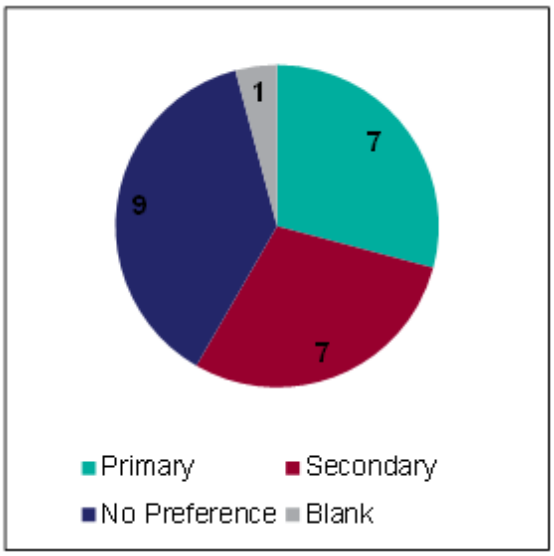




LSMDT (n = 26) *SSMDT (n = 24)*

Figure 23: Was there a preference as to which melanoma tissue to test?

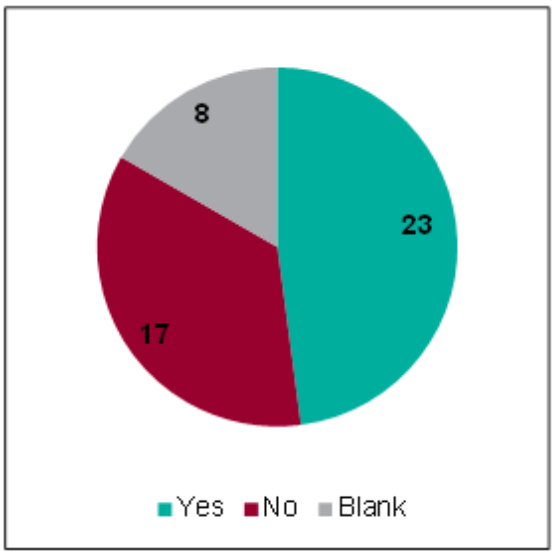


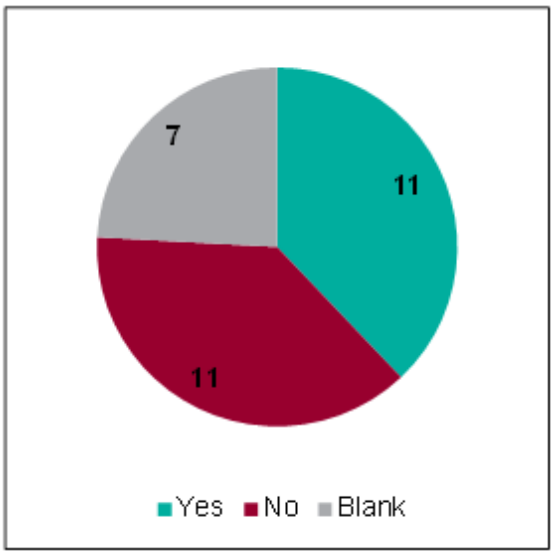


LSMDT (n = 26) *SSMDT (n = 24)*

1.7.3 Sentinel lymph node biopsy

Figure 24: Do you offer sentinel lymph node biopsy (SLNB) within your MDT?

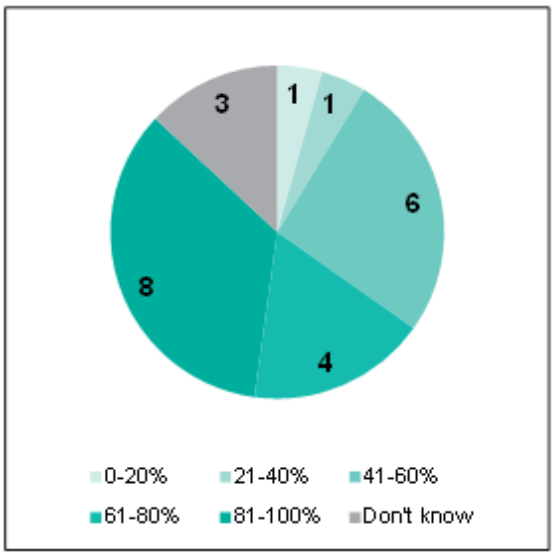


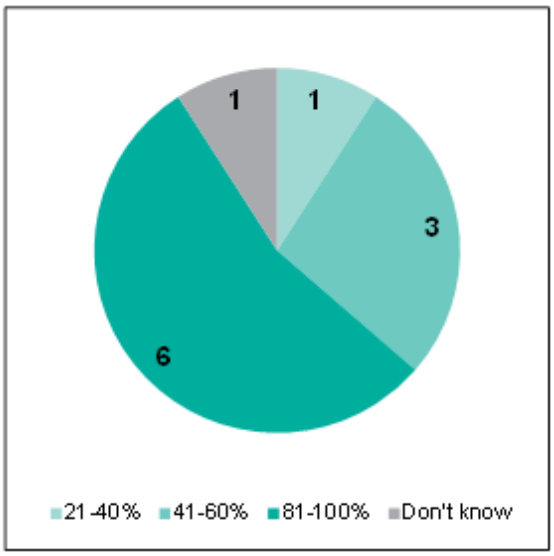


LSMDT (n = 48) *SSMDT (n = 29)*

A total of 28 LSMDTs and SSMDTs (45%) did not offer SLNB in their MDT

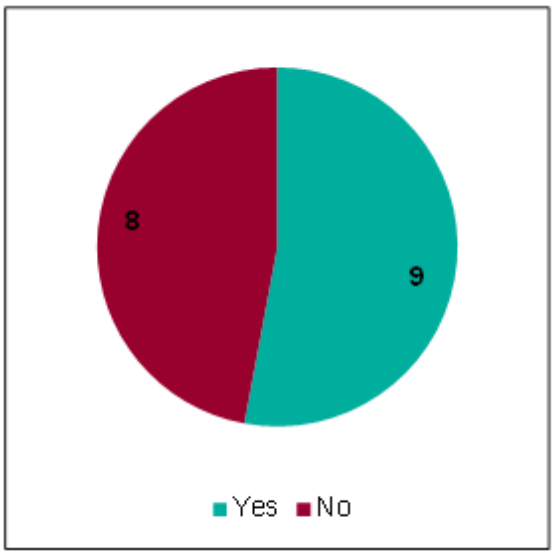
Figure 25: If so, roughly what percentage of patients offered SLNB accept?

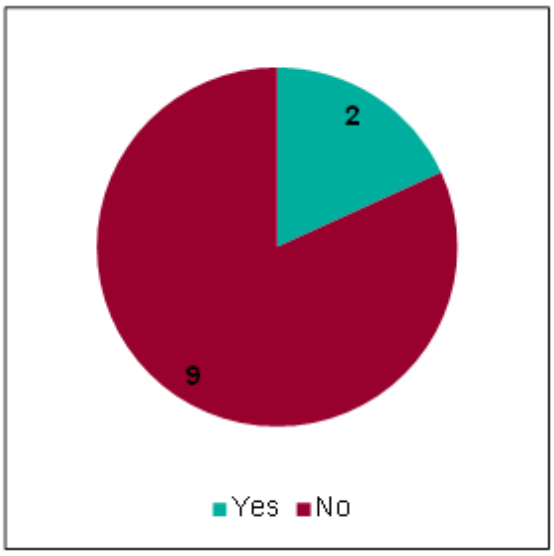




LSMDT (n = 23) *SSMDT (n = 11)*

Figure 26: If you do not offer SLNB within your MDT, do you offer it via other MDTs?

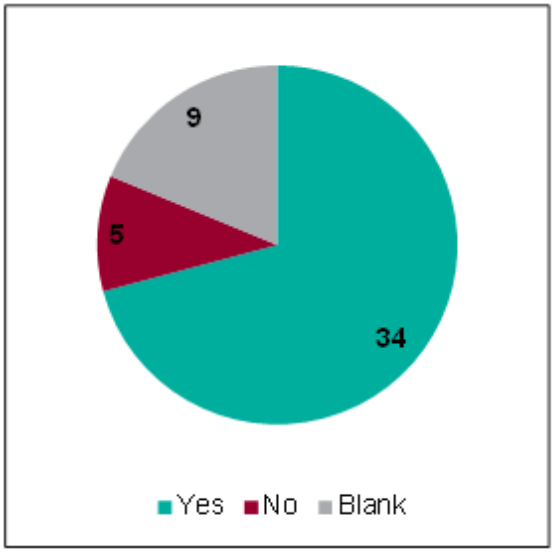




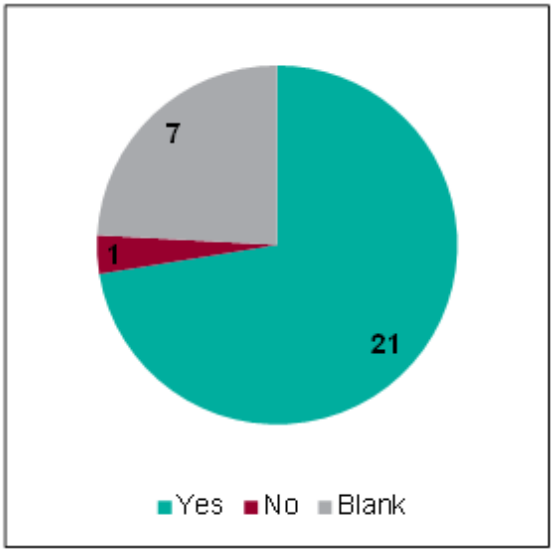
LSMDT (n = 17) *SSMDT (n = 11)*

1.7.41 Photography

Figure 27: Do you use photography in the pigmented lesion clinic or skin cancer clinic to aid in early detection of change?

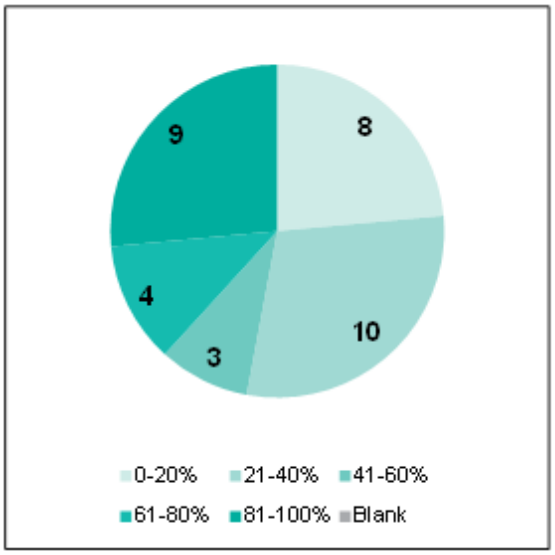


LSMDT (n = 48)

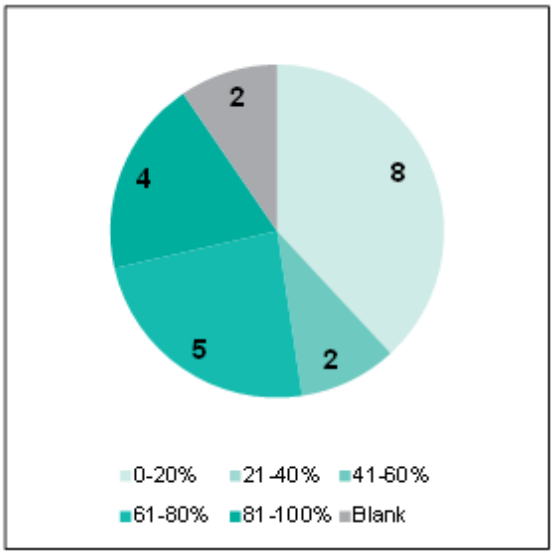


SSMDT (n = 29)

Figure 28: Could you estimate what percentage of patients with pigmented lesions who attend the clinic have photographs?

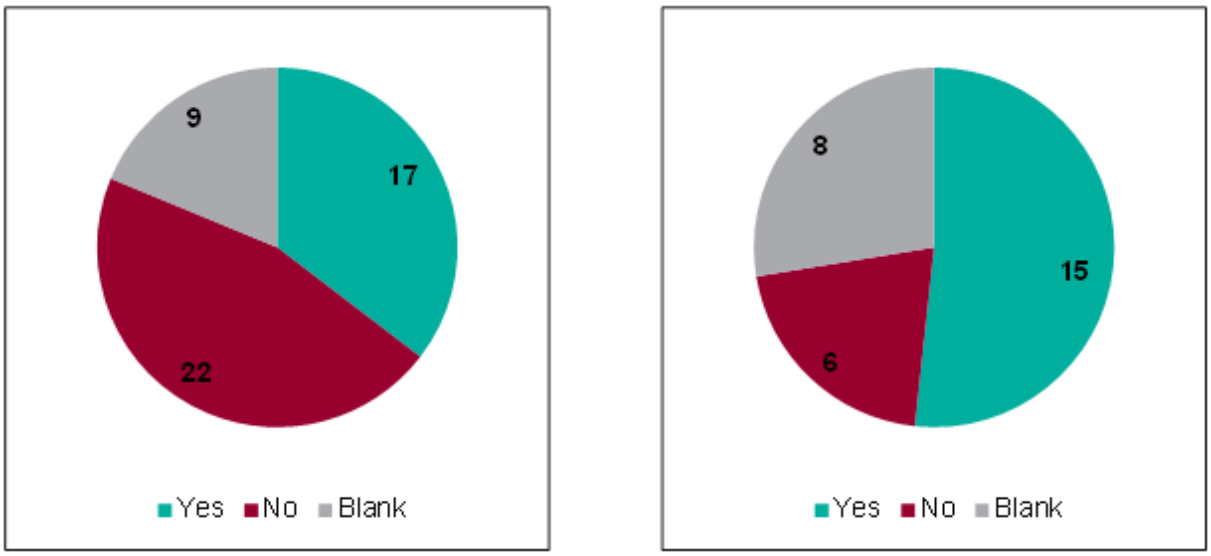


LSMDT (n = 34)



SSMDT (n = 21)

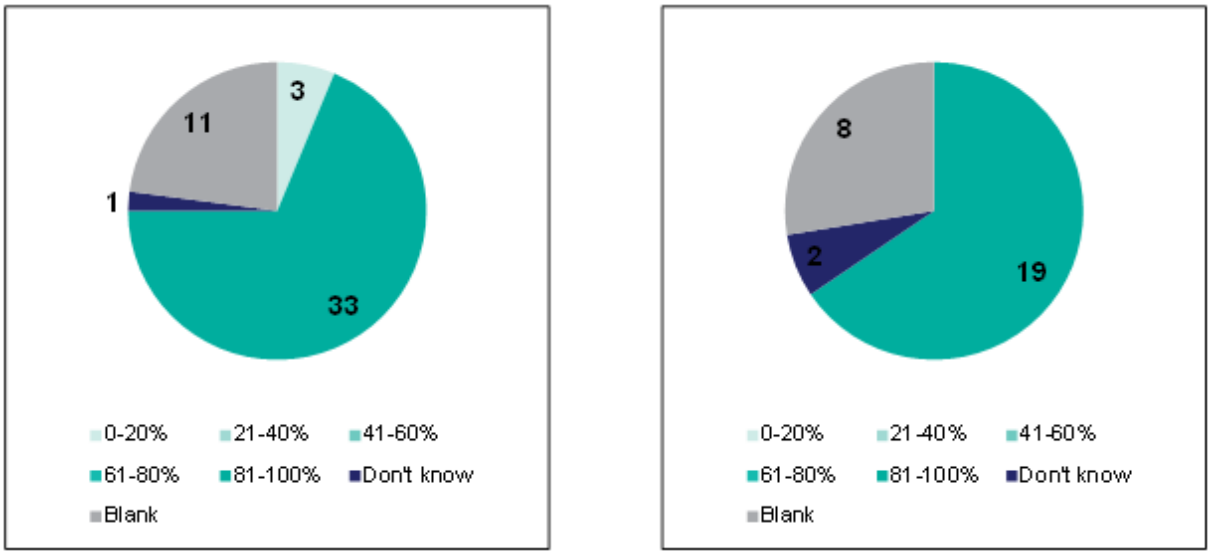
Figure 29: Do you have access to photography using a dermoscope?



LSMDT (n = 48) *SSMDT (n = 29)*

1.7.5 Patient support

Figure 30: Roughly what percentage of the MDT's melanoma patients are given the name and contact details of a skin cancer clinical nurse specialist (CNS) at diagnosis?



LSMDT (n = 48) *SSMDT (n = 29)*

Figure 31: What written information do you provide to patients?

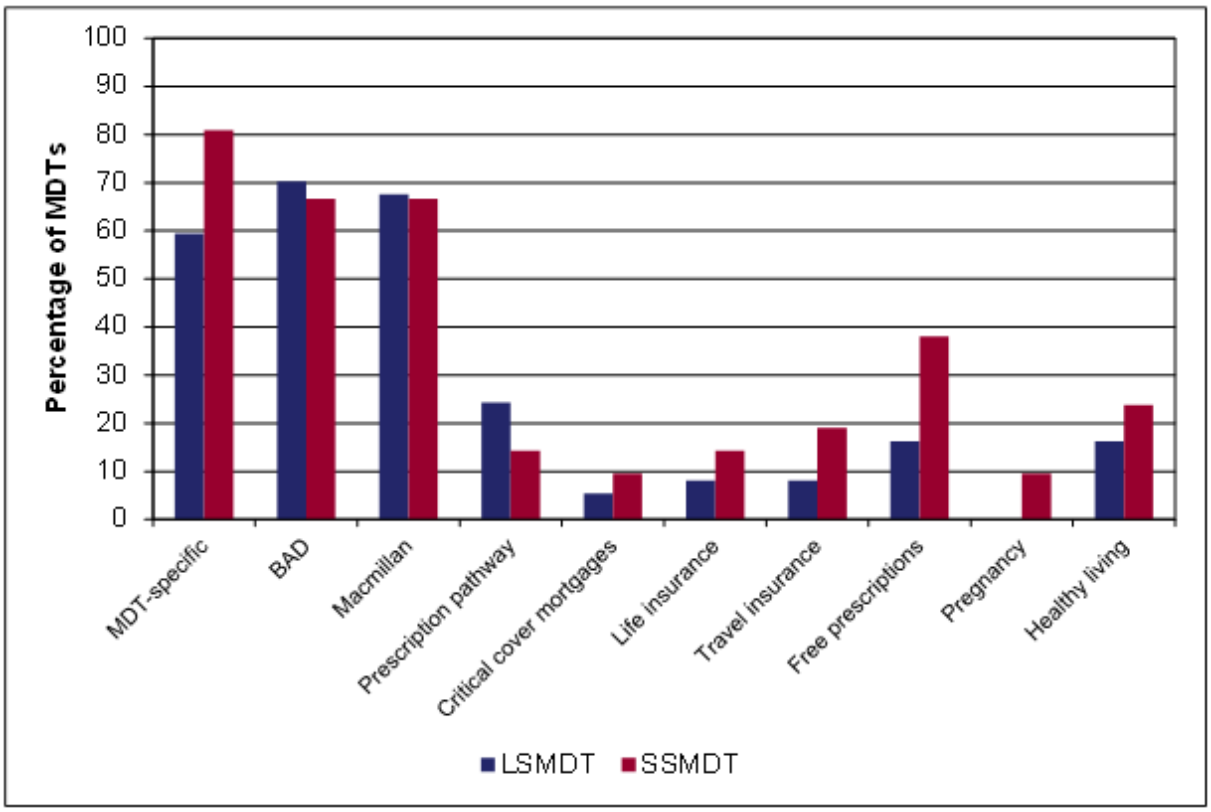
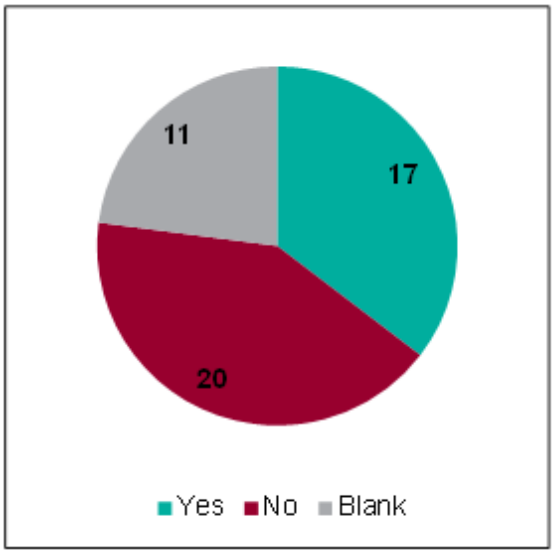
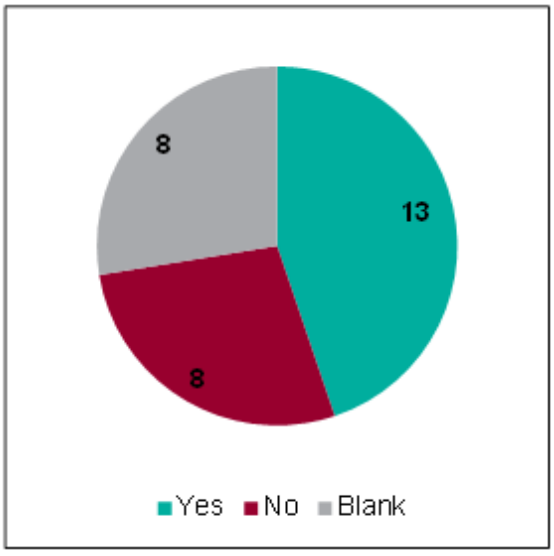


Figure 32: Do you give specific advice to melanoma patients about support groups?



LSMDT (n = 48)



SSMDT (n = 29)

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Mistry M, Parkin DM, Ahmad AS and Sasieni P. (2011) Cancer incidence in the United Kingdom: projections to the year 2030. British Journal of Cancer. 105, 1795-1803.

Pohar Perme M, Stare J and Esteve J. (2012) On estimation in relative survival. Biometrics. 68, 113-120.

2 Communication and support

The way in which patients are given their diagnosis is thought to be very important and significantly impacts on the patient's experience. It is accepted that a melanoma diagnosis should be given in a "face to face" consultation and that healthcare professionals need training in this particular skill and it is thought important that the patient should be given the opportunity to bring a friend or relative with them. Children must be accompanied by their legal guardian.

Although the emotional impact of cancer diagnosis is often considerable, the psycho-social support needs vary from patient to patient. Holistic needs assessment (HNA) is a tool, which is currently used to measure patient needs and as a means to open up communication between the patient, their carers or relatives and healthcare professionals. It is thought that this can help healthcare professionals, when appropriately trained, to recognise depression and other symptoms of distress and then to treat or to refer patients to additional sources of help, such as psychosocial support. Specific support for children, teenagers and young people should be facilitated through paediatric or teenage and young adult services (see NICE cancer service guidance on 'Improving Outcomes in Children and Young People with cancer') including advice on the effects of their illness on education.

Treatment decision making soon after diagnosis, may pose a particular challenge to patients and their carers or family, and so high quality, individualised, evidence based, stage specific information should be provided to enable informed patient choice. Patients do vary in how much detail they require but information empowers decision-making. It is accepted that the patient should be given time to consider the information and the various options, and if necessary to discuss with the clinical nurse specialist, their general practitioner or friends and family. Signposting to evidence-based sources of information, including web based, at this point is therefore thought crucial.

The Clinical Nurse Specialist (CNS) or Key Worker is a very important provider of information (Information Prescription) about the multidisciplinary team, the significance of results, stage specific information, treatment and side effects, local psycho-social support, free prescriptions/ benefits and contact details (see NICE cancer service guidance on 'Improving Outcomes for people with skin tumours including melanoma' and NHS England's 'Manual for Cancer Services skin measures version 1.2').

During and after treatment, information and support needs are thought likely to change and appropriate information would be required for each individual at each stage. Specific information may be required on managing problems such as lymphoedema, wound care, drug side effects or financial issues (life and travel insurance, mortgages, loans) and for patients at eventual discharge from follow-up. There may be specific survivorship concerns for patients at discharge including, long-term care planning, and educational interventions (see the National Cancer Survivorship Initiative document 'Living with and beyond cancer: Taking action to improve outcomes') and these should be assessed and discussed during holistic needs assessment before discharge.

Although there are many sources of written information, the 2012-13 Cancer Patient Experience Survey (CPES) indicated that 15% of skin cancer patients reported that they were not given written information about their cancer. This survey only collected data from patients who were inpatients or day cases. The survey of skin cancer MDTs carried as part of the needs assessment for this guideline (Appendix G) shows some variation in the provision of information and access to CNS.

Two recent UK studies (Molassiotis et al, 2014; Stamataki et al, 2014) showed that melanoma patients currently have significant unmet needs, irrespective of melanoma stage mainly in the psychosocial support, information/education, and physical health domains, contributing and leading not uncommonly to anxiety and depression. This poses challenges

for healthcare professionals working with this patient group and different ways of providing support and information may need to be considered.

Clinical questions:

- **What are the specific information needs of people with melanoma and their carers at different milestones/points in the patient pathway?**
- **What are the specific support needs of people with melanoma and their carers at different milestones/points in the patient pathway?**

Clinical evidence

Information needs

Timing of information

In one UK based survey (Stamataki et al, 2014) participants reported feeling there was no standard procedure for when patients were provided with information. Some participants reported getting too much information up front and some participants felt that information was provided too late, particularly in the case of sun protection advice.

Information needs at diagnosis

In the Cancer Patient Experience Survey (2012-2013), despite scoring highly in comparison to other cancers, around 15% of patients with melanoma felt they were not given clear information about their cancer or test results.

A UK based study (Stamataki et al, 2014) found that patients felt they could not comprehend the information provided about their prognosis or stage and this contributed to feelings of anxiety and uncertainty for the future.

Information needs during treatment

In the Cancer Patient Experience Survey (2012-2013) the experience of patients with melanoma ranked the lowest amongst cancer types for being given written information about side effects (68%) and being told they could get free prescriptions (56%).

Information needs during follow-up

Follow-up clinics were reported to be an important source of information about sun-related behaviours (Rychetnik et al, 2013) – the clinic doctor, books & magazines and the clinic nurse being the main sources. Some patients reported a lack of confidence in skin self examination in Olivera et al, (2013).

In the Cancer Patient Experience Survey (2012-2013) 13% of patients with melanoma felt that they were not given clear information about what to do after discharge.

In a UK-based study (Stamataki et al, 2014) patients reported a strong desire for more detailed information on sun protection. They reported feeling that the information provided was not detailed enough and did not cover issues such as travelling to hot countries, type of sunscreen and frequency of sunscreen application.

Source of information

In a survey of melanoma survivors (Hamilton et al, 2014) 90% of patients (n=28) had used the internet as a source of melanoma information. 69% of patients chose melanoma websites based on top hits returned by searches; 42% chose websites from a known reputable source and 15% chose websites based on recommendations from doctors or health care providers.

52% of internet users reported that internet use affected their specialist consultation by helping their decision making while 37% felt it did not influence their decision making and 7% considered it to make their decision more difficult (Hamilton et al, 2014).

Ease of access was considered the main strength of the internet (74%) followed by the volume and detail of information (52%), discussion of different perspectives/options (37%) and anonymity (7%) but 54% of users reported that the available information was difficult to understand (Hamilton et al, 2014)

Support needs

General support needs

There was consistent evidence that around 20% to 30% of patients with melanoma experience clinically significant levels of distress (Cornish et al., 2009, Kaspariain et al., 2009; Rychetnik et al., 2013). Rychetnik et al. (2013) reported that around half of patients surveyed would be interested in professional emotional support, preferably from their doctor rather than a psychiatrist or psychologist.

In the Cancer Patient Experience Survey (2012-2013) around 25% of patients with melanoma felt that emotional support was insufficient from hospital and GP practice staff. In the survey 85% of melanoma patients said that hospital staff gave them information about support groups but only 57% said hospital staff gave them information about financial support.

One cross-sectional study carried out in two UK centres (Molassiotis et al, 2014) reported that young patients had higher unmet needs relating to the psychological domain ($p<0.001$). Participants with lymph node involvement expressed significantly higher levels of unmet needs for physical and daily living ($p<0.001$), psychological needs ($p=0.045$), sexual needs ($p=0.015$) and overall score for needs ($p=0.006$). Psychological needs were the most common unmet needs particularly fears about cancer spreading (29%) and uncertainty about the future (25.2%).

Support needs at diagnosis

In a systematic review of qualitative studies, Barker (2011) reported that on receiving a diagnosis of skin cancer individuals experience strong emotional responses including anxiety, shock and panic. In a systematic review of quality of life studies in melanoma, Cornish et al (2009) noted that the immediate period following diagnosis was often associated with impairment in health related quality of life, with patients reporting increased pain, less energy and physical or emotional distress which impaired social functioning.

In the Cancer Patient Experience survey 64% of melanoma patients said they were told they could bring a friend with them when they were first told they had cancer; which was the lowest proportion of all the cancer types.

During treatment

Barker et al (2011) noted that once the initial emotional response to a skin cancer diagnosis had subsided individuals typically expressed satisfaction with their experience of care. Cornish et al. (2009) reported that during this phase patients were more likely to be anxious about disease recurrence than the physical limitations related to melanoma or its treatment.

During follow-up

There was evidence that follow-up was a source of both anxiety and reassurance for patients with melanoma. Psychological distress was reported during follow-up, potentially interfering with adherence to screening and preventative behaviours (Cornish et al, 2009; Olivera et al, 2013; Rychetnik et al, 2013) and some people delayed seeking medical advice for their skin cancer symptoms (Barker, 2011). In the Rychetnik et al (2013) systematic review around half

of surveyed patients said that follow-up appointments made them anxious (with clinically significant levels in approximately 20% of patients). This was sometimes accompanied by physical symptoms and sometimes started weeks before the appointment. Overall satisfaction with follow-up, however, was high and receiving good news from physician screenings was reassuring (Olivera at al, 2013; Rychetnik et al, 2013).

Clinical questions:

- **What are the most effective ways of meeting the patients information needs?**
- **What are the most effective ways of meeting the patients support needs?**

Interventions for information

Evidence about educational interventions for patients with melanoma came from a systematic review by McLoone et al (2013) which included five randomised controlled trials (RCTs) and five other studies. Most interventions involved a personal or group instruction session from a nurse, GP or dermatologist which was also reinforced by printed information. One study examined whole body photography as an aid to skin self examination (SSE).

Educational interventions were typically associated with increased melanoma knowledge, better adherence to SSE and better satisfaction with care, but not in all cases. Purely educational interventions did not appear to affect anxiety, depression or psychosomatic symptoms, in the studies that measured these outcomes.

Differences between the interventions used in the studies and the way outcomes were measured makes it difficult to identify the effective components of a successful educational intervention.

Interventions for support

Evidence from a systematic review of three randomised trials (McLoone et al, 2013) suggests uncertainty about the effectiveness of clinical psychologist or psychiatrist led cognitive behavioural therapy (CBT) for improving psychological well-being among people with melanoma. One qualitative study described a telephone peer-support intervention for people with melanoma, which both the patients and their supporting peers viewed as effective.

Combined information and support interventions

Three randomised controlled trials evaluated variations in the same combined educational and psychological intervention (McLoone et al, 2013). Each of these studies reported decreases in distress (anxiety, depression, hostility, and mood disturbance). The largest of these trials, however, reported only short-term emotional and physiological benefits, and there were no long term group differences in survival or time to recurrence. In a fourth randomised trial, participants who attended an average of 19 sessions with an oncology counsellor over a period of 6 months reported a greater decline in anxiety, hostility and depression than a control group.

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**To help people make decisions about their care, follow the recommendations on communication, information provision and support in NICE's guideline on improving outcomes for people with skin tumours including melanoma, in particular the following 5 recommendations:** • **'Improved, preferably nationally standardised, written information should be made available to all patients. Information should be appropriate to the patients' needs at that point in their diagnosis and treatment, and should be repeated over time. The information given must be specific to the histopathological type of lesion, type of treatment, local services and any choice within them, and should cover both physical and psychosocial issues.'** • **'Those who are directly involved in treating patients should receive specific training in communication and breaking bad news.'** • **'Patients should be invited to bring a companion with them to consultations.'** • **'Each LSMDT [local hospital skin cancer multidisciplinary team] and SSMDT [specialist skin cancer multidisciplinary team] should have at least one skin cancer clinical nurse specialist (CNS) who will play a leading role in supporting patients and carers. There should be equity of access to information and support regardless of where the care is delivered.'** • **'All LSMDTs and SSMDTs should have access to psychological support services for skin cancer patients.'** **Follow the recommendations on follow-up in NICE's guideline on improving outcomes for people with skin tumours including melanoma, in particular the following 2 recommendations:** • **'All patients should be given written instruction on how to obtain quick and easy access back to see a member of the LSMDT/SSMDT when necessary.'** • **'All patients should be given both oral and written information about the different types of skin cancer and instruction about self-surveillance.'** **Give people with melanoma and their families or carers advice about protecting against skin damage caused by exposure to the sun while avoiding vitamin D depletion.** **Carry out a holistic needs assessment to identify the psychosocial needs of people with melanoma and their needs for support and education about the likelihood of recurrence, metastatic spread, new primary lesions and the risk of melanoma in their family members.** **Follow the recommendations on communication and patient-centred care in NICE's guideline on patient experience in adult NHS services.**
Relative value placed on the outcomes considered	The GDG considered health related quality of life, patient satisfaction, treatment decision making and patient reported outcomes to be the best measures of the effectiveness of assessing and delivering information and support.
Quality of the evidence Trade off between clinical benefits and harms	The quality of the evidence was assessed using the NICE qualitative study checklist for studies of information and support needs and GRADE was used for studies comparing different ways

	of delivering information and support. While there was high quality qualitative evidence about information and support needs, the evidence about the effectiveness of interventions for delivering information and support was of low to moderate quality. Several issues with the evidence were noted. The 2013 National Cancer Patient Experience Survey excluded outpatients, who comprise a significant proportion of patients with melanoma. The survey also did not report results according to disease stage. The GDG were therefore limited in the conclusions they could draw from the National Cancer Patient Experience Survey. In the comparative studies of information and support delivery, differences in the interventions and outcomes used made it difficult to identify the effective components. This meant that the GDG could not make specific recommendations about psycho-educational support. Melanoma is increasing in incidence and the age distribution curve is such that many cases occur in younger adults. Therefore there is a rapidly increasing survivor population. Melanoma may recur however many years after diagnosis and patients are aware that they need to continue to monitor their lymph nodes for recurrence and their skin for new melanomas. There are a number of issues therefore that are particular to melanoma and although the need for assessment of the patients' psychosocial needs applies to all cancer patients, the GDG felt that it was especially important to recommend assessment and the identification of suitable support for melanoma patients. The GDG were aware there was no evidence demonstrating the effectiveness of any particular holistic needs assessment tool. However they noted the Cancer Action team in England had published a relevant holistic needs assessment tool (see - http://www.ncsi.org.uk/wp-content/uploads/The_holistic_needs_assessment_for_people_with_cancer_A_practical_Guide_NCAT.pdf) which forms part of their peer review standards. No health economic evidence was identified.
Trade off between clinical benefits and harms	The GDG considered the benefits of the recommendations and agreed that patients would be better informed, with an increased likelihood of likely better quality of life, less anxiety, potential for earlier identification of recurrence and preventative behaviour modification if they had access to appropriate information. The GDG thought that there is a chance of increasing patient anxiety as a result of offering advice to carry out self-surveillance for recurrent or new primary tumours. However the GDG felt the benefits outweighed the relatively small risks that had been identified.
Trade off between net health benefits and resource use	No health economic model was developed for this topic. The GDG believed that there may be costs associated with the implementation recommendations in Improving outcomes for people with skin tumours including melanoma including the provision of psychological support. The GDG postulated that these costs could be offset to a degree by reduced treatment costs due to earlier

	detection of recurrence or new primary tumours by better informed patients.
Other considerations	The GDG considered that there would only be a modest change in practice. The GDG felt that the support and follow-up recommendations in Improving outcomes for people with skin tumours including melanoma were still important and relevant and required reemphasis within this guideline. No equalities issues were identified.

References

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3 Diagnosing melanoma

3.1 Dermoscopy and other visualisation techniques

The earlier a melanoma is diagnosed and removed, the more likely the patient is to be cured. Until 20 years ago, melanoma was diagnosed from history and clinical examination alone. A number of new techniques have been developed recently to improve detailed inspection of skin lesions showing atypical features. Dermoscopy (dermatoscopy) is now widely used by skin cancer MDT members and some primary care doctors with an interest in dermatology. Although it appears that the use of dermoscopy in specialist hands can improve diagnostic accuracy, this may not be the case for less experienced practitioners. New technologies have been developed using dermoscopic images and artificial intelligence systems to replace clinical inspection but their diagnostic accuracy is uncertain. The GDG wanted to consider whether dermoscopy is now an essential tool for diagnosing melanoma and whether any of the other new techniques, such as artificial intelligence systems and confocal microscopy, have a role. It is also unclear whether the use of teledermatology with 'store and forward' images (including dermoscopic images) can be used to diagnose melanoma effectively.

Clinical question: To what extent can the diagnostic accuracy of, history-taking and visual examination for the clinical identification of melanoma be improved by dermoscopy or/and new visualisation techniques?

Clinical evidence

The evidence is summarised in Tables 10 and 11.

High quality evidence (Vestergaard 2008; Rosendahl et al, 2011) suggests that dermoscopy is both more sensitive and more specific in classifying lesions as melanoma versus not melanoma than clinical examination with the naked eye alone.

Evidence suggests that reflectance confocal microscopy (Stevenson et al, 2013) is more sensitive than dermoscopy (Vestergaard 2008) but less specific in classifying lesions as melanoma versus not melanoma.

There is uncertainty over whether computer aided diagnosis can improve upon the diagnostic accuracy of dermoscopy in classifying lesions as melanoma versus not melanoma. The results from studies of computer aided diagnosis using spectophotometry (Monheit et al 2011; Glud et al 2009) suggest their algorithms were optimised for high sensitivity at the expense of specificity.

Studies excluded lesions in sites that were inaccessible to the imaging technique used. In such lesions cases clinical examination with the naked eye would be the only option. There is also a test failure rate associated with computer aided diagnostic algorithms: Perrinaud et al (2007) reported failure rates ranging from 5% to 32% of lesions depending on which system was used.

There was inconsistent evidence about the accuracy of teledermoscopy. Some studies report relatively high diagnostic accuracy for classification of melanoma versus not melanoma (Piccolo et al, 2004; Tan et al, 2010). Warshaw et al (2009), however, reported a significant proportion of melanomas would be mismanaged with potentially serious consequences on the basis of teledermatology (19% for macro images alone, 6% if polarised light dermatoscopy was added, 16% if contact immersion dermatoscopy was added).

Table 10: Summary diagnostic accuracy statistics

Test	N studies	N lesions	Sensitivity* [95% C.I.]	Specificity* [95% C.I.]	PPV†	NPV†	LR+	LR-
Naked eye clinical examination	8	5628	70% [58-80%]	82% [57-94%]	35%	95%	3.89	0.37
Dermoscopy	12	6535	88% [83-91%]	88% [74-95%]	50%	98%	7.33	0.14
Reflectance confocal microscopy	5	910	93% [89-96%]	76% [68-83%]	35%	99%	3.88	0.09
Artificial intelligence using dermoscopy images	5	1317	78% [67-86%]	85% [78-90%]	41%	97%	5.20	0.26
Artificial intelligence using spectrophotometry images	2	1715	97% [91-99%]	29% [4-82%]	16%	99%	1.37	0.10

**Using bivariate meta-analysis (Reitsma et al 2005); †Assuming melanoma prevalence of 12% (the average prevalence across the dermoscopy studies, range was 3% to 22%)*

Table 11: Illustration of trade off when using tests to select pigmented lesions for biopsy in a cohort of 1000 lesions*

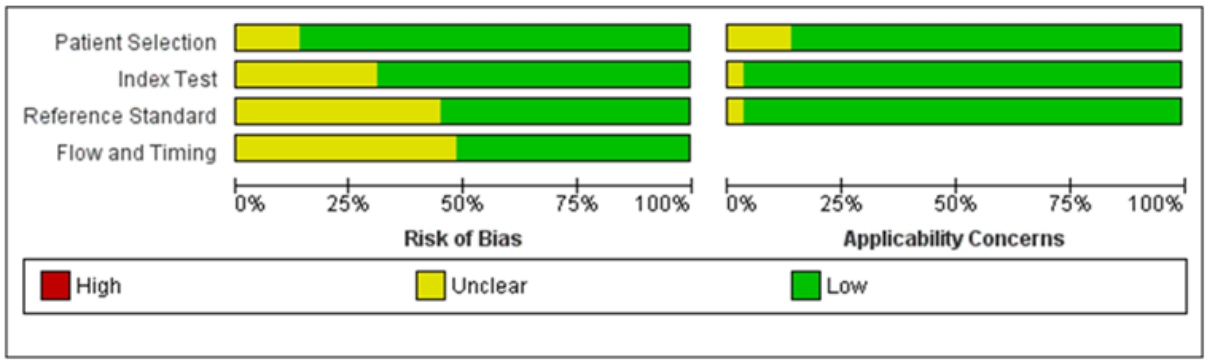
Test	Benign lesions selected for biopsy	Melanomas not selected for biopsy (missed)
Naked eye	158/880 (18%)	36/120 (30%)
Dermoscopy	106/880 (12%)	14/120 (12%)
Reflectance confocal microscopy	211/880 (24%)	8/120 (7%)
Computer aided dermoscopy	132/880 (15%)	26/120 (22%)
Computer aided spectophotometry	625/880 (71%)	4/120 (3%)

**The trade off between sending benign lesions for biopsy/histopathology and the risk of missing melanomas is illustrated using a hypothetical cohort of 1000 pigmented skin lesions with a melanoma prevalence of 12%, combined with the diagnostic accuracy data from Table 1*

Study quality and characteristics

Risk of bias and applicability were assessed using QUADAS-2 (Figure 33) the majority of studies were at low risk of bias with low concerns about applicability. The setting of the studies was as follows: primary care (Argenziano et al, 2006; Walter et al, 2012; Rosendahl et al, 2011; Moreno-Ramirez et al 2007), initial tests in secondary care: (Vestergaard, 2008; Benelli, et al 1999; Bono et al, 2002; Bono et al, 2006; Carli et al, 2003; Carli et al, 2004; Cristofolini et al, 1994; Dummer et al, 1993; Stanganelli et al, 2000; Driesetl et al, 2009; Barzegari et al, 2005; Fueyo-Casado et al, 2009; Warshaw et al, 2009; Piccolo et al, 2004; Tan et al, 2010; Borve et al, 2013) and further tests for equivocal lesions in secondary care (Ascierto et al, 2010; Perrinaud et al, 2007; Glud et al, 2009; Monheit et al, 2011; Stevenson et al, 2013).

Figure 33: Risk of bias and applicability (QUADAS-2)



Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Assess all pigmented skin lesions that are referred for further assessment, and during follow-up, using dermoscopy carried out by healthcare professionals trained in this technique.** **Do not routinely use confocal microscopy or computer-assisted diagnostic tools to assess pigmented lesions.** **See also recommendations on follow-up in section 8.1.**
Relative value placed on the outcomes considered	The GDG considered test sensitivity (not missing melanoma) and specificity (avoiding unnecessary excisions) to be the most important outcomes for this review question.
Quality of the evidence	The quality of the evidence was moderate to high using QUADAS-2. The research studies examined each test's ability to discriminate melanoma from non-melanoma lesions but in clinical practice these tests are used to select lesions for biopsy rather than requiring absolute accuracy. This issue was common across tests and did not influence the recommendations. No evidence was presented about the influence of reader variability or level of experience on diagnostic accuracy and so the GDG based their recommendation about dermoscopy training on their own clinical experience.
Trade off between clinical benefits and harms	The GDG agreed that the benefits of the recommendations would outweigh the harms such as false negative diagnoses. Use of a more sensitive and specific combination of tests should lead to earlier diagnosis of melanomas (with better prognosis) as well as a reduced biopsy rate for benign lesions.
Trade off between net health benefits and resource use	No health economic evidence was found for this question and no model was developed. The group considered that improvements in diagnostic accuracy and the associated reduction in the costs of unnecessary surgery and histopathology would outweigh the costs of equipment, training and clinical time. There are also potential cost savings in not routinely using confocal microscopy or computer aided diagnosis in this setting. Confocal microscopy is being developed in clinical practice in some countries in the management of some patients such as those with lentigo maligna, and its clinical role may eventually be established.

	However the clinical time required and the cost of the equipment is such that routine use was not recommended. The group believed that the recommendations would lead to an increased use of dermoscopy across the different specialties responsible for diagnosis and management of pigmented skin lesions and that dermoscopy training would need to be increased or consolidated. The routine use of confocal microscopy was not recommended because of its potential cost and relatively high false positive rate.
Other considerations	No equalities issues were identified for this topic.

3.21 Photography

Melanoma typically presents as a new enlarging pigmented lesion or as a change in size, shape or colour of an existing melanocytic naevus (mole). Early diagnosis and treatment is associated with better survival.

Assessing change in moles can be difficult both for patients and healthcare professionals. Monitoring moles by sequential photography might be helpful, especially in patients with a large number of moles. It is common practice to use dermoscopic pictures in combination with ordinary close-up pictures that show the measurements of the mole. Additionally, general photographs of the skin to 'map' where moles are on the body might help patients and professionals to notice when new moles are appearing and growing. This is called mole mapping, and mole mapping services, probably of quite variable quality, are provided by a range of private providers as well as within some units in the NHS.

The GDG was also uncertain about the most appropriate timing for sequential photography (with or without dermoscopic images) to detect significant change in a pigmented lesion in order to diagnose early melanoma.

The survey of skin cancer MDTs carried as part of the needs assessment for this guideline (Appendix G) showed that although there is generally good access to photographic services, there is variable use of photography for patients with pigmented lesions and that a significant proportion of MDTs reported its use in less than 20% of patients. No access to dermoscopic photography was reported in 22 of 48 LSMDTs and 6 of 29 SSMDTs.

Clinical question: Is photography an effective method of detecting progression of pigmented lesions, including dermoscopy pictures?

Clinical evidence

The evidence is summarised in Table 12.

Thickness of melanoma

One randomised controlled trial, one cohort study and two retrospective studies examined the thickness of melanoma after excision, in patients in whom photography had been used in the monitoring process, compared to patients that had not had photography. All of the studies found that the melanomas excised were thinner in the photography patients.

In the randomised trial (Del Mar et al 1995) over 50 medical practitioners, mostly in general practices, in two cities in Queensland, Australia were recruited into the trial. Practitioners in one city randomised to receive the intervention were provided with an algorithm for clinical management of patients with suspicious moles and a Polaroid instant camera. Pathology reports of all lesions excised during the 2 year intervention period were obtained and

analysed. The median thickness of melanomas excised in the intervention group (photography) was 0.50 mm compared with 0.60mm in the control group (no photography).

In the cohort study (Drugge et al 2009) an assessment of melanoma thickness was compiled from 6 melanoma biopsy cohorts which had undergone different clinical screening methods. The test cohort included patients who were screened using photography yearly, two cohorts represented melanoma biopsies obtained from separate pathology laboratories and the other 3 cohorts were from outside non-dermatologist physician referrals, patients who were self-refereed and a cohort of patients followed by a dermatologist but without photographic screening. The photography cohort had significantly thinner melanomas (0.13-1.4 mm thinner) compared to the 3 other clinical screening groups as well as the 2 pathology laboratory cohorts.

In the retrospective study (Salerni et al 2011) clinical and dermoscopic characteristics of 215 melanomas consecutively excised over a 2-year period were analysed. Melanomas diagnosed in patients in a follow-up programme (total body photography and digital dermoscopy) were compared with melanomas diagnosed in patients not in the follow-up programme over a 2 year period and were found to be 1.17mm thinner (mean thickness 0.55mm compared to 1.72mm).

In another retrospective study (Rademaker et al 2010) 52 invasive melanomas identified from the molemap NZ database (which involved whole body photography and sequential digital dermoscopy) were compared to 15839 invasive melanomas detected by traditional methods as reported to the new Zealand cancer registry and were found to be 0.20mm thinner (mean thickness 0.67mm compared to 0.87 mm). The study also examined proportions of melanomas at different thicknesses. 69% of melanomas from patients who had photography and 52% of melanomas from patients who did not have photography were less than 0.75mm. 2% of melanomas from patients who had photography and 11% of melanomas from patients who did not have photography were thicker than 3mm

Clinical stage of melanoma

One randomised controlled trial and one retrospective study examined the stage of melanoma in patients that had photography compared to patients that had not had photography.

In the randomised trial (Del Mar et al 1995) it was found that there was no difference in the percentage of invasive melanomas excised (72%) in the intervention group (photography) compared with the control group (no photography).

In the retrospective study (Salerni et al 2011) 30% of melanomas were invasive melanomas in the patients that had photography compared with 72% in patients without photography. The study also looked at the melanomas in greater detail and classified them according to the American joint committee on cancer staging system. In patients with photography 70% presented at as stage 0 at diagnosis and 30% at stage IA. No melanomas were diagnosed above this stage. However in patients without photography 27.9% presented at stage 0 at diagnosis, 37.6% at stage IA, 12.7% at stage IB, 10.9% as stage II, 8.5% at stage III and 2.4% at stage IV.

Table 12: GRADE profile: Is photography an effective method of detecting progression of pigmented lesions, including dermoscopy pictures?

Quality assessment							Summary of findings				
							No of melanomas excised		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Photography	No photography	Relative (95% CI)	Absolute	Quality
Stage of melanoma											
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	50	165	-	42% more *in situ* melanomas in patients that had photography compared to those who did not have photography.	LOW
Stage of melanoma											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	113	-	No difference in the numbers of *in situ* and invasive melanomas between patients that had photography compared to those who did not have photography.	MODERATE
Thickness of melanoma											
3	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	118	17846	-	Breslow depth of melanoma was 0.1 – 1.4 mm	LOW

Quality assessment							Summary of findings				
							No of melanomas excised		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Photography	No photography	Relative (95% CI)	Absolute	Quality
										thinner in patients that had photography compared to those who did not have photography.	
Thickness of melanoma											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114	113	-	Median Breslow depth of melanoma was 0.1mm thinner in patients that had photography compared to those who did not have photography.	MODERATE

[1] *Retrospective cohort study;* [2] *Bias - For the two retrospective studies and one cohort study there is selection bias in that it is high risk patients that are included in screening programs with photography. If these patients are at high risk the practitioner may be more likely to excise the lesion anyway and so we would expect to observe melanomas diagnosed at an earlier stage in this group of patients. The randomised trial is not subject to this bias. However it is not without its own limitations in that there is one city in each arm of the trial - ideally several cities would have been randomised to each arm. Also as the study cannot be blinded and practitioners know they are in the intervention city this could also introduce bias. Furthermore it is possible that the study underestimated the full potential of photography because of the duration of the follow up and review (4-8 weeks) may not have been long enough for the photography to detect morphologic change of atypical moles, given that many melanomas are slow growing*

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendation	**For a clinically atypical melanocytic lesion that does not need excision at first presentation:** • **use baseline photography (preferably dermoscopic) and** • **review the clinical appearance of the lesion, using the baseline photographic images, 3 months after first presentation to identify early signs of melanoma.**
Relative value placed on the outcomes considered	The GDG considered stage at diagnosis to be the most important outcome when drafting the recommendations because of the survival benefits associated with diagnosing melanoma at an earlier stage. There was no evidence relating to the outcome of time to diagnosis reported in the literature for this question. The outcome of Breslow thickness was not specified in the review question but was reported in the evidence and it was considered useful as an indirect measure of disease stage.
Quality of the evidence	The quality of the evidence for both of the reported outcomes of stage of melanoma and thickness of melanoma was low-moderate as assessed using GRADE. The reviewer did not highlight to the GDG any specific issues with the evidence that might have affected the results presented. No health economic evidence was identified for this topic.
Trade off between clinical benefits and harms	The recommendations made by the GDG should provide patients with an earlier diagnosis of melanoma and potentially a better prognosis. The recommendations should also reduce the rate of biopsy of benign lesions. As a consequence of the recommendations, however, there may be increased investigation of benign lesions. The GDG concluded that the benefits of earlier diagnosis outweigh the negative aspect of over-investigation of benign lesions.
Trade off between net health benefits and resource use	No relevant cost effectiveness analyses were identified and this topic was not considered a priority area for development of an economic model. No cost effectiveness analysis was therefore carried out for this topic. The GDG thought that photography equipment, manpower, storage of images and data protection would be an additional cost. However there would be a reduction the number of surgical excisions and their associated costs
Other considerations	No equalities issues were identified for this topic. The decision about reviewing the patient with the photograph at a 3 month interval was made on GDG consensus in the absence of any clear evidence and a desire not to overburden existing services.

3.3 Borderline and spitzoid melanocytic lesions

Melanocytic lesions cause diagnostic difficulty in both clinical and histopathology practice. Early and accurate diagnosis is very important in their management, but may be difficult to achieve. There are a number of different 'borderline' lesions, which require thorough investigation. These include atypical melanocytic proliferations, unusual variations of well-known entities and melanocytic lesions presenting in unusual age groups. Spitzoid melanocytic lesions are one of the most challenging differential diagnostic subgroups of pigmented lesions, especially in the younger age group.

Clinico-pathological correlation is very important and, although histopathological diagnosis is the current gold standard, there have been significant improvements in clinical assessment with the more extensive use of dermoscopy. Immunohistochemistry and molecular genetics tests have also provided additional information. The use of genetic testing of the tumour tissue such as FISH (to detect patterns of copy number variation) and the detection of driver mutations (*BRAF*, *NRAS* and *HRAS*) increases the histopathologist's ability to categorise atypical spitzoid melanocytic lesions, but their usefulness in determining prognosis is unclear.

The positivity rate of sentinel lymph node biopsy appears from small studies of selected histologically atypical spitzoid lesions, to be similar to that for typical melanoma. Sentinel lymph node biopsy has prognostic value in melanoma patients and the GDG felt that it would be important to consider its usefulness in patients with atypical melanocytic lesions.

Clinical question: What is the best approach to resolving clinico-pathological diagnostic uncertainty for borderline or spitzoid melanocytic lesions?

Clinical evidence

Melanoma versus melanocytic nevi/naevus

Low quality evidence from two studies suggests that clinical assessment is more sensitive when using dermoscopy for detecting melanoma in populations with melanocytic naevi lesions (Carli et al. 2004; Krähn et al. 1998). Low quality evidence from one study showed that in patients with melanocytic lesions (atypical cellular blue nevi, atypical congenital nevi, atypical desmoplastic nevi, and combined nevi) 44% had a positive sentinel lymph node biopsy (Cochran et al. 2010).

Melanoma versus spitzoid melanoma

Low quality evidence from one study did not identify a genetic test (*BRAF* Exon 11, 15; *NRAS* Exon 2, 3; *HRAS* Exon 2, 3) that reliably discriminates between melanoma and spitzoid melanoma. Low quality evidence from two studies suggests that between 35% (Hung et al. 2013) and 56% (Paradela et al. 2009) of patients with spitzoid melanoma will have positive sentinel lymph node biopsies.

Melanoma versus Spitz nevi

Low quality evidence from five studies suggests that some genetic tests (FISH detection of, *BRAF* Exon 15, CGH and *NRAS* Exon 2) are potentially useful in discriminating between melanoma and Spitz nevi (Bastian et al. 2003; Hossain et al. 2011; Martin et al. 2012; Raskin et al. 2011; Van Dijk et al. 2005)..

Melanoma versus atypical Spitz nevi

Low quality evidence from one study suggests that genetic tests for *BRAF* Exon 15 mutation may have a role in discriminating between melanoma and atypical Spitz nevi (Van Dijk et al. 2005). Low quality evidence from three studies suggests that between 0% and 47% of patients with atypical Spitz nevi will have positive sentinel lymph node biopsies (Caraco et al. 2012; Ludgate et al. 2009; Urso et al. 2006).

Melanoma versus atypical Spitz tumour

Low quality evidence from two studies suggests that genetic tests (FISH and *BRAF* Exon 15) are potentially useful in discriminating between melanoma and atypical Spitz tumour (Masi et al. 2011; Raskin et al. 2011).

Spitzoid melanoma versus Spitz nevi

Low quality evidence from one study suggests that FISH is a potentially useful test in discriminating between spitzoid melanoma and Spitz nevi (Gill et al. 2004).

Spitzoid melanoma versus atypical Spitz nevi

Low quality evidence from one study suggests genetic tests involving *BRAF* Exon 15 may have a role in discriminating spitzoid melanoma from atypical Spitz nevi (Van Dijk et al. 2005). Low quality evidence from one study suggests that rates of positive sentinel lymph node biopsy of 26% and 35% in patients with atypical Spitz nevi and spitzoid melanoma respectively (Hung et al. 2013).

Spitzoid melanoma versus atypical Spitz tumour

Low quality evidence from two studies did not identify a genetic test (FISH; *BRAF* V600E) that reliably discriminates spitzoid melanoma from atypical Spitz tumour (Kerl et al. 2012; Fullen et al. 2006).

Atypical spitzoid nevomelanocytic versus typical Spitz nevi

Low quality evidence from one study did not identify a genetic test (*BRAF* V600E; *NRAS* Exon 2) that reliably discriminates atypical spitzoid nevomelanocytic from typical Spitz nevi (Emley et al. 2010).

Primary cutaneous melanoma and Spitz nevi

Low quality evidence from one study did not identify a genetic test (*BRAF* V600E; *NRAS*; *HRAS*) that reliably discriminates primary cutaneous melanoma from Spitz nevi (Takata, 2007).

Atypical spitzoid tumour

Low quality evidence from one study suggests that 28.6% patients with atypical spitzoid tumours will have positive sentinel lymph node biopsy (Murali et al. 2008).

Study quality and characteristics

Risk of bias and applicability were assessed using QUADAS-2 (Figures 34 to 36). Overall there was a low risk of bias with low concerns about applicability of the evidence. The primary areas for concern related to patient selection where the risk of bias was unclear in a number of studies. This was due to poor reporting in individual studies regarding the inclusion criteria for the patient sample in the individual studies. For studies of sentinel lymph

node biopsy, reporting of the index text was also an area of potential concern, with an unclear risk of bias though this is likely due to the fact that histopathological assessment is an inherent part of the SLNB procedure and therefore a specific index test is not necessary.

Figure 34: Risk of bias and applicability (QUADAS-2) - clinical assessment and dermoscopy

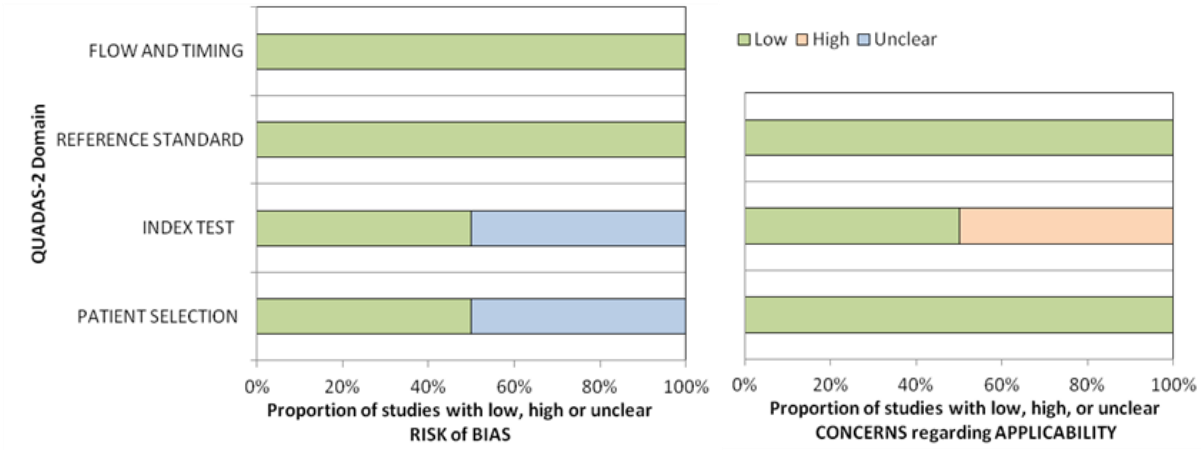


Figure 35: Risk of bias and applicability (QUADAS-2) - immunohistochemistry

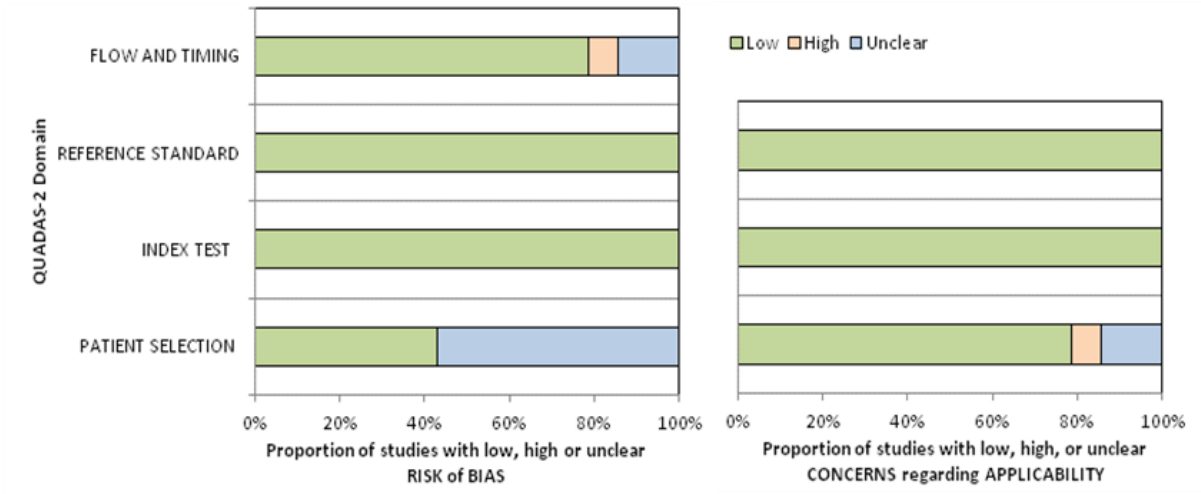
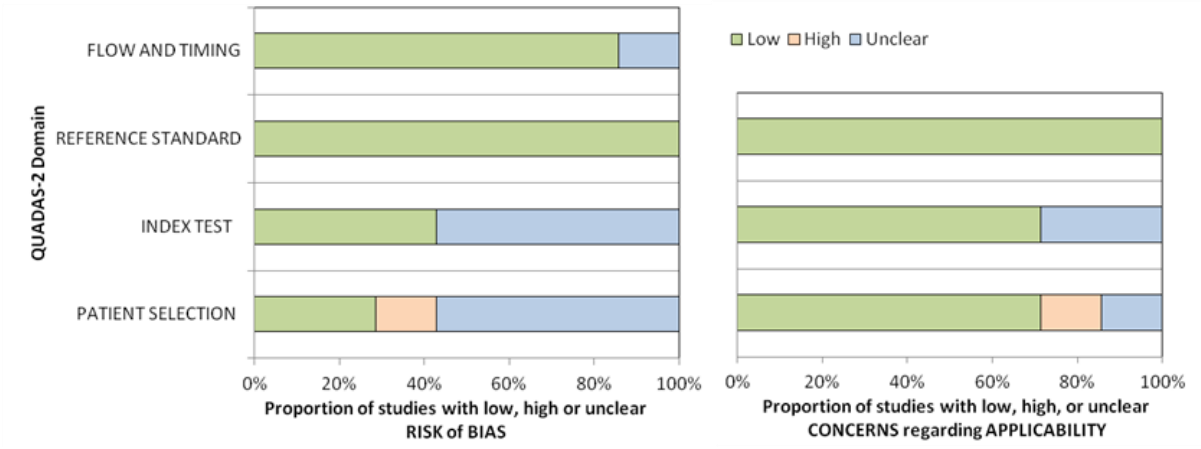


Figure 36: Risk of bias and applicability (QUADAS-2) – sentinel lymph node biopsy



Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Discuss all suspected atypical spitzoid lesions at the specialist skin cancer multidisciplinary team meeting.** **Make the diagnosis of a spitzoid tumour of unknown malignant potential on the basis of the histology, clinical features and behaviour.** **Manage spitzoid tumours of unknown malignant potential as melanoma.**
Relative value placed on the outcomes considered	Positive predictive value, negative predictive value, sensitivity and specificity of the tests were the outcomes the GDG considered to be the most important for this topic. Sensitivity and specificity estimates could be calculated for the evidence for clinical assessment versus dermoscopy (two studies) and the use of immunohistochemistry (14 studies). Positive and negative predictive values were calculated for the use of immunohistochemistry (14 studies) but could not be calculated to assess the use of clinical assessment versus dermoscopy (two studies). There was insufficient data to calculate the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of the use of sentinel lymph node biopsy (seven studies), limiting the usefulness of these outcomes in the drafting of the recommendations for this intervention. Reader variability and inter-observer variability were considered important to the GDG because of the possible impact on the other outcomes in this question, but none of the studies reviewed provided either outcome.
Quality of the evidence	The only data identified related to spitzoid melanocytic lesions and therefore the recommendations do not address other borderline lesions. The quality of evidence was rated as low for each outcome as assessed using the QUADAS-2 checklist for diagnostic studies. A number of issues were highlighted by the reviewer including a lack of good quality evidence. The literature base was composed entirely of retrospective case-series reviews (often thought to be of highly selected samples) and there were concerns about the risk of bias in these studies (because of poor reporting of patient selection). In addition, concerns were raised about the applicability of the samples used in the dermoscopy/clinical assessment alone interventions (patients with melanocytic lesions and not specifically Spitz/spitzoid) and in the studies of sentinel lymph node biopsy.

	Finally, the genetic test studies used varying terminology (e.g. Spitz tumour, Spitz naevi, atypical Spitz, atypical spitzoid) and multiple variations of driver mutations (e.g., *BRAF*; *NRAS*) which reduced the sample sizes in the comparisons and affected the ability to pool data across studies. As a result of the issues highlighted, the GDG felt that because of the low quality evidence and the selected nature of the samples used in the dermoscopy/clinical assessment alone interventions, they were unable to make appropriate recommendations about the use of dermoscopy in diagnosing people with atypical spitzoid lesions. The GDG were concerned about the applicability of the sentinel lymph node biopsy intervention studies because of the low quality evidence, small sample sizes, and poorly reported patient selection. Specifically the GDG were concerned about the high positive lymph node rates in patients with atypical spitzoid lesions, suggesting a highly selected patient population, and therefore that there was insufficient evidence to assess the role of sentinel lymph node biopsy in this situation. Although the low quality evidence did suggest that FISH and *BRAF/RAS* mutation detection increased the histopathologist's ability to categorise atypical spitzoid melanocytic lesions, the GDG felt that these data were insufficient to make a recommendation on the use of these tests. Therefore the GDG decided to make a research recommendation on this topic. Low quality evidence limited the ability to make recommendations on the tests available (e.g. genetic testing) and as a result, the GDG made more general recommendations. Because of the insufficient and low quality evidence, the GDG used their clinical experience and knowledge and the current NICE Improving Outcomes Guidance for people with skin tumours including melanoma relating to malignant skin lesions of uncertain pathological diagnosis to recommend that patients presenting with atypical spitzoid lesions be discussed and managed at the SSMDT.
Trade off between clinical benefits and harms	The GDG agreed that the recommendations could improve the management of patients with atypical spitzoid lesions by the inclusion of a discussion of these patients in the SSMDT reviews. In addition, the research recommendation could clarify the value of genetic tests in the diagnosis and prognosis of patients with atypical spitzoid lesions. A proportion of patients with histologically atypical or spitzoid melanocytic lesions may be treated as melanoma unnecessarily (overtreatment). The GDG felt that some patients may be overtreated, this was preferable to failing to treat a melanoma
Trade off between net health benefits and resource use	No evidence about cost effectiveness was identified for this topic and this topic was not considered a priority area for the development of an economic model. The potential costs considered by the GDG were in relation to the additional discussion of patients with atypical spitzoid lesions at SSMDTs. There may also be an increase in wide local excisions

	in patients with atypical spitzoid lesions. However, the GDG considered that there could be potential savings resulting from earlier treatment and wide local excisions in patients with melanoma, because of a reduction in risk of local regional recurrence.
Other considerations	The GDG did not feel that there were any equalities issues, although a significant proportion of the patients affected by the topic are young adults or children. The GDG felt that any change in current clinical practice was likely to be minimal as atypical spitzoid lesions are rare. In addition, it was noted that the recommendations would not change current practice as this path of action is currently recommended by the NICE Improving outcomes for people with skin tumours including melanoma.

1

Research recommendation	**In people with reported atypical spitzoid melanocytic lesions, how effective are fluorescence *in situ* hybridization (FISH), comparative genomic hybridization (CGH) and tests to detect driver mutations compared with histopathological examination alone in predicting disease-specific survival? This should be investigated in a prospective diagnostic study. Secondary outcomes should include sensitivity, specificity, accuracy, positive predictive value, disease-specific survival and progression-free survival.**
Why this is important	Borderline and atypical spitzoid lesions continue to be diagnostically challenging. There are no reliably reproducible histological, immunohistochemistry or molecular features that allow exact typing and prognostic assessment of these lesions. The current 'gold standard' is histological examination with expert review, but it is not always possible to distinguish spitzoid melanoma from benign spitzoid melanocytic lesions. Current molecular technologies such as FISH and CGH provide some help, but the results are difficult to interpret and may not be conclusive. Understanding and mapping changes in molecular pathways could predict outcome and inform individual treatment planning.

3.42 Tumour samples for genetic testing

3 Genetic testing for driver mutations in melanoma tumours has become important with the
4 recent advances in therapy. Different molecular pathways, which are involved in the
5 development and growth of melanoma cells, can be targeted with specific medicines, and
6 whether a patient is suitable for these therapies is assessed by testing tumour samples
7 stored after pathological reporting for driver mutations (predominantly to date in the *BRAF*
8 gene). The successful production of a clear genetic test result depends upon the following
9 factors:

10 • whether the stored sample can be found
11 • the amount of tumour in the block
12 • heterogeneity within and between blocks
13 • the age of the block (as DNA degrades over time)
14 • how the tissue was preserved (because of variation in degradation of the DNA)
15 • whether the tissue is rich in melanin (as melanin interferes with the testing process)

- the nature of the mutation detection test to be performed
- probably other as yet unknown factors.

There are therefore a number of specific practical issues which have to be considered.

When the patient's disease progresses and systemic treatment is indicated, mutation testing is needed as soon as possible, and the delay as a result of the need to locate the stored tumour blocks, sample and then test them can be distressing for patients. This delay would be avoided if all primary tumours were tested at diagnosis, but no more than 20% of patients will ultimately require drug therapy, and so testing the tumour sample at the time of diagnosis would be unnecessary in 80% of them.

Recent evidence suggests that genetic changes in tumours may increase as the cancer progresses, so that metastases may have different profiles from the primary and it is probably therefore preferable to test the secondary tumour. Sampling secondary tumours may furthermore give a more reliable result as the samples are likely to have higher cellularity as well as being more recent, with less degraded DNA. Metastases may however be genetically heterogeneous and it is not clear whether the test should be performed on more than one tumour block

If there is no stored tissue, genetic testing may require further biopsies with the risk of morbidity which would be greater if multiple secondary tumours were sampled. Finally it is likely that block selection is important in order to avoid tumour with large quantities of melanin or necrotic tissue.

The main genetic tests now carried out are for *BRAF*, *NRAS* and *c-kit* mutation, but new tests are likely to be developed in the future, and for newly diagnosed patients it may be preferable to delay testing till the optimal range of tests is available.

The survey of skin cancer MDTs carried as part of the needs assessment for this guideline (Appendix G) showed very variable policies about which samples to test and whether the tests were carried out locally or in central laboratories.

Clinical question: What is the most appropriate tumour sample (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies?

Clinical evidence

Concordance between primary and metastatic samples for BRAF mutations

Low quality evidence suggests that paired primary and metastatic melanoma tumour samples are discordant for *BRAF* mutation status in between 5% and 40% of patients (Boursault et al, 2013; Capper et al, 2012; Colombino et al, 2012; Colombino et al, 2013; Edlundh-Rose et al, 2006; Heinzerling et al, 2013; Houben et al, 2004; Omholt et al, 2003; Yancovitz et al, 2012; Yazdi et al, 2012).

In one study (Yancovitz et al 2012) all patients whose primary tumour sample was *BRAF* wild type had a *BRAF* mutant metastatic tumour sample. In the remaining studies between 0% and 45% of patients whose primary tumour sample was *BRAF* wild type had a *BRAF* mutant metastatic tumour sample.

In one study (Yancovitz et al 2012) all patients whose metastatic tumour sample was *BRAF* wild type had a *BRAF* mutant primary tumour sample. In the remaining studies between 0% and 50% of patients whose metastatic tumour sample was *BRAF* wild type had a *BRAF* mutant primary tumour sample.

Concordance between primary and metastatic samples for NRAS mutations

Low quality evidence suggests that paired primary and metastatic melanoma tumour samples are discordant for *NRAS* mutation status in between 2% and 13% of patients (Colombino et al, 2012; Colombino et al, 2013; Edlundh-Rose et al, 2006; Heinzerling et al, 2013; Houben et al, 2004; Omholt et al, 2002).

Between 0% and 11% of patients whose primary tumour sample was *NRAS* wild type had an *NRAS* mutant metastatic tumour sample.

Between 2% and 6% of patients whose metastatic tumour sample was *NRAS* wild type had an *NRAS* mutant primary tumour sample.

Concordance between primary and metastatic samples for CKIT mutations

Our literature searches identified no studies comparing *CKIT* mutations in paired primary and metastatic tumour samples.

Sample adequacy

In two studies comparing paired primary and metastatic tumours samples there was no primary tumour sample available to test in between 11% and 39% of eligible patients (Boursault et al 2013; Heinzerling et al 2013). It was unclear why this was: the delay between obtaining the primary and metastatic tumour samples was not reported in any of the included studies. Colombino et al (2012) reported that DNA sequencing was not possible in 8% of samples because of DNA degradation.

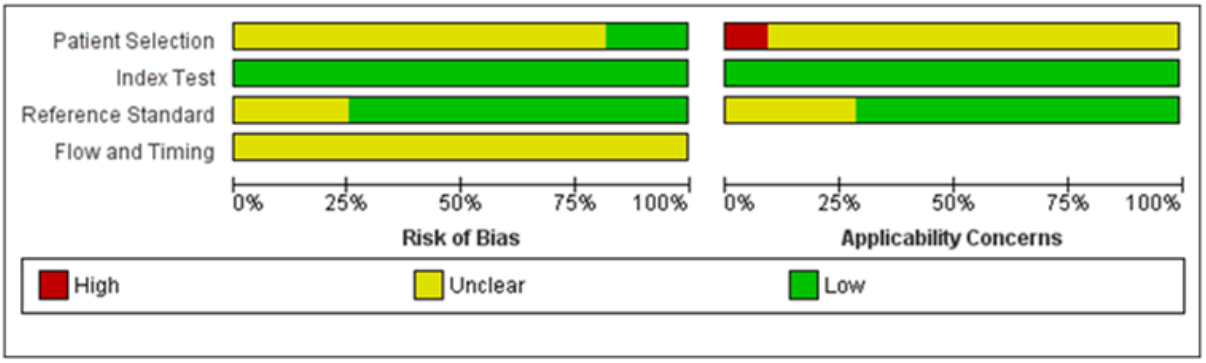
Morbidity

The morbidity associated with obtaining tumour samples for mutation tests was not reported in any of the included studies.

Risk of bias in the included studies

Risk of bias and applicability were assessed using QUADAS-2 (Figure 37).Only one study (Boursault et al, 2013) fully reported the patient sampling strategy: studies typically relied on institutional tumour banks. It was also unclear whether the patients included in the studies had been candidates for chemotherapy. One of the studies (Capper et al, 2012) included only samples from brain metastases. The flow and timing of tests was not well reported in the studies – for example the delay between obtaining the tumour samples and the mutation tests was unclear. Some of the studies used more than one test for genetic mutation – in these cases one of the tests was considered the reference standard (gold standard) test.

Figure 37: Risk of bias and applicability (QUADAS-2)



Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently *de novo* modelling was not done for this topic.

Recommendation	**If targeted systemic therapy is a treatment option for stage 4 disease, offer genetic testing using:** • **a secondary melanoma tissue sample if there is adequate cellularity or** • **a primary melanoma tissue sample if a secondary sample is not available or is of inadequate cellularity.**
Relative value placed on the outcomes considered	The GDG considered the outcomes relating to diagnostic accuracy, sample adequacy and morbidity (because of biopsies) to be the primary outcomes of interest for this question, and that avoiding false negatives and false positives were particularly important. All of the outcomes were considered important but the evidence identified was mostly about diagnostic accuracy. There were no data about morbidity in the included evidence.
Quality of the evidence	The quality of the included evidence was judged moderate to high using the QUADAS-2 checklist. In general, there were few concerns about bias in those studies for which this could be assessed, but the potential for bias was often unclear for patient selection and for patient flow and timing. The included papers used tests that were available at the time the study was carried out. The GDG believed that because of the rapidly changing nature of the available tests, they could only make limited recommendations and so no reference was made to any specific test. In addition, the number of tissue samples included in most of the studies was small thus increasing the uncertainty about which test to use. The GDG reviewed evidence that suggested some inconsistency between genetic testing results from primary and secondary tumours, giving some support to the view that new biopsies of secondary tissue might be indicated. However, it was thought likely that some of this variation related to technical issues and the data were therefore not thought strong enough to support a recommendation. The GDG discussed the potential problems of timing in relation to the storage. Older blocks may be destroyed or stored offsite, but melanoma may recur many years later. Additional time will also be required to access blocks stored off site or in another hospital. The GDG also acknowledge the quality of the tissue samples and particularly the effects of degradation of DNA in old blocks. However they agreed that these problems were not sufficient to prevent them from making recommendations, as these problems would probably only affect a reasonably small number of melanoma patients. The uncertainties with flow and timing were not considered important because tissue was paraffin embedded and formalin

	fixed.
Trade off between clinical benefits and harms	Using metastatic rather than primary tumour samples first for testing may yield more reliable results because of higher cellularity and less degradation of the DNA in a more recent sample. The secondary sample may also be more immediately available for testing. Both primary and metastatic samples have a small false negative rate on molecular testing, but the GDG felt that using the primary sample was preferable to re-biopsy of a secondary due the morbidity and risk of additional biopsies. A small proportion of patients may be offered an additional biopsy of metastatic tissue with the associated risks of morbidity and mortality in particular for patients in whom a long time interval between initial diagnosis and detection of metastasis has elapsed. The GDG considered the benefits of more effective therapy outweighed the small risks associated with an additional biopsy.
Trade off between net health benefits and resource use	No evidence about cost effectiveness was identified for this topic and this topic was not considered a priority area for the development of an economic model. Testing will carry an economic cost to histopathology and radiology departments. Testing for *BRAF* mutations was free to the NHS until 31st December 2014. It is estimated that each test will now cost around £97 based on data from NICE TA269. More accurate genetic test results may lead to a better use of resources and the survival benefits of more effective therapy were considered worth the additional costs.
Other considerations	No equalities issues were identified for this topic. The GDG acknowledged that the recommendations may result in a small change in practice – there may be some impact on histopathology and radiology services because of the number of patients having additional biopsies and extra tests but the number was not considered to be large. The use of genetic tests for driver mutations on stored melanoma samples is in a state of evolution. The recommendations made here were agreed in that context and it is likely that changes will be necessary as the tests and the drugs available change over time.

3.5 Genetic testing in stage 1 - 3 melanoma

Early stage melanoma in this context includes primary melanomas and melanomas with nodal, in transit or satellite metastases, but no distant organ metastases – i.e. Stages 1, 2 and 3. The other issues relating to tumour samples for genetic testing have been included in section 3.4.

Clinical question: What is the role of genetic testing of the tumour at diagnosis for a person with early stage [1-3] melanoma?

Clinical evidence

Our literature searches identified no studies comparing genetic testing at diagnosis with no genetic testing at diagnosis.

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Do not offer genetic testing of stage 1A–2B primary melanoma at presentation except as part of a clinical trial.** **Consider genetic testing of stage 2C primary melanoma or the nodal deposits or in transit metastases for people with stage 3 melanoma.** **If insufficient tissue is available from nodal deposits or in transit metastases, consider genetic testing of the primary tumour for people with stage 3 melanoma.**
Relative value placed on the outcomes considered	The list of outcomes considered by then GDG to be important for this topic were: • Rate of stratification for treatment • Prognosis estimation • Survival • Rate of recurrence • Failure to obtain a valid mutation test result • Treatment delays • Morbidity • HRQoL Although all these outcomes were considered important, no evidence was identified for this question.
Quality of the evidence	In the absence of any evidence, the recommendations were made on the basis of the clinical experience of the GDG and the evidence appraised for the review question in section 3.4 (What is the most appropriate tumour sample (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies?). There is limited evidence that testing the primary tumour block is of prognostic value, except possibility for *BRAF* V600K positive tumours. However for patients with stage 2C-3 melanoma who have a 60-70% risk of developing metastatic disease requiring systemic treatment, the GDG felt that testing at the time of diagnosis would result in more timely disease management of stage 4 disease for a significant number of patients.
Trade off between clinical benefits and harms	The cost of testing blocks in the absence of clinical utility for many patients with early stage melanoma would be avoided as a result of these recommendations. The GDG considered the likelihood that better genetic tests would be available soon to test for multiple genetic changes of predictive

	value. Therefore currently it would be preferable to reserve the small amount of tumour in primary melanomas of stage 1 to 2B for use if and when metastases develop. A proportion of genetic tests would not be used (stage 2C and stage 3 melanoma patients who either do not progress or who do not proceed to treatment). The GDG did not think that there would be any major harms associated with these recommendations, although concerns were raised about the delay in treating stage 4 patients because of the potential for delays in accessing archival tissue for testing and even the possibility that old blocks may have been destroyed leading to a need for a new biopsy. For stage 1-2B patients, histological tissue should be stored in the long term for future genetic testing when required because late metastasis is not uncommon in melanoma patients. Overall, the GDG felt that there was a net health benefit in favour of the recommendations.
Trade off between net health benefits and resource use	No evidence about cost effectiveness was identified for this topic and this topic was not considered a priority area for the development of an economic model. The GDG considered that testing all melanoma patients at the time of diagnosis would be an inappropriate use of NHS resources given that approximately 80% of patients would currently never require a test result.
Other considerations	No equalities issues were identified for this topic. These recommendations may result in a modest change in practice as current practice is variable. Some areas will stop testing early stage disease while some will start testing late stage. The GDG used evidence from the review question in section 3.4 to inform recommendations and their knowledge of evidence about prognostic factors in melanoma. They also discussed their experiences of difficulties in accessing tumour blocks in a timely fashion at the time of relapse.

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4 Staging of melanoma

Primary melanoma is routinely treated with surgical excision. The excised melanoma is sectioned and stained using haematoxylin and eosin and examined by the histopathologist. Sometimes additional immunohistochemical stains are required. The pathologist will report on the depth of the melanoma within the skin, commonly called the Breslow thickness. The thickness is an important predictor of the likelihood of subsequent recurrence of the melanoma and therefore of the treatment required. There are additional components of the pathology report which are also important prognostically and which form part of the most widely used international staging system developed by the American Joint Committee on Cancer (AJCC) (see page 20). These are the presence or absence of microscopic ulceration and mitoses (number of dividing cells). When primary melanoma is diagnosed then the pathology report can be used to assign a preliminary AJCC stage of 1A, 1B, 2A, 2B or 2C.

Spread of melanoma to local lymph nodes or other parts of the body can occur at any time after diagnosis but the likelihood is indicated by the AJCC stage. The higher the stage, the greater is the likelihood of relapse/recurrence of the tumour. Additional investigations such as sentinel lymph node biopsy (SLNB) or imaging (e.g. ultrasound, CT, MRI, PET-CT, PET-MRI) can be used to increase the accuracy of staging. Sentinel node biopsy is a procedure performed at the time of wide local excision or the primary tumour. It requires the injection of a radioactive tracer and blue dye into the skin and sampling (removal) of the small number of "sentinel" nodes to which the tracer drains. Better staging gives patients more information about the likely outcome from their cancer and may give access to trials of adjuvant therapies or to earlier treatment of stage 4 disease.

When microscopic deposits of melanoma are identified within sentinel nodes, many patients proceed to completion lymphadenectomy. Where SLNB is not performed and nodal disease subsequently occurs as a palpable lump the standard treatment is block dissection of the nodal basin and in clinical trials this is often referred to as "delayed completion lymphadenectomy".

Clinical questions:

- **What is the most effective method of accurately staging melanoma in patients with clinicopathological stage 1A melanoma?**
- **What is the most effective method of accurately staging melanoma in patients with clinicopathological stage 1B-2C melanoma?**
- **What is the most effective method of accurately staging melanoma in patients with clinicopathological stage 3 melanoma?**
- **What is the most effective method of accurately staging melanoma in patients with clinicopathological stage 4 melanoma?**

Clinical evidence

Diagnostic outcomes

The evidence for diagnostic outcomes is summarised in Tables 13 to 18.

Evidence for the diagnostic outcomes was taken primarily from a number of systematic reviews and supplemented where necessary with data from any other relevant studies. Overall the quality of the evidence for diagnostic outcomes ranged from low to high quality for a number of reasons.

There were no randomised trials of any of the diagnostic interventions and as a result the studies included in the meta-analysis were at high risk of bias with the included populations highly selected for SLNB or imaging and in many cases it was unclear whether the

intervention was being used as part of staging at diagnosis or as part of follow-up and surveillance.

Other reasons for downgrading the quality of the evidence were similar across the studies and included unmet quality criteria relating to insufficient reporting of patient withdrawals, intermediate results and selection and training of raters (Xing et al, 2010) Several potential sources of bias were identified with many studies failing to report inclusion and exclusion criteria as well as not reporting sufficient population information. Other possible sources of bias identified included potential review bias resulting from a lack of blinding of test reviewers. In many cases, test results were not blinded for reference test results or index test results and only a small proportion of included studies reported how to deal with indeterminate results (Krug et al, 2008).

Patients with clinically negative nodes

Breslow thickness

Evidence from a randomised trial (Morton et al, 2014), a systematic review (Lens et al, 2002) and an observational study (Han et al 2013) shows that in patients undergoing sentinel lymph node biopsy, Breslow thickness is associated with the likelihood of a positive result. In those with a Breslow thickness of 0.75mm or less (Lens et al 2002; Han et al, 2013) the positive sentinel lymph node rate was 1% to 3%. This compares with 6% for those with a Breslow thickness of 0.75mm to 1.0mm (Han et al 2013) and 8% for those with a Breslow thickness of 0.75mm to 1.5mm (Lens et al 2002).

Sentinel lymph node biopsy (SLNB)

Meta-analysis of 47 studies indicates a sensitivity and specificity of 86.6% and 100% respectively for SLNB. Clinical stage was I or II where mentioned and it was likely that these SLNB studies only included patients with clinically negative nodes given their relatively low prevalence of positive nodes (ranging from 9% to 41%), compared to the studies of other tests.

Imaging (ultrasound or PET)

In patients with clinical stage I melanoma, ultrasound (US) had a sensitivity of 49.5% and specificity of 91.9% (from meta-analysis of 3 studies). In patients with clinical stage I-II primary melanoma, positron emission tomography (PET) had a sensitivity of 22.3% and specificity of 94.9% for the detection of regional lymph node metastases (from meta-analysis of 4 studies; see Table 1).

Voit et al (2014) used lymphoscintagraphy to target ultrasound at the sentinel node in patients scheduled for SLNB. Any suspicious nodes on US underwent fine needle aspirate cytology (FNAC), with the rationale that patients with a positive FNAC could be spared the morbidity of surgical SLNB. The sensitivity of targeted ultrasound and FNAC for lymph node metastasis was 50% with 99% specificity. According to these figures about half of those with positive nodes could avoid surgical SLNB, but the absolute number of patients spared SLNB would depend on the prevalence of lymph node metastasis.

Patients with clinically positive nodes

FNAC for regional nodes

The evidence about FNAC came from studies with a relatively a high prevalence of positive nodes (ranging from 48% to 87%), where the patients included were more likely than not to have a positive node. It is assumed that FNAC was used as a targeted test for clinically or radiologically suspicious nodes, rather than as a routine test in all patients. Meta-analysis

indicated a sensitivity and specificity of FNAC for the identification of regional lymph node metastasis of 95.7% and 97.8% respectively (12 studies).

PET for regional nodes

In patients with clinical stage II-III primary melanoma, PET had a sensitivity of 64.7% and specificity of 93.9% for the detection of regional lymph node metastases (3 studies).

Imaging for any metastasis (including distant metastasis)

Meta-analysis of available data for each modality reported a sensitivity and specificity of PET for the identification of any metastases of 87.4% and 88.6% respectively (5 studies) compared with a sensitivity and specificity of 90.6% and 77.2% for PET-CT (1 study).

In patients with clinical stage III-IV primary melanoma, PET had a sensitivity of 70.4% and specificity of 83.7% for the detection of any metastases (1 study).

Table 13: Diagnostic accuracy of fine needle aspiration cytology for identifying regional nodes

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	12 (3203)	48% to 87%	95.7% (93.2% to 97.4%)	97.8% (96.1% to 98.8%)	46.5 (24.0 to 81.9)	0.04 (0.03 to 0.07)
I	-	-	-	-	-	-
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Table 14: Diagnostic accuracy of PET for identifying regional nodes

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	9 (753)	15% to 66%	51.3% (26.3% to 75.6%)	92.4% (86.3% to 95.9%)	6.6 (3.9 to 10.7)	0.5 (0.3 to 0.8)
I	-	-	-	-	-	-
I,II	4 (433)	15% to 29%	22.3% (15.1% to 31.6%)	94.9% (86.6% to 98.2%)	5.2 (1.4 to 13.6)	0.8 (0.7 to 0.9)
II	-	-	-	-	-	-
II,III	3 (175)	29% to 66%	64.7% (8.9% to 97.2%)	93.9% (65.0% to 99.8%)	10.5 (2.6 to 28.0)	0.4 (0.01 to 0.9)
III	1 (83)	46%	73.7%	93.3%	13	0.3
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Table 15: Diagnostic accuracy of ultrasound for identifying regional nodes

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	7 (868)	16% to 46%	53.5% (25.7% to 79.3%)	88.0% (81.0% to 92.7%)	4.5 (2.2 to 7.6)	0.5 (0.2 to 0.8)
I	3 (510)	16% to 26%	49.5% (8.9% to 90.8%)	91.9% (87.5% to 94.8%)	6.0 (1.3 to 11.3)	0.5 (0.1 to 1.0)

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	1 (97)	27%	7.7%	87.3%	0.8	1.1
III	1 (83)	46%	76.3%	93.3%	13.4	0.3
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Table 16: Diagnostic accuracy of sentinel lymph node biopsy for identifying regional nodes

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	47 (19607)	9% to 41%	86.6% (84.6% to 88.4%))	100%	407 (266 to 598)	0.1 (0.1 to 0.2)
I	-	-	-	-	-	-
I,II	5 (1766)	16% to 25%	88.7% (76.1% to 95.1%)	100%	460 (104 to 1330)	0.1 (0.05 to 0.2)
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	-	-	-	-	-	-
IV	-	-	-	-	-	-

Table 17: Diagnostic accuracy of PET for identifying metastases

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	5 (965)	23% to 90%	87.4% (38.9% to 98.7%)	88.6% (77.6% to 94.6%)	7.6 (3.6 to 14.0)	0.2 (0.02 0.7)
I	1 (184)	23%	20.9%	97.2%	8.6	0.8
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	1 (420)	70%	70.4%	83.7%	4.4	0.4
IV	-	-	-	-	-	-

Table 18: Diagnostic accuracy of PET-CT for identifying metastases

Stage	N studies (N data points)	Prevalence	Sensitivity (95% CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
Any	1 (420)	71%	90.6%	77.2%	4.0	0.1
I	-	-	-	-	-	-
I,II	-	-	-	-	-	-
II	-	-	-	-	-	-
II,III	-	-	-	-	-	-
III	-	-	-	-	-	-
III,IV	1 (420)	71%	90.6%	77.2%	4.0	0.1
IV	-	-	-	-	-	-

Clinical outcomes

The evidence for clinical outcomes is summarised in Table 19.

Disease-free survival

From one moderate quality randomised trial (Morton et al, 2014) comparing sentinel node biopsy with nodal observation in a total of 1661 patients, disease-free survival in patients with intermediate thickness melanoma was significantly higher in the biopsy group (HR 0.75 95% CI 0.62-0.94; p=0.001) but there was no significant difference in 10 year melanoma specific survival.

From one moderate quality randomised trial (Morton et al, 2014) comparing SNLB with nodal observation in a total of 1661 patients, disease free survival in patients with thick melanoma was significantly higher in the biopsy group (HR 0.7 95% CI 0.5-0.96; p=0.003) and no significant difference was observed between the groups for 10 year melanoma specific survival

From one moderate quality randomised trial (Morton et al, 2014) comparing SNLB with nodal observation in a total of 1661 patients, in patients with no nodal metastases (no tumour on biopsy or during clinical observation), no treatment related difference in 10 year melanoma specific survival rates was observed between patients in the biopsy group compared with the observation group for either intermediate or thick melanomas.

From one low quality, retrospective case series study including 1,000 patients (Voit et al, 2014), 5-year Kaplan-Meier estimated melanoma specific survival was 95% for patients with a negative US-FNAC compared with 59% for patients with a positive US-FNAC (p<0.001) and the 5-year Kaplan-Meier estimated disease free survival was 84% for patients with a negative US-FNAC compared with 33% for patients with a positive US-FNAC (p<0.001).

From one low quality, retrospective case series study including 1,000 patients (Voit et al, 2014), 5 year Kaplan-Meier estimated melanoma specific survival per sentinel node (SN) tumour burden was 96% for SN negative patients versus 100% for patients with metastases <0.1mm in diameter. 5 year Kaplan-Meier estimated melanoma specific survival for patients with metastases 0.1-1.0mm was 73% (p<0.001). 5 year Kaplan-Meier estimated melanoma specific survival for patients with lesions >1.0mm was 68% (p<0.001), 57% (p<0.001) for patients with a lymph node dissection or unknown SN tumour burden.

Corresponding disease-free survival estimates were 87% for SN negative patients compared with 83% for patients with <0.1mm lesions (p=0.45) versus 49% in patients with lesions 0.1-1.0mm (p<0.001) versus 37% for patients with lesions >1.0mm (p<0.001) versus 33% for lymph node dissection (LND) or unknown SN tumour burden patients (p<0.001).

Overall survival

From one systematic review and meta-analysis (Freeman et al, 2013), pooled results from six studies showed that in patients with tumours ≥4mm, SLN positive patients were more likely to die compared with SLN negative patients (HR=2.42, 95% CI 2.00-2.92).).

Complications

From one high quality randomised trial (Faries et al, 2010) lymphoedema was significantly more common in the delayed completion lymph node dissection (CLND) group (20.4% vs. 12.4%, p=0.04) lymphoedema was strongly associated with basin site with 9% oedema after axillary dissection and 26.6% oedema after inguinal dissection (p<0.001).

Complications related directly to surgery occurred in 62/309 nodal basins and were strongly associated with location of melanoma in the extremities (p=0.0002), specifically sentinel node retrieval from the groin (p=0.001)

One retrospective case series study including 250 patients (Wasserberg et al, 2004) reported wound complications in 42/309 basins. Independent factors significantly associated with wound infection included inguinal SLNB (p=0.001) and primary lesion in the extremity (p=0.02)

One retrospective case series study including 250 patients (Wasserberg et al, 2004) reported nerve related complications in 14 basins. Age younger than 50 years (p=0.003), axillary site (p=0.04) and number of excised sentinel nodes (>2) (p=0.02) were found to be independent prognostic indicators of sensory/mobility complications.

Table 19: GRADE profile: What is the most effective method of accurately staging melanoma in patients with clinicopathological stage IA - IV melanoma?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Positive Sentinel Node Biopsy**	**Negative Sentinel Node Biopsy**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall Survival (Freeman et al, 2013)											
6 (n=936 Breslow depth ≥4mm)	observational studies	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	?/393[5]	?/543[5]	HR 2.42 (2.00 to 2.92)		Very Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Wide excision of primary melanoma plus sentinel-node biopsy with immediate lymphadenectomy if metastases were detected**	**Wide excision plus post-operative nodal observation with lymphadanectomy if nodal metastases developed during observation**	**Relative (95% CI)**	**Absolute**	**Quality**
Disease Free Survival (Morton et al, 2014)											
1(n=1661)	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Disease free survival was significantly higher		Intermediate thickness HR 0.75 95% CI		Moderate

							in the biopsy group for both intermediate thickness and thick melanomas		0.62-0.94 Thick melanoma HR 0.7 95% CI 0.5-0.96		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ultrasound ± FNAC**	**Ultrasound ± FNAC + SLNB**	**Relative (95% CI)**	**Absolute**	**Quality**
Disease Free Survival (Voit et al 2014)											
1(n=1000)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None			5 year Kaplan-Meier estimated disease free survival was 84% for patients with a negative US-FNAC compared with 33% for patients with a postive US-FNAC		Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ultrasound ± FNAC**	**Ultrasound ± FNAC + SLNB**	**Relative (95% CI)**	**Absolute**	**Quality**
Melanoma Specific Survival (Voit et al 2014)											

1 (n=1000)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None			5 year Kaplan-Meier estimated melanoma specific survival was 95% for patients with a negative US-FNAC compared with 59% for patients with a postive US-FNAC		Low
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Wide local excision + SLNB + CLND**	**Wide local excision + delayed CLND**	**Relative (95% CI)**	**Absolute**	**Quality**
Adverse Events (Acute Toxicity) (Faries et al (2010)											
1(n=255)	RCT	None	No Inconsistency	No Indirectness	No Imprecision	None	lymphoedema was significantly more common in the delayed CLND group (20.4% vs. 12.4%, p=0.04) lymphoedema was strongly associated with basin site		-		High
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SLNB**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Adverse Events (wound/sensory complications) (Wasserberg et al, 2004)											

1(n=250)	Observational Study	Serious[4]	No Inconsistency	No Indirectness	No Imprecision	None	wound complications reported in 42/309 basins. nerve related complications reported in 14 basins.	-	Low

[1]*This was a systematic review and meta-analysis which included 29 cohort studies of which it was possible to include 6 studies in a meta-analysis;* [2]*The was a risk of bias due to selective outcome reporting (the results for the group of patients with thin melanomas were not reported);* [3] *No serious heterogeneity (I2=34%);* [4] *Retrospective case series study,* [5]*The study does not report the number of events in each of the groups just the pooled HR for the six studies which indicates that survival is better in patients with negative SLNB*

Children and adolescents

The evidence is summarised in Table 20.

From one retrospective study including 55 patients aged <20 years with stage I-II cutaneous melanoma (Howman-Giles et al; 2009) the SLNB positivity rate was 25% (14/55) and children aged <10 years had a higher SLNB positivity rate than those aged ≥10 years (33% versus 17%)

From one retrospective study including 55 patients aged <20 years with stage I-II cutaneous melanoma (Howman-Giles et al; 2009) overall survival was 94.1% for the total population and in the SLNB positive patients overall survival was 79%.

From one retrospective study (Toro et al; 2003) including 12 patients aged <18 years with clinically node negative melanoma no complications were reported as a result of SLNB.

Table 20: GRADE profile: What is the most effective method of accurately staging melanoma in children and adolescents?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Overall survival							
5	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW
Disease free survival							
3	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW
Adverse events							
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	VERY LOW

[1] All studies were retrospective case series studies with very small sample sizes; [2] Small sample sizes in all of the studies

Cost effectiveness evidence (see also Appendix A)

Primary melanoma is treated by surgical excision. The removed melanoma is examined by a pathologist who measures the depth of skin penetration by the tumour, the Breslow thickness, which is an important prognostic marker. Invasion of blood vessels or lymphatics and microscopic ulceration of the melanoma surface, are also prognostic indicators. The clinical presentation of metastatic melanoma to regional lymph nodes or other parts of the body is most common in the first three years after diagnosis of primary melanoma but can occur many years later.

Staging is a process by which reported histopathological features of the primary, and evidence of metastasis are used to estimate prognosis. Sentinel lymph node biopsy (SLNB) has become part of that staging process. SLNB was developed in the hope that the procedure would also have a therapeutic effect but the procedure is associated with some morbidity. The safety and cost effectiveness of the use of SLNB has therefore been the subject of some debate.

Aims of analysis

The aim of the economic evaluation was to assess the cost effectiveness of SLNB for the staging of melanoma alongside wide excision (WEX) versus WEX and nodal observation in patients with clinicopathological stage IA to stage IIC melanoma.

Economic evidence statement

A systematic literature review identified two papers (Morton et al, 2009; Wilson et al, 2002) relevant to the decision problem.

Wilson et al (2002) produced a cost-utility analysis comparing four alternative treatment strategies for patients with stage II melanoma. Two different SLNB strategies followed by tailored interferon treatment (IFN) strategies and two non SLNB strategies (treat all patients with low dose IFN or with surgery only). The base case analysis concluded that SLNB followed by treating patients who have a positive result with high dose IFN, and those with a negative result with low dose IFN was the most effective treatment in terms of quality adjusted relapse free life years (QArfLY). This equated to an ICER of $18,700/QArfLY compared to the surgical only approach, and $31,100 compared to only treating patients with a positive SLNB. The ‘treat-all’ approach was deemed not to be cost effective as a result of extended dominance.

The study was considered to be only partially applicable to the decision problem as it considered a US third party payer perspective and considered interventions post SLNB which were not widely used within the NHS. The study was also deemed to have serious limitations including a potential conflict of interest (the study was funded by a manufacturer of IFN), the duration component of the QALYs using relapse-free survival as opposed to overall survival and an inappropriate time horizon.

Morton et al reported a cost-utility analysis comparing wide-excision (WEX) alone to SLNB (with complete lymph node dissection (CLND) for patients with positive SLNBs) alongside WEX in patients with primary melanoma of >1mm in thickness using a decision tree and a Markov model. The base-case concluded that adding SLNB to WEX resulted in an incremental cost per QALY of AU$1,923 compared to WEX alone. The estimated cost ranged from SLNB being both cheaper and more effective to AU$90,595 per QALY during sensitivity analysis. These results were sensitive to the probability of distant metastasis post-intervention, the probability of nodal metastasis post WEX and the cost of WEX, SLNB and delayed CLND. The study was deemed only partially applicable as it considered an

Australian healthcare perspective. Potentially serious limitations were also identified most notably that probabilistic sensitivity analysis was not presented in the report.

Given the large differences in treatments considered following SLNB the results of the two studies are difficult to compare.

Table 21: Modified GRADE profile for included economic studies

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
Wilson et al. 2002 (USA)	Hypothetical cohort of patients with Stage II malignant melanoma after surgical excision. Age, performance status and other demographic details were not reported for this cohort.	Treat no one with IFN, surgery and clinical observation only.	$18,400	3.06	Reference			One-way sensitivity analysis For test and treat some versus surgery and test and treat appropriately versus test and treat some reducing the cost of relapse to $10,000 increased the ICER to $21,900/QALY and $35,900/QALY respectively. Increasing the cost of relapse to $50,000 reduced the ICERs by $14,500/QALY and $26,100/QALY respectively Sensitivity and specificity of SLNB and the probability of dose changing toxicities were reported to have an insignificant effect on the ICER for both comparisons. Probabilistic Sensitivity Analysis (PSA) Varying across all variables for test and treat some versus surgery the median, 25th and 75th percentiles of the PSA are $19,605, $10,291 and $36,659 per QALY respectively. For test and treat appropriately versus test and treat some the median, 25th and 75th percentiles $30,229, $16,766 and $58,823 per	Partially Applicable Not conducted from a UK health service perspective.	Very serious limitations. Study funded by manufacturer. Inappropriate time horizon.
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative low dose IFN (test and treat appropriately).	$24,200	3.37	$5,800	0.31	$18,700/QALY			
		Treat all with low dose IFN following surgery.	$30,500	3.48			Extended dominated			
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative with surgery alone	$33,800	3.68	$9,600	0.31	$31,100/QALY			

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
		(Test and treat some)						QALY respectively.		
	Comments: The survival component of the QALY uses relapse free survival and not overall survival.									
Morton et al 2009 (Australia)	Hypothetical cohort of patients with biopsy proven Melanoma ≥1mm	WEX	AU$23,182	9.90 QALYs	Reference			Increasing the probability for distant metastasis post WEX to 0.02 or reducing the post WEX+SLNB probability to 0.01 resulted in SLNB+WEX becoming less costly and more effective (dominant). Decreasing post WEX probability to 0.01 decreases the ICER to $90,959/QALY whilst increasing the WEX+SLNB to 0.022 increases the ICER to $52,436/QALY. Increasing and decreasing the probability of nodal metastasis post WEX to 0.04 and 0.0275 results in WEX+SLNB becoming dominant and $6,273/QALY respectively. Increasing the cost of delayed CLND to $27,000 again results in WEX+SLNB becoming dominant whilst reducing the cost to $8,717results in an ICER of $3,815. Increasing and decreasing the costs of WEX+SLNB between $4,339 and $9811 results in ICERS of $397/QALY and	Partially applicable Not conducted from a UK health service perspective.	Potentially serious limitations Probabilistic sensitivity analysis was not performed.
		WEX+SLNB	AU$24,045	10.34 QALYs	$863	0.44	$1,983/ QALY			

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
								$12,976/QALY.		
	Comments:									

**Incremental values in comparison to strategy above except when ruled out rhrough extended dominance.*

De Novo economic model

The current economic literature did not adequately address the decision problem, and so a *de novo* economic evaluation was created to assess cost effectiveness.

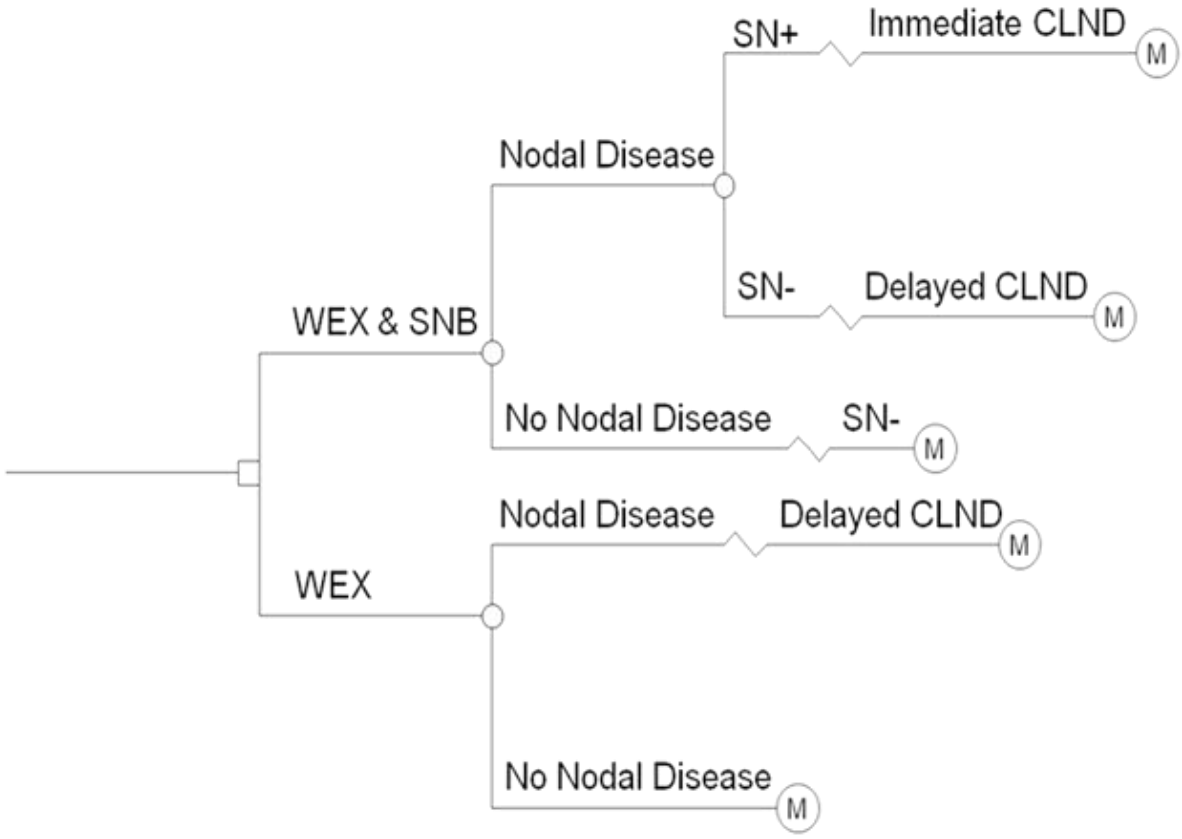
Model structure

A decision tree model comparing staging with or without SLNB was developed, in Microsoft Excel 2007, with a cycle length of one year and a time horizon of 20 years. In the model the following assumptions were made: (Figure 38)

In the model the following assumptions were made:

- all patients receive a wide excision to remove their primary melanoma
- depending on the arm of the model, patients receive either no SLNB or a SLNB at the time of excision to identify any nodal disease
- patients identified with nodal disease receive an immediate complete lymph node dissection (ICLND)
- all patients are followed-up by regular clinical examination
- patients who did not have SLNB or who had a negative SLNB who develop palpable nodal disease receive a delayed complete lymph node dissection (DCLND)
- all patients with nodal disease, not identified or investigated by SLNB, will eventually develop observable nodal disease and go on to receive a DCLND
- there will be no false positives from staging with SLNB (based on the evidence from the accompanying evidence review).

Figure 38:Decision tree structure



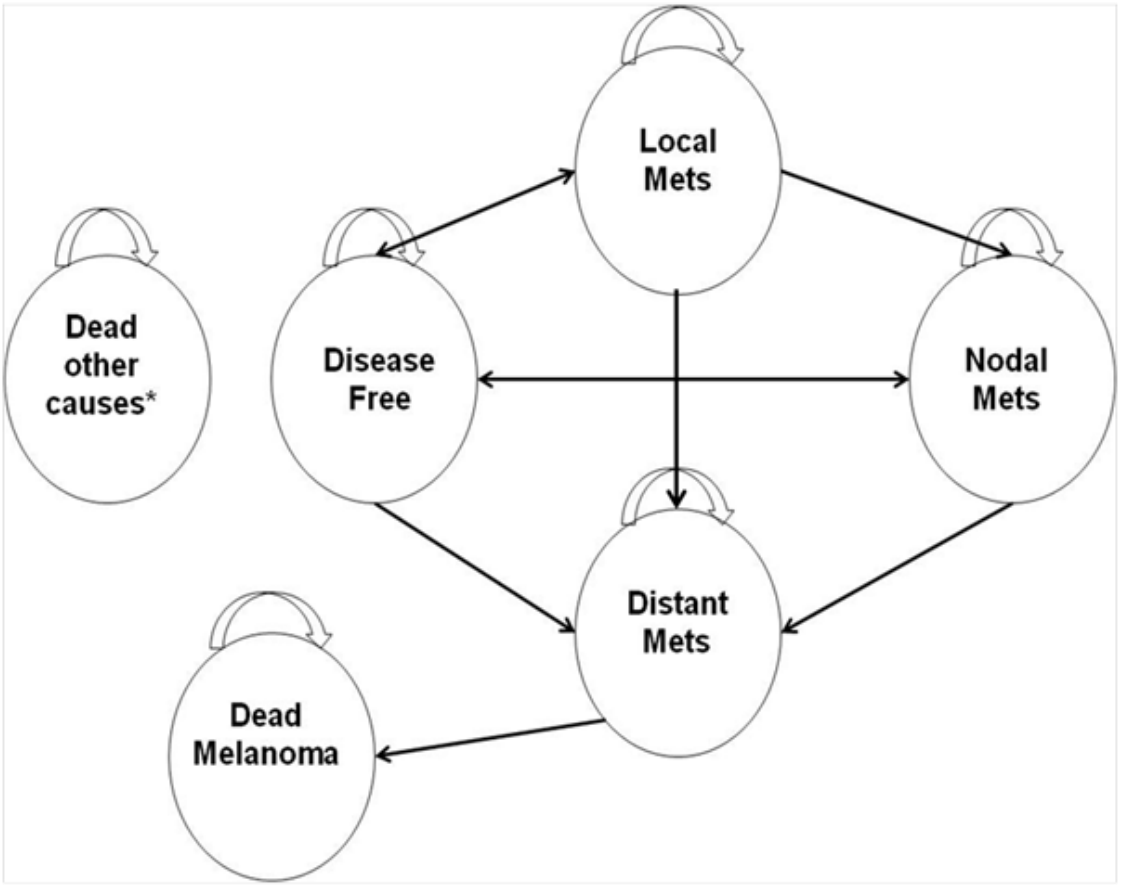
Following SLNB, patients progress through one of three Markov models depending on whether they have received a CLND or not. (Figure 39) The Markov model consisted of six mutually exclusive health states:

- disease-free
- local metastases
- nodal metastases
- distant metastases
- dead from melanoma
- dead other causes.

The Markov transition probabilities for both the CLND and the no CLND group only differed in the probability of nodal recurrence from 'disease-free'. For ease of modelling once patients had moved to the 'distant metastases' state they remained in the distant metastases group until death. The probability of moving from this state to death allows for a proportion of the cohort to have similar survival to that of the disease-free state.

A hypothetical cohort of patients was modelled. The cohort had an age of 52 years and were 57% male taken from the MSLT-1 trial as explained in detail below. The prevalence of micrometastases (20%) when entering the model was taken from the accompanying clinical evidence review. Lifetime total costs and QALYs were captured. The total costs included all costs associated with initial treatment, surveillance, further treatment and management. QALYs were calculated by multiplying the life years that patients spend in each health state by the associated quality of life weighting. QALYs and quality of life weights are discussed more detail in later sections.

Figure 39:Markov model structure



**The model cohort can enter the 'dead other causes' state from any other non-dead health state*

Clinical input data

All clinical inputs for the model were taken from the MSLT-I trial (Morton et. al, 2009; Faries et al, 2010; Morton et al, 2014; Morton et al, 2006) reports and cost effectiveness analysis and the accompanying review of the clinical evidence for this guideline. The MSLT-I trial was a randomised controlled trial comparing WEX+SLNB to WEX alone. Office of National Statistics interim life tables were used to inform the probability of death from other causes based on the age of the cohort during the relevant cycle.

The MSLT-1 trial reported a prevalence of micrometastases of 15.9% (Morton et al, 2005). This differed from studies identified by the accompanying clinical evidence review, with studies having a prevalence of between 16% and 25%. The GDG therefore felt an estimate of 20% would more closely reflect the true prevalence in this population.

Transition probabilities between each disease state, for ICLND and DCLND were those reported by Morton et al (2009) (Tables 21 - 22). The model assumed that the only difference in recurrence rate between the two groups was in terms of transitions from the 'disease free' health state to 'nodal metastases' and that all other transition probabilities were identical between the groups. Transitions for patients not receiving any CLND were not modelled other than for adverse events, although the model assumes that this proportion would be identical between the two arms and therefore health outcomes and non-adverse event related costs in both groups would cancel out during incremental analysis.

Table 22: Annual transition probabilities following ICLND for year 1 of the model

	Disease free	Local metastases	Nodal metastases	Distant metastases	Dead melanoma	Dead other causes
Disease Free	93.1%	1.6%	3.3%	1.6%	0.0%	0.3%
Local metastases	93.2%	1.5%	3.4%	1.6%	0.0%	0.3%
Nodal metastases	72.0%	0.0%	2.8%	24.9%	0.0%	0.3%
Distant metastases	0.0%	0.0%	0.0%	58.2%	41.8%	0.0%
Dead melanoma	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Dead other causes	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Table 23: Annual transition probabilities following DCLND for year 1 of the mode

	Disease free	Local metastases	Nodal metastases	Distant metastases	Dead melanoma	Dead other causes
Disease free	92.2%	1.6%	4.3%	1.6%	0.0%	0.3%
Local metastases	93.2%	1.5%	3.4%	1.6%	0.0%	0.3%
Nodal metastases	72.0%	0.0%	2.8%	24.9%	0.0%	0.3%
Distant metastases	0.0%	0.0%	0.0%	58.2%	41.8%	0.0%
Dead melanoma	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Dead other causes	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Sensitivity and specificity were taken from the accompanying systematic review of the clinical evidence for this guideline. The sensitivity of SLNB in identifying micrometastatic nodal disease, for patients with clinicopathological stage I-II melanoma was estimated to be 88.7% (95%CI: 76.1% to 95.1%) based on five studies with 1766 data points. Specificity was 100% as reported in all five studies included in the review.

Adverse events for patients receiving SLNB were taken from Wasserberg et al (2004). For our base case we used a complication rate of 13.6% for SLNB. Morbidity and additional bed days of ICLND and DCLND were taken from the MSLT-1 trial (Faries et al, 2010). The trial also found that both mild/moderate (17.4% vs. 11.4%) and severe lymphoedema (3.0% vs. 1.0%) were significantly higher in the DCLND group than for patients receiving ICLND. These values were used in the model as the rate of lymphoedema for both treatments. Differences in weakness and dysesthesia for between ICLND and DCLND were not modelled.

Costs and utilities

No high quality evidence on quality of life was identified for melanoma. Quality of life data were therefore taken from a range of sources and were similar to those sourced in previous economic evaluations (Morton et al, 2009). 'No evidence of disease' was set as equal to the 'disease-free' state in Kilbridge et al. (2001) Utilities for local metastases were taken from general cancer population values given a lack of evidence specific to melanoma (Torrance et al, 1989). The utility for 'nodal metastases' were based on an average of old and new stage III patients from a US population (Bendeck et al, 2004).Utilities for 'distant metastases' were assumed to be identical to those reported by Morton et al for 'diagnosis of distant disease'. This figure was based on a cost effectiveness analysis for interferon alpha-2a (Lafuma et al, 2001). Utility weights are reported in table 24.

Table 24: Quality of life weightings applied in the model

Health state	Utility Value
Disease Free	0.96
Local Metastases	0.67
Regional Metastases	0.52
Distant Metastases	0.50
Death	0.00

Costs were taken from NHS Reference Costs 2012-2013 unless otherwise stated. (Table 25) Costs were inflated to 2013 prices, using the hospital & community health services (HCHS) index, where appropriate.

The additional costs for performing SLNB alongside WEX were estimated to be £2,088 per patient. Surgical costs for wide excision, SLNB and CLND were taken from NHS reference costs. Faries et al (2010) reported an increase in bed days following inpatient admission following DCLND of 1.6 days compared to ICLND. These additional bed days, calculated from NHS reference costs, have been added to the cost of DCLND.

No sources of costs were identified for adverse events. The costs of lymphoedema were estimated based on estimates from one NHS lymphoedema service. Costs for complications associated with SLNB were based on Morton et al (2009).Health states costs were based on a typical follow-up regime for patients entering each transition state.

Table 25: Key costs applied to the model

	Value	Reference
Definitive surgery	£1141	NHS reference costs 2012-201311
SLNB	£2088	NHS reference costs 2012-2013
MRI scan	£169	NHS Reference Cost 2012-2013
Follow-up appointment	£139	NHS Reference Cost 2012-2013
Complications		
Surgery follow up	£119	NHS reference costs 2012-2013

	Value	Reference
Wound follow-up	£102	NHS Reference Cost 2012-2013
Physiotherapy	£44	NHS Reference Cost 2012-2013
Cost ICLND	£3,534	NHS reference costs 2012-2013
Additional bed days DCLND	1.6	Faries et al (2010)
Mild/moderate lymphoedema	£67	Lymphoedema service estimate
Severe lymphoedema	£3,360	Lymphoedema service estimate
Health state costs		
Disease free	£2105	NHS reference costs 2012-2013
Local metastases	£3246	NHS reference costs 2012-2013
Nodal metastases	£7187	NHS reference costs 2012-2013
Distant metastases	£78,805	Ipilimumab STA
Death (one off cost)	£5,527	Ipilimumab STA

All costs and health outcomes were discounted at a rate of 3.5% per annum in line with NICE guidance.

Base case results

The deterministic base case results estimate that WEX+SLNB had an increased in lifetime cost of £1,638 and a small increase in QALYs of 0.048. This equates to an incremental cost effectiveness ratio (ICER) of £34,402 per QALY above the NICE threshold of £20,000 per QALY (Table 23). The stochastic results based on the averages of the PSA were very similar in terms of costs and QALY with an ICER of £30,103 per QALY.

Table 26: Deterministic base case results

Outcome	WEX+SNB	WEX	Incremental
Cost	£33,320	£31,682	£1,638
Quality adjusted life years (QALYs)	11.34	11.29	0.048
Cost per QALY gained			**£34,402**

Sensitivity analyses

The deterministic sensitivity analysis (Table 24) showed that the ICER was sensitive to the difference in costs between WEX+SLNB and WEX alone. When the difference in cost between the two was halved, the ICER reduced to £12,468 per QALY. The ICER was also sensitive to the prevalence of nodal micrometastases with the ICER ranging from £24,820 to £46,380 per QALY when prevalence was varied between the range of that identified by the accompanying evidence review. The ICER was also sensitive to the rate of disease free survival; when the difference in disease free survival was halved between the SLNB and SLNB+WEX group the ICER increased to £138,364 above the NICE threshold.

Table 27: Deterministic sensitivity analysis results

Change made	Incremental Cost	Incremental QALY	ICER
100% Sensitivity SLNB	£1,590	0.054	£29,631
Prevalence=16%	£1,766	0.038	£46,380
Prevalence=25%	£1,477	0.060	£24,820

Change made	Incremental Cost	Incremental QALY	ICER
Half difference disease free survival.	£1,829	0.031	£59,130
No difference in disease free survival	£2,016	0.015	£138,364
Complications SLNB=3%	£1,487	0.048	£31,237
Difference in costs between WEX=SLNB and WEX halved	£594	0.048	£12,468
Cost ICLND=DCLND	£1,740	0.048	£36,559
Identical lymphoedema rates for CLND	£1,813	0.033	£54,898
QoL=0.8 for all non-dead health states	£526	0.019	£27,667

The probabilistic sensitivity analysis (Figure 40) was run for 1000 iterations and resulted in WEX+SLNB being more or as expensive in 87% and more effective in over 99% of iterations compared to WEX alone. The cost effectiveness acceptability curve (Figure 41) for WEX+SLNB compared with WEX alone showed that WEX+SLNB was preferred 43.8% of the time at the NICE threshold of £20,000 per QALY. WEX+SLNB was the preferred choice in over 50% of iterations when the WTP threshold was above £24,000 per QALY.

Figure 40: Cost effectiveness plane

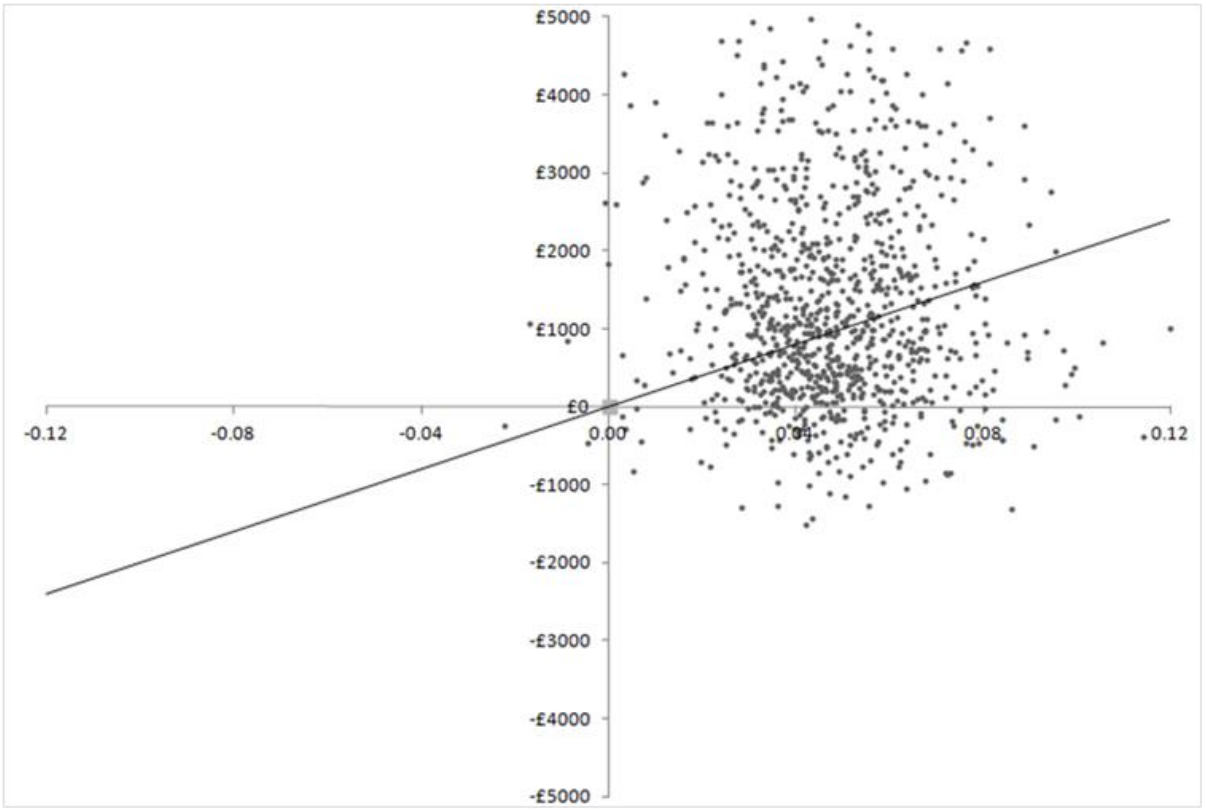
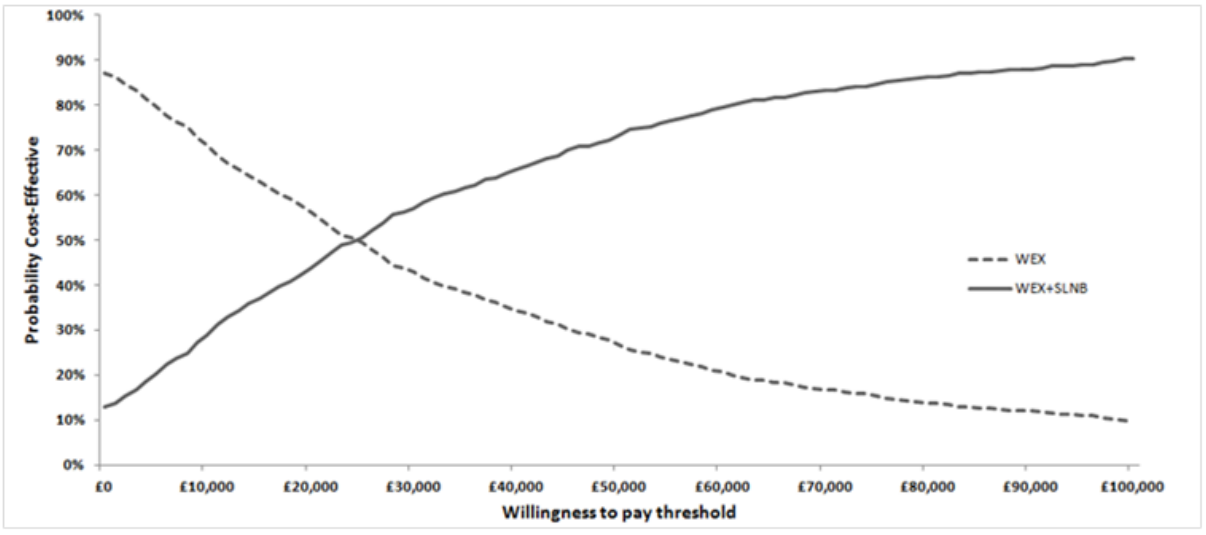


Figure 41: Cost effectiveness acceptability curve



Conclusion

Under the base case assumptions WEX+SLNB was not cost effective at a £20,000 threshold although there is uncertainty around our estimate. This result is sensitive to both difference in disease-free survival between the two groups and the size of the impact in terms of quality of life from any increase in disease-free survival.

Recommendations

Sentinel lymph node biopsy

Do not offer imaging or sentinel lymph node biopsy for stage 1A or 1B melanoma with a Breslow thickness of less than 1 mm.

Consider sentinel lymph node biopsy as a staging rather than a therapeutic procedure for people with stage 1B-2C melanoma with a Breslow thickness of 1 mm or more, and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.

Possible advantages of sentinel lymph node biopsy	Possible disadvantages of sentinel lymph node biopsy
The operation helps to find out whether the cancer has spread to the lymph nodes. It is better than ultrasound scans at finding very small cancers in the lymph nodes.	The purpose of the operation is not to cure the cancer. There is no good evidence that people who have the operation live longer than people who do not have it.
The operation can help predict what might happen in the future. For example, in people with a primary melanoma that is between 1 and 4 mm thick: • around 1 out of 10 die within 10 years if the sentinel lymph node biopsy is negative • around 3 out of 10 die within 10 years if the sentinel lymph node biopsy is positive.	The result needs to be interpreted with caution. Of every 100 people who have a negative sentinel lymph node biopsy, around 3 will subsequently develop a recurrence in the same group of lymph nodes.
People who have had the operation may be able to take part in clinical trials of new treatments for melanoma. These trials often cannot accept people who haven't had this operation.	A general anaesthetic is needed and this causes complications for 4-10 out of every 100 people who have the operation.

Imaging

Offer CT staging to people with stage 3 or suspected stage 4 melanoma.

Include the brain as part of imaging for people with suspected metastatic disease.

Consider whole-body MRI for children and young people (from birth to 24 years) with stage 3 or suspected stage 4 melanoma.

Relative value placed on the outcomes considered	The GDG considered the following outcomes to be the most important when drafting the recommendations: • Accuracy (sensitivity / specificity / positive predictive value / negative predictive value) of the interventions for staging); and • Survival outcomes, particularly overall survival but also melanoma specific survival • Adverse Events • HRQL HRQL was the only outcome for which no evidence was identified. No additional outcomes that were not specified in the review question were used to make recommendations. The GDG considered that disease-free survival in studies looking at sentinel lymph node biopsy (SNLB) was not a useful outcome. This was because the GDG was not surprised that there would be better disease-free survival rates in patients who underwent SLNB + completion lymph node dissection (CLND) (given that the most frequent site for recurrence is excised as a result of SLNB), and it was felt that this did not affect the overall survival rates.
Quality of the evidence	The quality of the evidence relating to the clinical outcomes ranged from high to very low as assessed with GRADE. The quality of the diagnostic outcomes was either assessed by QUADAS, or other tools as specified in the individual systematic reviews and ranged from high to very low. There were a number of issues with the one randomised trial available for this topic (MSLT-1) with a risk of bias resulting from selective outcome reporting and *post-hoc* subgroup analysis. The trial also failed to report overall survival as an outcome which was considered to be a serious omission as this was the outcome of most relevance to the GDG. During development of the guideline scope it was decided that additional input and evidence should be sought on this topic from clinical practitioners who were experts in SLNB for patients diagnosed with melanoma. However the GDG felt that this input should be from individuals with reported differing opinions about the value and effectiveness of this technique in order to provide a balanced and fair assessment of current opinion and practice. The presentations from the two expert advisors (see Appendix F for names and affiliations) and the subsequent discussion were used to supplement the information provided by the evidence review. As a result of the poor quality published evidence and after carefully considering the different views presented by the expert advisors, the GDG did not feel it appropriate to make a strong recommendation on the use of sentinel lymph node biopsy. The GDG compared the sensitivity of SLNB with imaging such as PET-CT for identifying nodal disease. PET-CT may identify additional disease outside the nodal basin, but there was no evidence on patients with stage 1 and 2 disease. Therefore this was not included in the health economic model and it was not possible to make a recommendation.

Trade off between clinical benefits and harms	<u>SLNB</u> The GDG felt that the recommendations could lead to more accurate staging giving a better indication of outcome (including survival and risk of relapse) which the GDG felt would be helpful for the majority of patients. The GDG also felt that the recommendations would allow possible access to clinical trials of adjuvant therapies for eligible patients. It was felt that the recommendations on SLNB would lead to earlier diagnosis of lymphatic spread as it is more sensitive than ultrasound. The GDG acknowledged that in patients who undergo a sentinel lymph node biopsy, a proportion of those with a negative SLNB, melanoma still recurs. In addition, SLNB requires a general anaesthetic and there is a risk of surgery-related morbidity (a range of 4-10% was reported in the evidence). The GDG also expressed concern about the potential for patients to be falsely reassured by a negative result. The GDG felt that provided the patient was fully aware that SLNB was a staging tool only and conferred no survival benefit the possible advantages from the recommendations outweighed the potential harms on the basis that more accurate staging would enable better management for the patient and possibly an earlier diagnosis of lymphatic spread. The group also felt that the patient would be better informed about their prognosis and better equipped to make informed treatment choices. <u>Imaging</u> A recommendation was made to offer CT imaging in order to stage patients with clinical evidence of nodal or more widespread disease. This was made on the basis that it was considered to be the more efficient test, than other alternative forms of imaging and was more tolerable for patients and less costly. Although PET-CT is more sensitive in terms of staging, no evidence was found to suggest that earlier treatment of metastatic disease improves survival and therefore increased sensitivity was viewed currently as not an important issue. Radiotherapy given with curative intent is not used for patients with melanoma therefore upstaging on the basis of a PET-CT to determine whether or not radiotherapy would be indicated is not relevant. The frequent occurrence of brain metastases in melanoma patients was used to justify inclusion of brain imaging in the recommendation, as was the evidence that small brain metastases respond well to stereotactic radiotherapy. The GDG also considered that emerging evidence of the effectiveness of immunotherapies might mean that earlier diagnosis of small occult metastases might lead to improved outcomes.
Trade off between net health benefits and resource use	The identified published evidence about the cost effectiveness of SNLB was deemed to be of low quality (partially applicable and with serious or very serious limitations) and did not consider a UK NHS+PSS perspective.

	Two previous cost effectiveness analyses were identified. Wilson et al, 2002 considered treatments guided by SLNB which were not routinely used in the NHS. There were also issues around the time horizon used, elicitation of model inputs and quality of life weights of this study. Morton et al (2009), although applicable to the review question, also did not consider a UK NHS+PSS perspective. Uncertainty in the model was also not adequately explored. There is some evidence that brain MRI is more sensitive than CT. However the GDG considered that adding a brain MRI to a body CT was not justified despite its increased sensitivity (see above) given the additional cost to the health service and to the patient who might need to come for a separate visit. This evidence was not considered in making the recommendations because it was either of low applicability and had serious limitations, or was superseded by the *de novo* analysis. A *de novo* model was developed for this topic. The GDG noted the model results which estimated that sentinel lymph node biopsy alongside wide excision was, in the base case, not cost effective at the NICE threshold of £20,000 per QALY. Also the probabilistic sensitivity analysis (PSA) showed that although there was great uncertainty around this estimate, there was only a 43.9% chance of it being cost effective at a threshold of £20,000 per QALY. The effectiveness inputs for the model were based on Morton et al (2014) which showed a difference in overall survival at 10 years, of 3%, although this was not statistically significant. Based on the clinical evidence the GDG concluded there to be no evidence of a survival benefit as a result of SLNB. The GDG therefore considered the deterministic sensitivity analysis, where there was no difference in survival or quality of life as a result of the addition of SLNB, as important in their recommendations. This analysis resulted in a cost per QALY of £138,364. The GDG was aware that there was great uncertainty around the cost effectiveness of the addition of SLNB, particularly in the absence of any survival benefit, but believe that the benefits of better staging information (resulting in access to clinical trials and better information about prognosis), which were not evaluated in the economic model, were important to their recommendations.
Other considerations	Evidence relating to children and young people was considered separately and a specific recommendation was made about imaging in that group. The decision to recommend MRI rather than CT scanning was because it is standard paediatric practice to image with the modality that causes the least exposure to ionising radiation unless there is an obvious need for greater diagnostic accuracy. The group felt that the recommendations may lead to a significant change in practice resulting from the potential for longer clinic times to provide full information and from the provision of SLNB for patients from areas where it is not currently available.

	There group also discussed the possible impact on clinical nurse specialist/key workers, specifically in relation to clinic times and time spent with patients, and concluded that this would result in more time and resource use in areas where SLNB is not currently discussed in such detail with patients. The GDG acknowledged that the use of SLNB is a rapidly changing field with new adjuvant treatments becoming available all the time. They agreed that accurate staging is likely to be needed to identify patients who might benefit from these new adjuvant treatments and SLNB would play an important role.

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5 Stage 0-2 melanoma

5.1 Surgical management

Following a histological diagnosis, the management of primary cutaneous melanoma is wide local excision with an appropriate clinical margin to minimise the risk of local recurrence and achieve histological confirmation and accurate local staging whilst optimising functional and cosmetic outcomes. The extent of the clinical resection is based on the Breslow thickness of the lesion. The GDG wished to consider the evidence that wide local excision reduces local recurrence rate and of its effect on overall survival.

Mohs micrographic surgery is a microscopically controlled surgical technique designed to allow complete excision of the tumour with minimal tissue loss. It is sometimes used in lentigo maligna (stage 0) as these lesions may be very large and in cosmetically sensitive sites where surgery may cause significant scarring.

Clinical question: What is the most effective surgical treatment for stage 0-2 melanoma to achieve clear margins and improved patient outcomes?

Clinical evidence

The evidence is summarised in Tables 28 to 30..

Surgical excision margins of 1 cm compared to surgical excision margins of ≥3 cm were not associated with differences in local recurrence (2 RCTs, N = 1512; low quality), melanoma-specific survival (1 RCT, N = 900; low quality), 5-year overall survival (2 RCTs, N = 1512; low quality), 10-year overall survival (1 RCT, N = 612; low quality), or distant metastasis (2 RCTs, N = 1512; low quality), whereas there was some suggestion that regional recurrence may be higher in the 1 cm group at 3 years, but not later (2 RCTs, N = 1512; low quality), that the surgical complication rate may be lower in the 1 cm group (1 RCTs, N = 900; low quality), and that the two excision margins are associated with slightly different health-related quality-of-life profiles (1 RCT, N = 900; low quality).

Surgical excision margins of 2 cm compared to surgical excision margins of 4 cm were not associated with differences in local recurrence (2 RCTs, N = 1399; low quality), regional recurrence (2 RCTs, N = 1399; low quality), melanoma-specific survival (1 RCT, N = 929; low quality), 5-year overall survival (2 RCTs, N = 1399; low quality), 10-year overall survival (2 RCTs, N = 1399; low quality), distant metastasis (2 RCTs, N = 1399; low quality), or wound infection or dehiscence rates (1 RCT, N = 470; low quality) whereas the skin grating rate was higher in the 4 cm group (46%) than in the 2 cm group (11%, $p < 0.0001$; 1 RCT, N = 470; low quality).

Surgical excision margins of 2 cm compared to surgical excision margins of ≥5 cm were not associated with differences in local recurrence (2 RCTs, N = 1326; low quality), regional recurrence (2 RCTs, N = 1326; low quality), melanoma-specific survival (1 RCT, N = 989; low quality), 10-year overall survival (2 RCTs, N = 1326; low quality), health-related quality-of-life (1 RCT, N = 989; low quality), distant metastasis (2 RCTs, N = 1326; low quality), or ‘problems with the scar (1 RCT, N = 989; low quality).

Table 28: GRADE profile: What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes (excision with 1 cm clinical margin versus excision with ≥3 cm clinical margin)

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 1 cm clinical margin	Excision with ≥3 cm clinical margin	Results	Quality
Local recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences, although one study showed a higher locoregional recurrence rate in 1 cm at 3 years.	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	No significant difference	LOW
5-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	No significant differences	LOW
10-year overall survival										
1	randomised trials[5]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 305	N = 307	No significant	LOW

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 1 cm clinical margin	Excision with ≥3 cm clinical margin	Results	Quality
									differences in 8-, or 12-year overall survival	
Health-related quality-of-life										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	Some apparently minor differences	LOW
Distant metastasis										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 758	N = 754	Appear to be similar	LOW
Adverse events										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 453	N = 447	Surgical complication rate: 1 cm (7.8%) ≤ 3 cm (13.9%), p = 0.05	LOW

[1] Cascinelli et al (1998), Thomas et al (2004); [2] The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias; [3] Low event rate(s); [4] Thomas et al (2004); [5] Cascinelli et al (1998)

Table 29: What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes (excision with 2 cm clinical margin versus excision with 4 cm clinical margin)

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 2 cm clinical margin	Excision with 4 cm clinical margin	Results	Quality
Local recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 470	N = 459	No significant difference	LOW
5-year overall survival										
	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
10-year overall survival										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	No significant differences	LOW
Distant metastasis										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 708	N = 691	Appear to be similar	LOW
Adverse events										
1	randomised trials[5]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 238	N = 232	Skin grafting rate: 2 cm (11%) < 4 cm (46%), p < 0.001; Wound	LOW

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 2 cm clinical margin	Excision with 4 cm clinical margin	Results	Quality
									infection/ dehiscence rate: 2 cm = 4 cm	

[1] *Balch et al (2001), Gillgren et al (2011);* [2] *The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias;* [3] *Low event rate(s);* [4] *Gillgren et al (2011);* [5] *Balch et al (2001)*

Table 30: What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes (excision with 2 cm clinical margin versus excision with ≥5 cm clinical margin)

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 2 cm clinical margin	Excision with ≥5 cm clinical margin	Results	Quality
Local recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Regional recurrence										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Melanoma-specific survival										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	No significant difference	LOW
10-year overall survival										

Quality assessment							Summary of findings			
							No of patients		Effect	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Excision with 2 cm clinical margin	Excision with ≥5 cm clinical margin	Results	Quality
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	No significant differences	LOW
Health-related quality-of-life										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	No significant differences	LOW
Distant metastasis										
2	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 643	N = 683	Appear to be similar	LOW
Adverse events										
1	randomised trials[4]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	N = 476	N = 513	Problems with the scar: No significant differences	LOW

[1] Cohn-Cedermark et al (2000), Khayat et al (2003); [2] The included studies were associated with under-reporting of a number of design features that therefore put the studies at unclear risk of bias; [3] Low event rate(s); [4] Cohn-Cedermark et al (2000)

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

Recommendations	**Consider excision with a clinical margin of at least 0.5 cm for people with stage 0 melanoma.** **If an adequate histological margin is not achieved after excision for stage 0 melanoma, discuss further management with the multidisciplinary team.** **Offer excision with a clinical margin of at least 1 cm to people with stage 1 (Breslow thickness less than 2 mm) melanoma.** **Offer excision with a clinical margin of at least 2 cm to people with stage 2 (Breslow thickness 2 mm or more) melanoma.**
Relative value placed on the outcomes considered	The GDG considered survival (overall and disease-specific) to be the most important outcomes for this topic. The other outcome considered to be important was loco-regional recurrence. Cosmesis and function were considered to be important patient-related outcomes, because narrower margins result in less functional disturbance and cosmetic damage. Evidence on histologically clear margins was considered to be important, but no studies included in the evidence review reported this outcome.
Quality of the evidence	The quality of the evidence was low as assessed with GRADE There was a risk of imprecision in randomised trial results due to the low number of events. This was highlighted by the reviewer and subsequently discussed by the GDG. Poor reporting of methodology in individual randomised trials resulted in the quality of the evidence being downgraded because of the potential risk of bias, which could not be assessed. These issues were considered by the GDG and not felt to be important enough to prevent them from making strong recommendations. Current clinical guidelines (for example those produced by the British Association of Dermatologists – see http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines) were also considered by the GDG and broadly supported the recommendations made. In particular, as there was no evidence on the most appropriate margin for stage 0 melanoma, the recommendation to excise with a 0.5 cm margin was made on the basis of clinical experience suggesting that local recurrence may be seen when smaller margins are used.
Trade off between clinical benefits and harms	The GDG felt that the recommendations would reduce the number of very wide excisions leading to less invasive surgery, fewer inpatient procedures, lower morbidity and better quality of life for a

	small number of patients. The GDG acknowledged that there was a possible increased risk of locoregional recurrence in patients with tumours of an intermediate thickness (Breslow 1-2 mm) excised with a 1cm margin. There was considerable uncertainty about the risks. There were no statistically significant differences in reported levels but there was possible imprecision and the studies were under-powered. However the GDG were confident of the likely benefits in relation to less invasive surgery, fewer inpatient procedures, lower morbidity and better quality of life for patients.
Trade off between net health benefits and resource use	No evidence about cost effectiveness was identified for this topic and this topic was not considered a priority area for the development of an economic model. The GDG recommended minimum margins of excision which were judged reasonable on the basis of published evidence. However the GDG were aware that considerably larger margins were taken in the past for patients with thick tumours and that in some places this may still be the norm. The GDG agreed that this might result in less invasive surgery, fewer inpatient procedures, lower morbidity and better quality of life for some patients as a result. As a result of more MDT discussion, there may however be an increase in Mohs surgery for facial stage 0 melanoma (although insufficient evidence for its use was identified) which may have resource implications. The group felt that the recommendations would possibly lead to a small increase in overall costs if the recommendation to use a 0.5 cm margin for stage 0 melanomas meant that some patients needed a second surgical procedure.
Other considerations	In drafting the recommendations for stage 0 melanoma, current clinical guidelines were considered (for example those produced by the British Association of Dermatologists – see http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines) and broadly supported the recommendations made by the GDG. The group felt that the recommendations would possibly lead to a reduction in variation in practice. No specific recommendation was made about Mohs micrographic surgery because there is currently no high quality evidence to support its use in this patient group. The GDG made a consensus recommendation to discuss cases with inadequate histological margins following surgical excision in stage 0 patients because the management of this group is difficult, and if there is a recurrence it has the potential to become an invasive melanoma. No equalities issues were identified for this topic.

1

Research recommendation	For people with lentigo maligna (stage 0 in sun-damaged skin, usually on the face) how effective is Mohs micrographic surgery, compared with excision with a 0.5 cm clinical margin, in preventing biopsy-proven local recurrence at 5 years? This should be investigated in a randomised controlled trial. Secondary outcomes should include cosmetic and functional outcomes.
Why is this important?	Mohs micrographic surgery is a microscopically controlled surgical technique designed to allow complete excision of the tumour with minimal tissue loss. This technique can be useful for people with lentigo maligna because their lesions can be very large and located in a cosmetically sensitive site where surgery may cause significant scarring. However, the histological detection of small numbers of melanocytes at the edge of a sample is difficult and can lead to false negative results. In addition, lentigo maligna may occur in an area of field change with a risk of skip lesions at the edge. Therefore, although Mohs micrographic surgery may ensure the complete excision of lentigo maligna, it can be accompanied by the recurrence of a similar lesion in adjacent skin.

5.2 The use of imiquimod in stage 0 melanoma and skin metastases

Currently surgical excision is the treatment of choice for stage 0 melanoma but this can be difficult for some patients if

- the stage 0 melanoma is extensive
- surgery would be of significant cosmetic or functional detriment
- the patients have other illnesses which make them a surgical risk
- there is any combination of the above.

The GDG wanted to consider whether imiquimod cream could be as effective a treatment for stage 0 melanoma as surgery or other treatments such as radiotherapy, cryotherapy, laser treatment or 5-fluorouracil cream. Imiquimod cream is applied to the melanoma daily for up to 3 months. It causes redness, irritation and may cause discomfort or pain, all of which are temporary. Imiquimod is also used to treat melanoma skin metastases, especially if the patient has multiple skin metastases making surgical excision difficult.

Clinical question: How effective is imiquimod in the treatment of stage 0 melanoma and skin metastases?

Clinical evidence

The evidence is summarised in Tables 31 to 32.

Stage 0 melanoma (lentigo maligna)

There was no evidence on the relative effectiveness of imiquimod compared with other treatments for people with stage 0 melanoma.

Very low quality evidence suggests that when punch biopsy is used to assess treatment success, complete response rates range from 73% to 87% (Buettiker et al, 2008; Wong et al, 2012; Powell et al, 2009 and Naylor et al, 2003).

Very low quality evidence suggests that when wide local excision of the tumour location is used to assess treatment success, complete response rates range from 53% to 64% (Ly et al, 2011; Hyde et al, 2012).

Very low quality evidence suggests that inflammation, erythema and irritation of the treatment area are common adverse effects with imiquimod treatment in people with stage 0 melanoma. Imiquimod treatment is stopped because of intolerable toxicity in between 0% and 7% of cases.

Melanoma skin metastases

There was no evidence on the relative effectiveness of imiquimod compared with other treatments for people with melanoma skin metastases.

Very low quality evidence suggests that imiquimod combined with IR-laser (Li et al, 2010) or interleukin-2 (Green et al, 2007) can visibly clear some skin metastases in patients with melanoma. Grade 3 adverse events occurred in 25% of patients in Li et al, 2010 and 20% of patients in Green et al, 2007 required antibiotic treatment for local infections.

Table 31: GRADE profile: How effective is imiquimod in the treatment of stage 0 melanoma (imiquimod versus surgery, radiotherapy, cryotherapy, 5FU, laser or no treatment)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	Quality
Complete treatment response (Buettiker, 2008; Wong, 2012; Powell, 2009; Naylor, 2003; Ly, 2011; Hyde, 2012)											
6	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	154/216 (71.3%)	-	-	-	VERY LOW
Regional disease - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Overall survival - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Treatment discontinued because of intolerable side effects (Powell, 2009; Naylor, 2003; Ly, 2011; Hyde, 2012)											
4	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	7/167 (4.2%)	-	-	-	VERY LOW
Health related quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Case series and one RCT comparing imiquimod with and without tazarotene; [2] Low number of events

Table 32: GRADE profile: How effective is imiquimod in the treatment of skin metastases (imiquimod versus surgery, radiotherapy, cryotherapy, 5FU, laser or no treatment)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up 21 to 64 months) (Li, 2010)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	6/11 (54.5%)	-	-	-	VERY LOW
Complete macroscopic response of treated metastases (per lesion) (Green, 2007)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	74/182 (40.7%)	-	-	-	VERY LOW
Complete macroscopic response of treatment site lesions (per patient) (Li, 2010)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	8/11 (72.7%)	-	-	-	VERY LOW
New metastatic lesions appearing during treatment (Green, 2007)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	7/10 (70%)	-	-	-	VERY LOW
Treatment discontinued because of intolerable side effects (Green, 2007)											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	0/10 (0%)	-	-	-	VERY LOW
One or more Grade 3 adverse events during treatment (Li, 2010)											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imiquimod	Surgery, Radiotherapy, Cryotherapy, 5FU, Laser, No treatment	Relative (95% CI)	Absolute	Quality
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	3/11 (27.3%)	-	-	-	VERY LOW
Health related quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] *Case series;* [2] *Treatment differs to that specified in the review question: imiquimod was combined with IR-laser (Li, 2010) or interleukin-2 (Green, 2007) in the included studies;* [3] *Low number of events*

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

Recommendations	**Consider topical imiquimod[a] to treat stage 0 melanoma in adults if surgery to remove the entire lesion with a 0.5 cm margin would lead to unacceptable disfigurement or morbidity.** **Consider a repeat skin biopsy for histopathological assessment after treatment with topical imiquimod for stage 0 melanoma, to check whether it has been effective.** **Consider topical imiquimod[b] to palliate superficial melanoma skin metastases.**
Relative value placed on the outcomes considered	Local control was the outcome the GDG considered to be the most important for management of stage 0 melanoma for which complete control should equate to cure. Similarly local control of superficial melanoma metastases was considered the most important when palliation was the aim. There was no evidence identified relating to HRQoL and cosmesis and no additional outcomes of interest were identified in the literature reviewed for this topic. After seeing the evidence, the GDG did not consider any of the outcomes other than local control to be of any value in informing recommendations.
Quality of the evidence	The quality of evidence identified was very low for all outcomes as assessed using GRADE. A number of issues were highlighted especially a lack of high quality evidence. The literature consisted mostly of non-comparative, observational studies and there was a high risk of bias. The issues with the evidence resulted in the GDG making limited recommendations. This was due to the lack of evidence and the fact that the evidence that was available was of such low quality. In particular, there was no evidence on treatment duration or treatment regimens and so no relevant recommendations could be made on either of these two outcomes.
Trade off between clinical	Treatment with imiquimod may prevent development of invasive melanoma in patients with Stage 0 as well as leading to a

a At the time of consultation (January 2015) topical imiquimod did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

b At the time of consultation (January 2015) topical imiquimod did not have a UK marketing authorisation for this indication or for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

benefits and harms	reduction in morbidity from surgery, but may cause temporary pain and inflammation, a flu-like syndrome and rarely, bone marrow suppression. It was therefore felt that the potential benefit of local control outweighed the possible short-term adverse effects.
Trade off between net health benefits and resource use	No relevant cost effectiveness analyses were identified and this topic was not considered a priority area for the development of an economic model. No cost effectiveness analysis was conducted for this topic. Savings may be associated with the use of topical imiquimod (50p per sachet, BNF - January 2015) compared with other treatment options such as surgery. In addition, there is the possibility of downstream savings associated with the prevention of invasive melanoma. The cost of follow-up may be greater for patients treated with imiquimod.
Other considerations	No equalities issues were identified for this topic. This is an off-label, widely used indication.

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6 Stage 3 melanoma

6.1 Surgical management

Stage 3 disease is when melanoma has spread from the original site on the skin to the (regional) draining lymph nodes or has grown in the intervening soft tissues, referred to as local (within 2cm of the scar) and in transit metastases (between 2cm from the scar and the draining nodes). The management of in transit disease was considered in section 6.3. The term “nodal basin” is usually used to describe the group of lymph nodes within the neck, axilla or groin. Nodes may also lie outside these “basins” and the GDG used the term “aberrant” for such nodes.

The AJCC staging system subdivides this stage into three (see page 20):

- Stage 3A: microscopic disease in the node (defined by Sentinel Lymph Node Biopsy (SLNB) positivity),
- Stage 3B:
  - the presence of metastases in the draining nodes which can be felt as a lump
  - or microscopic metastases seen in the skin around a primary
  - or microscopic disease in the lymph nodes and an ulcerated primary
- Stage 3C:
  - the presence of a palpable lump in the draining nodes and an ulcerated primary
  - or palpable metastases involving multiple draining lymph nodes.

The GDG wanted to consider the evidence for surgical treatment of the lymph nodes once microscopic or palpable nodal disease has been identified. The questions asked were:

- Should patients with a positive sentinel node biopsy be offered further surgery to remove all the nodes in that lymph node basin (known as a completion lymphadenectomy (CLND))?
- What surgery should be offered to patients when the positive sentinel node was outside the nodal basin (aberrant)?
- If palpable metastases have occurred (usually stage 3B or 3C), what extent of surgery is required to reduce the risk of subsequent local recurrence?
- For the neck, does the parotid gland need to be removed? For the axilla should all the nodes be removed (level 3)?
- For the groin should resection of the iliac nodes be offered as well as the inguinal nodes?

The GDG also sought evidence about the most effective surgical approaches where nodal disease has been found in unusual sites such as around the elbow

The survey of skin cancer MDTs carried as part of the needs assessment for this guideline (Appendix G) showed that of the 62 Local and Specialist Skin MDTs which responded 28 (45%) did not offer sentinel lymph node biopsy and that of those 28 MDTs, 17 (60%) did not offer it elsewhere. It was reported that the majority of patients offered sentinel lymph node biopsy accepted it.

Clinical question: What is the most effective surgical treatment for stage 3 melanoma?

Clinical evidence

Sentinel lymph node biopsy ± completion lymph node dissection

The evidence is summarised in Table 33.

Recurrence (local and regional)

In one retrospective study including 495 patients with a positive sentinel lymph node, there was no significant difference in median time to recurrence when comparing patients undergoing immediate completion lymph node dissection to patients undergoing nodal observation (9 months versus 12 months, p=0.46) (Bamboat et al, 2014).

Regional recurrence rates were not significantly different between the completion lymph node dissection (CLND) group and the observation group (18% versus 16%, p=0.58); however there was a statistically significant difference in nodal recurrence rates (CLND=6% versus No CLND=15%, p=0.002) and in systemic recurrences (CLND=27% versus Observation = 8%, p=<0.001) (Bamboat et al, 2014).

From one retrospective study in 313 patients no difference in patterns of first recurrence was observed when comparing patients who had a CLND and those who did not (54% versus 48%) (Kingham et al, 2010).

Melanoma specific survival

In one retrospective study in 1174 patients undergoing SLNB there was no significant difference in disease-specific survival; 3-year disease specific survival was 74% in patients who did not undergo complete lymph node dissection (n=61) versus 76.9% in patients who underwent CLND (n=1113) while 5-year disease- specific survival was 66% for patients not undergoing CLND and 66% for the CLND group (Van der Ploeg, 2012).

In one retrospective study in 495 patients with a positive sentinel lymph node, melanoma-specific survival for patients who underwent immediate CLND was 36.5 months (median) and was not reached for patients undergoing salvage lymph node dissection (p=0.005). Increasing age (p=0.006), tumour thickness (p=0.001) and degree of ulceration (p<0.001) were all associated with lower melanoma specific survival (Bamboat et al, 2014).

One retrospective study in 350 patients reported no significant difference between treatment groups (SLNB versus SLNB+CLND) in relation to disease-specific survival. Age was significantly associated with an increased risk of death from melanoma in patients older than 60 years and tumour thickness >2mm was a significant predictor of worse survival in the older age group (HR=3.11, p<0.001) (Smith et al, 2012).

Overall survival

In one retrospective study in 937 patients, overall survival was significantly better for patients undergoing SLNB and early lymph node excision compared with patients undergoing delayed excision (p=0.002). Estimated 3-year survival was 80.1±2.8% in patients with a positive SLNB and immediate lymph node dissection compared with 67.6±1.9% in patients undergoing delayed lymph node dissection and estimated 5-year survival was 62.5± 5.5% for SLNB + immediate lymph node dissection and 50.2±5.4% for SLNB + delayed lymph node dissection (Kretschmer et al, 2004).

Adverse events

In one retrospective study in 66 patients who underwent sentinel lymph node biopsy with or without completion lymphadenectomy, there were no reported deaths as a result of surgical intervention. There was a significantly higher rate of post surgery complications in the SLNB + groin dissection group when compared with the SLNB only group (p<0.001) (deVries et al, 2006).

In one retrospective study with a total of 66 patients, a significant difference in leg volume (measure of lymphoedema) was observed with patients undergoing SLNB + groin dissection having a greater volume compared with patients undergoing SLNB only ($p<0.001$) (deVries et al, 2006).

Table 33: GRADE profile: What is the most effective surgical treatment for stage III melanoma (immediate lymphadenectomy or observation for microscopic disease detected by SLNB)

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	SLNB + Immediate Lymphadenectomy	SLNB + Observation	Relative (95% CI)	Absolute	
Recurrence (Bamboat et al, 2014; Kingham et al, 2010)											
2 (n=808)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/599[3]	?/209[3]	Not Pooled		Very Low
Melanoma Specific Survival (van der Ploeg et al, 2012; Bamboat et al 2014; Smith et al, 2012)											
3 (n=2019)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/1651[3]	?/368[3]	Not Pooled		Very Low
Overall Survival (Kretschemmer et al, 2004)											
1 (n=937)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/314[3]	?/623[3]	Estimated 3 year survival was 80.1±2.8% in patients positive SLNB and immediate lymph node dissection compared with 67.6±1.9% in patients undergoing delayed lymph node dissection		Very Low

Adverse events (deVries et al, 2006)										
1 (n=66)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/11[3]	?/55[3]	There was a significantly higher rate of post surgery complications in the SLNB + groin dissection group when compared with the SLNB only group (p<0.001) -	Very Low

1 *[1] Not a randomised trial; [2] The studies do not clearly specify what AJCC stage included patients have been assigned, [3]Event rate is not reported.*

2

3

4

Standard lymphadenectomy versus extended lymphadenectomy for palpable lymph node disease in the groin

The evidence is summarised in Table 34.

Recurrence (local and regional)

In one retrospective study in 104 patients undergoing either ilio-inguinal dissection or inguinal dissection, the type of operation did not have a significant effect on local control of the dissected lymph node (Kretschemer et al, 2001).

In one retrospective study in 169 patients undergoing either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD), there was no significant overall difference in rates of recurrence, with 74% of CGD patients and 73% SGD patients experiencing recurrence. Regional recurrence rates were more common in the SGD group than in the CGD group thought the difference was not statistically significant (p=0.498) (Van der Ploeg et al, 2011).

In one retrospective study in 143 patients undergoing either inguinal dissection or a combined inguinal and iliac/obturator dissection, rates of pelvic lymph node recurrence did not differ significantly when considering patients with microscopic disease. For patients with macroscopic disease, pelvic node recurrence rates did not differ significantly (Egger et al, 2014).

In one retrospective study in 143 patients undergoing either inguinal dissection or a combined inguinal and iliac/obturator dissection, systemic recurrence was the most common type of recurrence with 43% of patients undergoing inguinal dissection and 48% of patients undergoing combined inguinal and iliac/obturator dissection experiencing systemic recurrences. Systemic recurrences were more common in patients with macroscopic disease than in patients with microscopic disease (Egger et al, 2014).

Melanoma-specific survival

In one retrospective study in 52 patients undergoing completion groin node dissection or superficial groin node dissection, 5-year disease free survival was 53% in the superficial node dissection group compared with 61% in the complete groin dissection group (van der Ploeg et al, 2008).

In one retrospective study in 169 patients undergoing either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD), no significant difference in disease-free survival was observed between the groups. 5-year estimated disease-free survival rate was 15.7% in the SGD group and 18.3% in the CGD group. Considering the whole cohort, significant prognostic factors for disease-free survival included number of positive superficial nodes (HR=1.6, 95% CI 1.03-2.51, p=0.038) and superficial lymph node ratio (HR=2.33, 95% CI 1.25-4.34, p<0.008) (van der Ploeg et al, 2011).

In one retrospective study in143 patients undergoing either inguinal dissection or a combined inguinal and iliac/obturator dissection, disease-free survival was significantly longer in patients with macroscopic disease compared to those with microscopic disease (p=0.0002) (Egger et al, 2014).

Overall survival

In one retrospective study in 52 patients undergoing completion groin node dissection or superficial groin node dissection, 5-year overall survival for patients who underwent only a superficial groin node dissection was 76% (95% CI 62-95%) compared with 80% (95% CI 61-100%) for patients who underwent completion groin node dissection (van der Ploeg et al, 2008).

In a retrospective study in which 104 patients underwent either ilio-inguinal dissection or inguinal dissection, 5 year overall survival for the whole cohort was 30.4% and 10 year overall survival for the whole cohort was 18.4% and extent of lymph node dissection did not have a significant effect on survival (Kretschmer et al, 2001).

A second retrospective study in which 169 patients underwent either combined superficial and deep groin dissection (CGD) or a therapeutic superficial groin dissection (SGD) also reported no significant difference in overall survival when comparing extent of lymph node dissection (van der Ploeg et al, 2011).

In one retrospective study in which 264 patients either underwent femoral nodal dissection for palpable groin disease or underwent an iliac nodal dissection for melanoma metastasis, no significant difference in median overall survival was observed (32.7 months versus 39.5 months, p=0.17) and the type of groin dissection did not affect survival when patients were stratified by tumour burden (Singletary et al, 1992)

In one retrospective study in 37 patients comparing those undergoing radical neck dissection, modified radical dissection or selective dissection, overall survival at 60 months was 33% with no difference observed in survival rates for the 3 different types of dissection (White et al, 1992).

Adverse events

In one retrospective study in which 13 patients underwent minimally invasive inguinal lymph node dissection (MILND) and 28 patients underwent open inguinal lymph node dissection (OILND), operative time was significantly longer for MILND patients compared with OILND patients (p=0.003) but length of hospital stay was significantly shorter (p=0.01) and the incidence of hospital readmission was higher in the OILND group (21%) than in the MILND group (7%), though the difference was not statistically significant (p=0.25). The rates of wound dehiscence (p=0.07) and infection (p=0.13) were greater in the OILND group compared with the MILND group (Abbot et al, 2013).

Table 34: What is the most effective surgical treatment for stage III melanoma (superficial lymph node dissection versus extended lymphadenectomy for palpable lymph nodes)?

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Superficial Lymph Node Dissection	Extended lymphadenectomy	Relative (95% CI)	Absolute	Quality
Recurrence (Kretschemer et al, 2001; van der Ploeg et al, 2011; Egger et al, 2014)											
3 (n=416)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/183[3]	?/416[3]	Not Pooled[4]		Very Low
Melanoma Specific Survival (van der Ploeg, 2008; van der Ploeg et al, 2011; Egger et al, 2014)											
3 (n=374)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/158[3]	?/207[3]	Not Pooled[4]		Very Low
Overall Survival (van der Ploeg, 2008; van der Ploeg et al, 2011; Kretschemer et al, 2001; Singletary et al, 1992; White et al, 1992)											
5 (n=636)	observational studies	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	?/213[3]	?/423[3]	Not Pooled[4]		Very Low
Adverse Events (Abbot et al, 2013)											
1 (n=41)	observational studies	serious[3]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	Operative time was significantly longer for minimally invasive inguinal lymph node dissection patients compared with open inguinal lymph node dissection patients (p=0.003) but length of hospital stay was significantly shorter (p=0.01) and incidence of hospital readmission was higher in the OILND group				Very Low

[1] Not a randomised trial; [2] The studies do not clearly specify what AJCC stage included patients have been assign, [3]Event rate is not reported,[4]Data were not pooled as the individual studies were comparing different types and locations of surgical intervention.

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

<table>
<tr><td>Recommendations</td><td>Consider completion lymphadenectomy for people with a positive sentinel lymph node biopsy (stage 3A melanoma) and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.
<table>
<tr><th>Possible advantages of completion lymphadenectomy</th><th>Possible disadvantages of completion lymphadenectomy</th></tr>
<tr><td>Removing the rest of the lymph nodes before cancer develops in them reduces the chance of the cancer returning in the same part of the body.</td><td>Lymphoedema (long-term swelling) may develop, and is more likely if the operation is in the groin than in other parts of the body.</td></tr>
<tr><td>The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them.</td><td>In 4 out of 5 people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily.</td></tr>
<tr><td>People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. These trials often cannot accept people who have not had this operation.</td><td>There is no evidence that people who have this operation live longer than people who do not have it.</td></tr>
<tr><td></td><td>Having any operation can cause complications.</td></tr>
</table>
Offer therapeutic lymph node dissection to people with stage 3B-3C melanoma (those with clinically detectable nodal disease).</td></tr>
<tr><td>Relative value placed on the outcomes considered</td><td>The GDG considered a number of outcomes to be important for this topic including local recurrence, regional recurrence, disease-specific survival (5 and 10 years), overall survival (5 and 10 years), HRQoL, accurate staging, long term adverse events, (including lymphoedema) and shorter-term adverse events (surgical).</td></tr>
<tr><td>Quality of the evidence</td><td>The quality of the evidence for each outcome was considered to be very low as assessed using GRADE.

There was limited evidence on the extent of lymph node dissection for stage 3 head and neck melanoma which was considered by the group to be one of the topics of clinical uncertainty.

There was no evidence on the management of aberrant nodes.</td></tr>
</table>

	There was limited evidence on the extent of lymph node dissection for stage 3 melanoma in the groin. A specific recommendation for patients with stage 3A melanoma was included as the GDG recognised that SLNB is the most sensitive staging procedure for melanoma and is likely to remain important in clinical practice for some time. It was therefore important to make a recommendation about proceeding to completion lymphadenectomy in terms of balancing possible benefit and the morbidity associated with the procedure. Although the quality of the evidence for completion lymphadenectomy after a positive SLNB was very low the GDG felt that the patient should be made aware of the positive and negative consequences of the surgery and that the decision whether or not to proceed should be made by them. For patients with palpable nodal disease (stage 3B-3C) a specific recommendation for therapeutic lymph node dissection was made because these patients require surgery for local disease control. However because of a lack of good evidence, no recommendation on the extent of lymphadenectomy could be made for palpable disease. There was no evidence that iliac nodal surgery resulted in better disease control but the studies were so small and of such poor quality that benefit could not be ruled out.
Trade off between clinical benefits and harms	The GDG felt that as a result of the recommendation to consider completion lymphadenectomy in patients with a positive SLNB, there would probably be a reduction in local recurrence and consequent morbidity in the estimated 20% of stage 3A patients who would have subsequently recurred locally, if they did not have a completion lymphadenectomy. For patients who would not have subsequently recurred locally, and might therefore be judged to have had unnecessary surgery, there was a higher risk of lymphoedema.
Trade off between net health benefits and resource use	No relevant cost effectiveness analyses were identified and this topic was not considered a priority area for the development of an economic model. No cost analysis was conducted for this topic. The GDG agreed that it was difficult to predict whether there would be increased or decreased costs as a result of these recommendations. There may be less completion lymphadenectomy in centres which routinely recommend SNB if the patients are given more information about the possible advantages and disadvantages of the procedure.
Other considerations	No equalities issues were identified for this topic.

6.21 Adjuvant radiotherapy

Melanoma metastatic to draining lymph nodes is treated by resection, but a proportion of patients will progress to further recurrence over time. The risk of further local recurrence is higher when a greater tumour volume has been resected or the histopathologist has reported extra-capsular spread (tumour was seen to be extending outside the thin capsule around the lymph node). Adjuvant radiotherapy has therefore been advocated for patients in this group as a means of reducing the risk of subsequent local recurrence.

Clinical question: What is the effectiveness of adjuvant radiotherapy to the resected lymph node basin for stage 3 melanoma in people who have undergone curative resection?

Clinical evidence

The evidence is summarised in Table 35.

One low quality randomised trial in 248 patients (Burmeister et al, 2012) reported a significantly lower risk of lymph node field relapse in patients treated with adjuvant radiotherapy compared to patients in the observation arm: HR=0.47 (95% CI, 0.28-0.81) p=0.005. A second, very low quality retrospective cohort study (Strom et al, 2014) reported better local control in patients treated with adjuvant radiotherapy (HR=0.15, 95% CI 0.06-0.39, p=0.001) and poorer local control was significantly associated with male sex, Clark's level V and positive resection margins.

Very low quality evidence from one retrospective observational study including 130 patients, 5-year actuarial melanoma specific survival was 84% and 10-year actuarial melanoma specific survival was 80% for the whole cohort.

Low quality evidence from two randomised trials in 304 patients (Burmeister et al, 2012; Creagan et al, 1978), no significant difference in relapse-free survival between patients in the radiotherapy arm versus the observation arm was reported.

Low quality evidence from one randomised trial in 56 patients (Creagan et al, 1978) median disease-free survival was 43 months for irradiated patients versus 30 months for those having surgery alone (p=0.15).

Low quality evidence from one randomised trial in 248 patients (Burmeister et al, 2012) reported no statistically significant difference in overall survival for patients receiving adjuvant radiotherapy compared with patients in the observation arm: HR 1.35 (95% CI; 0.94-1.92) p=0.12.

Very low quality evidence from one prospective case series study followed 234 patients treated with adjuvant radiotherapy for a median of 58.4 months (range 21.2-158 months) and reported that radiotherapy was well tolerated in most patients with lymphodema being the most significant adverse event. 9% of patients with axillary disease and 19% of patients with ilio-inguinal disease experienced grade 3 lymphodema (Burmeister et al, 2006)

Table 35: What is the effectiveness of adjuvant radiotherapy to the resected lymph node basin for stage III melanoma in people who have undergone curative resection?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Radiotherapy of the resected lymph node basin	Observation	Relative (95% CI)	Absolute	Quality
Lymph node field relapse (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/109 (18.3%)	34/108 (31.5%)	HR 0.47 (0.28 to 0.81)	152 fewer per 1000 (from 51 fewer to 214 fewer)	LOW
Local Control (Strom et al, 2014)											
1	observational study	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/277 patients failed locally (details not reported according to treatment)		HR 0.15 (0.06 to 0.39)		VERY LOW
Melanoma Specific Survival (Guadagnolo et al, 2013)(											
1	observational study	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	None	5 year actuarial melanoma specific survival 84% for the whole cohort 10 year actuarial melanoma specific survival 80% for the whole cohort				VERY LOW
Relapse free survival/Disease Free Survival (Burmeister et al, 2012 and Creagan et al, 1978)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	79/149 (53%)	86/155 (55.5%)	not pooled	not pooled	LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Radiotherapy of the resected lymph node basin	Observation	Relative (95% CI)	Absolute	Quality
Lymphodema (Burmeister et al, 2006)											
1	observational studies	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Grade 3-4 lymphoedema reported in a total of 19 patients (Axilla=9%; Inguinal=19%)				VERY LOW
Early adverse events (surgical) (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19 patients reported grade 3-4 dermatitis resulting from radiotherapy (head & neck n=3; axilla n=10; ilio-inguinal n=6) 2 patients reported grade 3-4 pain resulting from radiotherapy to the axilla				LOW
Overall survival (Burmeister et al, 2012)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/122 (54.1%)	55/126 (43.7%)	HR 1.35 (0.94 to 1.92)	102 more per 1000 (from 20 fewer to 231 more)	LOW
Late toxicity (Burmeister et al, 2006)											
1	observational studies	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW
								0%		0 fewer	

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Radiotherapy of the resected lymph node basin	Observation	Relative (95% CI)	Absolute	Quality
										per 1000 (from 0 fewer to 0 fewer)	

[1] *There was no blinding in this trial, but it is not possible to blind patients and investigators because of the nature of the comparison;* [2] *There was reduced power in the study because of the number of ineligible patients who were excluded. Analysis was carried out on the intent to treat population;* [3] *Retrospective observational study comparing wide local excision + adjuvant radiotherapy with wide local excision alone in which patients receiving adjuvant radiotherapy were highly selected according to clinical features;* [4] *Retrospective observational study reporting disease specific survival rates with no confidence intervals or p values;* [5] *There was reduced power in the Burmeister study because of the number of ineligible patients which were excluded. Analysis was carried out on the intent to treat population. The Creagan study was also underpowered and had a high number of ineligible patients which were not analysed. Analysis in the Creagan study was not carried out in the intent to treat population;* [6] *Prospective observational study with no comparison group*

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Do not offer adjuvant radiotherapy to people with stage 3A melanoma.** **Do not offer adjuvant radiotherapy to people with stage 3B or 3C melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects.**
Relative value placed on the outcomes considered	The GDG considered local recurrence, overall survival and adverse effects, (specifically lymphoedema) as being the most important outcomes. Other outcomes of interest included disease-specific survival and metastasis-free survival.
Quality of the evidence	The evidence for local recurrence (defined as lymph node basin relapse), overall survival and adverse events was found to be of low to very low quality on GRADE assessment. Some evidence on relapse- and disease-free survival was reported and although not listed as an outcome of interest was subsequently deemed to be of interest and included for information and completeness, but the quality of the evidence was low. There was some very low quality evidence relating to lymphoedema specifically and adverse events were reported as early (low quality) and late (very low quality). No evidence was identified relating to disease-specific survival or for metastasis-free survival. There was a lack of blinding in the randomised trials which may have resulted in an increase in bias but the GDG felt that as it was not possible to blind patients and investigators from the interventions because of the nature of the comparisons under review, and so they did not consider that the lack of blinding would preclude use of the data. The GDG felt it was necessary to make specific recommendations about stage 3A melanoma and stage 3B-3C melanoma separately because of the lack of evidence about stage 3A melanoma. The GDG also agreed that it was not appropriate to apply the Stage 3B-3C recommendations to stage 3A as, in their clinical experience, the prognostic difference between these two patient groups is considerable. The recommendation on stage 3A patients was therefore based on clinical consensus because of the lack of any evidence for this patient group.

Trade off between clinical benefits and harms	For stage 3B-3C the GDG considered that the evidence of a significant reduction in local recurrence did not justify recommending routine use of adjuvant radiotherapy for these patients. The reasons for this were the absence of any evidence of an overall survival benefit of using adjuvant radiotherapy in stage 3B-3C melanoma patients, and the evidence of increased risk of grade 3 lymphoedema after radiotherapy. The GDG also considered the possibility that by potentially reducing the number of patients receiving adjuvant radiotherapy this could lead to an increased risk of local recurrence, but felt that in a significant proportion of these patients the recurrence could be controlled by further surgery. However, the GDG felt that the recommendation allowed for clinical situations in which the MDT and patient would consider the trade off between these risks and benefits and could decide that adjuvant radiotherapy was indicated. For stage 3A patients no evidence was identified during the evidence review for this topic. The GDG considered the low risk of loco-regional recurrence after completion lymphadenectomy for stage 3A disease, and the lack of a survival benefit from adjuvant therapy for stage 3B and stage 3C melanoma. As a result the GDG agreed that adjuvant radiotherapy for stage 3A disease should be avoided in view of the possible harmful effects of the adverse events (lymphoedema and late effects of radiation). The GDG felt therefore because of the lack of evidence, coupled with only low quality evidence of clinical benefit for stage 3B-3C patients, that it would be inappropriate to recommend the use of adjuvant radiotherapy in stage 3A patients.
Trade off between net health benefits and resource use	No relevant cost effectiveness analyses were identified and this topic was not considered a priority area for the development of an economic model. No cost effectiveness analysis was therefore carried out for this topic. There are potential cost savings resulting from the reduction in the number of patients undergoing radiotherapy and management of post radiotherapy complications, balanced against the risk of increased local recurrence.
Other considerations	There is currently variable practice in the UK with treatment decisions made on a patient by patient basis following discussion at the SSMDT and the recommendations are unlikely to lead to a major change in the current practice. No equalities issues were identified for this topic.

6.3 In transit metastases

In transit melanomas are metastases in the regional dermal and subdermal lymphatics occurring between >2cm from the excision scar and the regional nodes. The risk of developing in transit metastases is directly related to the stage of the disease at diagnosis but multiple in transit metastases are most common on the leg. For isolated or limited numbers of in transit metastases, surgical resection is the current usual practice. The suitability for surgical resection is usually determined by expert clinical opinion based on the number, location and the frequency of the recurrences and the anticipated treatment morbidity. Many patients will relapse, but for those with intermittent recurrence of a few

metastases the morbidity associated with surgical resection is generally considered acceptable. If relapse occurs more frequently or if in transit nodules which are not readily resectable develop, a variety of alternative regional or systemic treatments are currently used. The GDG thought it important to consider the evidence for local control balanced against the morbidities of the different therapeutic options. The role of new targeted systemic and immunotherapy in unresectable in transit metastases compared with currently available regional therapies is changing rapidly. It is therefore likely that the threshold for use of systemic treatments for in transit disease will be lower in the future.

Treatments for in transit metastases include:

- local treatments such as surgery, cryotherapy, $C0_2$ laser,
- topical agents (such as imiquimod addressed in section 5.2) and
- electrochemotherapy (ECT)
- regional treatment with isolated limb infusion (ILI) or isolated limb perfusion (ILP),
- radiotherapy
- amputation
- systemic treatments.

Clinical question: What is the most effective treatment for in transit melanoma metastases (for example, surgery, isolated limb infusion, isolated limb perfusion, palliative radiotherapy, cryotherapy, electro-chemotherapy or the laser)?

Clinical evidence

The evidence is summarised in Tables 36 to 40.

Electrochemotherapy

Very low quality evidence from one systematic review and meta-analysis (Mali et al, 2013) reported a complete response rate of 56.8% and an objective response rate of 80.6% for patients with melanoma who were treated with electrochemotherapy.

CO_2 laser

Very low quality evidence from two observational case series studies in 76 patients and 5059 lesions (Hill et al, 1993); Kandamany et al, 2009) reported survival in patients treated with CO2 laser. Overall survival at 12 months was 67% (40/60) (Hill et al, 1993) and disease free survival at 12 months was 62.5% (10/16) (Kandamany et al, 2009).

Radiotherapy

Very low quality evidence from one retrospective case series in 57 patients with stage UICC III, of which a small subset had in transit melanoma, were treated with radiotherapy (Seegenschmiedt et al, 1999). A total of 44% of stage UICC III patients had a complete response while 21% of stage UICC III patients showed progressive disease.

Surgical excision

Very low quality evidence from one retrospective case series with a total of 33 patients treated for loco-regional metastases of the lower extremities (Fotopoulos et al, 1998) reported a median disease-free survival of 16 months (1-104 months) and median overall survival of 31 months (2-264 months).

Isolated limb perfusion versus isolated limb infusion

Very low quality evidence from one retrospective case series with 214 patients, (Sharma et al, 2012) reported a significantly higher rate of complete response in patients treated with ILP compared with patients treated with ILI (44% versus 28%; p=0.01).

At 3-year follow-up following a complete response to treatment; very low quality evidence from a single retrospective case series with 214 patients (Sharma et al, 2012) reported a recurrence rate of 65% (95% CI 43%-79%) for patients treated with HILP compared with a recurrence rate of 85% (95% CI 53%-94%) for patients treated with ILI. Time to first recurrence was longer for HILP (23 vs. 8 months, p=0.02).

Very low quality evidence from one retrospective case series with 214 patients, (Sharma et al, 2012) showed that in patients achieving complete response to treatment, in field recurrence rates were 44% (95% CI 16%-58%) for HILP compared with 56% (95% CI 30&-72%) for ILI. Median time to in field recurrence was not statistically significantly different (HILP 46 months vs. ILI 25 months; p=0.15).

Very low quality evidence from one retrospective case series with 214 patients, (Sharma et al, 2012) showed that in patients achieving complete response, the out of field recurrence rate was 44% (95% CI 23%-60%) for HILP compared with 77% (95% CI 51%-89%) for ILI. Time to out of field recurrence was longer for HILP (42 versus 14 months, p=0.02).

Very low quality evidence from one retrospective case series with 214 patients, (Sharma et al, 2012) showed that in patients achieving complete response, there was no statistically significant difference in median overall survival between HILP and ILI (100 vs. 39 months, p=0.10).

Table 36: GRADE profile: What is the most effective treatment for in transit melanoma metastases (surgical excision)?

Quality assessment							Summary of Findings				Quality
local control											
0	no evidence available										
Melanoma specific survival											
0	no evidence available										
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgical Excision**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall Survival (Fotopoulos et al, 1998)											
1 (n=33)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	/33[4]	No comparison	Median overall survival of 31 months (2-264 months)-		Very Low
Time to next treatment											
0	no evidence available										
Adverse Events											
0	no evidence available										
Health Related Quality of Life											
0	no evidence available										

[1] This is a retrospective case series study with no comparison to surgical excision; [2] Not all patients in the study had in transit melanoma; [3] Very small numbers of relevant patients in the study and wide ranges in survival times, [4]Event rage not reported

1 **Table 37: GRADE profile: What is the most effective treatment for in transit melanoma metastases (radiotherapy)?**

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**		**Relative (95% CI)**	**Absolute**	
Local Control (Seegenschmiedt et al, 1999)											
1 (n=57; 24 patients with in-transit metastases)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none		No comparison	44% of stage UICC III patients had a complete response while 21% of stage UICC III patients showed progressive disease		Very Low
Melanoma Specific Survival											
0	no evidence available										
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Radiotherapy**	**None**	**Relative (95% CI)**	**Absolute**	**Quality**
Overall Survival (Seegenschmiedt et al, 1999)											
1 (n=57; 24 patients with in-transit metastases)	observational studies	serious[1]	no serious inconsistency	serious	serious[3]	none		No Comparison	Patients with in-transit metastases* had a median survival of 19		Very Low

									months; 1 year survival was 69±17% and 5 year survival was 32±20%.	
Time to next treatment										
0	no evidence available									
Adverse Events										
0	no evidence available									
Health Related Quality of Life										
0	no evidence available									

[1] This is a retrospective case series study with no comparison to radiotherapy; [2] The study included patients without in transit melanoma; [3] The numbers of patients with in transit melanoma included in the study was a small proportion of the total patient numbers, [4]Study states that N=33 patients had in transit metastases and n=24 patients had regional lymph node metastases however the table within the study states n=33 patients had regional lymph node metastases and n=24 patients had in transit metastases. It is not clear which the correct number of patients for each

Table 38: GRADE Profile: What is the most effective treatment for in transit melanoma metastases (electrochemotherapy)?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electrochemotherapy**	**control**	**Relative (95% CI)**	**Absolute**	
Local Control (Mali et al, 2013)											
22 (150 patients with 920 tumours)	observational studies	serious[1]	serious[2]	serious[3]	serious	None		No Comparison	A complete response rate of 56.8% and an objective response rate of 80.6% for patients with		VERY LOW

									melanoma who were treated with electrochemotherapy	
Melanoma Specific Survival - not measured										
0	-	-	-	-	-	None			- -	
Time to next treatment - not measured										
0	-	-	-	-	-	None			-	
Adverse Events - not measured										
0	-	-	-	-	-	None			-	
Health Related Quality of Life - not measured										
0	-	-	-	-	-	None			-	

1 *[1] Studies are not randomised trials, many are retrospective studies and case series with a high risk of bias; [2] Response to treatment varied widely across the individual studies*
2 *(0%-100% for compete response); [3] The studies included in the review included patients other than those with in transit melanoma*

3 **Table 39: GRADE profile: What is the most effective treatment for in transit melanoma metastases (CO_2 laser)?**

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CO2 laser**	**control**	**Relative (95% CI)**	**Absolute**	
Local Control (Hill et al, 1993; Kandamany et al, 2009)											

2 (76 patients with 5059 lesions)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none		No Comparison	Not Pooled	Very Low
Melanoma Specific Survival - not measured										
0	-	-	-	-	-	none	-	-	-	
Time to next treatment - not measured										
0	-	-	-	-	-	none	-	-	-	
Adverse Events - not measured										
0	-	-	-	-	-	none	-	-	-	
Health Related Quality of Life - not measured										
0	-	-	-	-	-	none	-	-	-	

1 *[1] Non-randomised studies with no comparator and small numbers (n=76 patients total); [2] Patients with all stages of Melanoma are included in one of the studies; [3] Numbers*
2 *are too small for precise results to be obtained*
3

Table 40: GRADE profile: What is the most effective treatment for in transit melanoma metastases (isolated limb perfusion versus isolated limb infusion)?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Isolated Limb Perfusion	Isolated Limb Infusion	Relative (95% CI)	Absolute	
Response Rates (Sharma et al, 2012)											
1 (n=214)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	?/81[3]	?/133[3]	-complete response rate of 44% for patients receiving first time hyperthermic isolated limb perfusion (HILP) compared with a complete response rate of 28% for patients undergoing first time isolated limb infusion		Very Low
3 Year Recurrence Rate (Sharma et al, 2012)											
1(n=214)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	?/81[3]	?/133[3]	HILP: 65% (95% CI 43-79%) ILI: 85% (95% CI 53-94%).		Very Low
Overall Survival (Sharma et al, 2012)											
1 (n=214)	Observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	?/81[3]	?/133[3]	In patients achieving complete		Low

									response, no statistically significant difference in median overall survival between HILP and ILI (100 vs. 39 months)	

[1] *Retrospective analysis of a prospective database;* [2] *Only patients who achieved complete response were evaluated for recurrence resulting in small numbers of patients and events,* [3]*Event rage not reported*

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

Recommendations	**Refer the care of all people with newly diagnosed or progressive in transit metastases to the specialist skin cancer multidisciplinary team.** **Offer surgery as a first option to people with isolated or limited in transit metastases if local treatment is indicated.** **If surgery or systemic treatment are not suitable for people with in transit metastases, consider other local and regional treatment options, including:** • **isolated limb infusion** • **isolated limb perfusion** • **radiotherapy** • **electrochemotherapy in line with NICE's interventional procedure guidance on electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma.** • **CO_2 laser** • **topical agents.**
Relative value placed on the outcomes considered	Local control was considered to be the most important outcome by the GDG because of the morbidity associated with progressive local disease. Successful local control can have a positive impact on quality of life and is therefore important to the patient. Overall survival was also considered to be important. Evidence was identified for all outcomes other than time to next treatment, adverse events and HRQoL.
Quality of the evidence	The quality of the evidence was assessed as being very low for all reported outcomes using GRADE. The only comparative evidence identified was a non-randomised comparative study comparing isolated limb perfusion with isolated limb infusion. All other identified studies were retrospective, non-comparative case series. Sample sizes in all studies were very small and populations included patients other than those with in transit metastases and this made the comparisons difficult. There was no consistency of reporting of outcomes across the individual studies meaning that any kind of meta-analysis was not possible. For those patients for whom surgery or systemic treatment was not suitable the GDG were unable to recommend one treatment option above any other because, despite the very low quality evidence available, all treatment options showed some evidence of a positive clinical effect and not to recommend any treatment was not considered to be appropriate. The GDG agreed therefore that there was no evidence to exclude any of the treatment options, other than those for which there was no evidence at all

	(amputation, cryotherapy and imiquimod). As a result of the low quality evidence, all of the recommendations were made on the basis of clinical judgement and expertise. No evidence to support the recommendation of a specific sequence of treatments was identified but the GDG agreed that the first treatment option for these patients should be surgery whenever possible and that other treatment options should only be considered following surgical failure or in the small proportion of patients for whom surgery was not an appropriate first treatment option. The specific recommendation that surgery should be offered as the first option was made because the GDG felt this was the current usual care for these patients, and that the evidence examined did not support a move away from this. The GDG felt that it is unlikely that a comparative trial of surgery with other treatment options for localised disease would ever be carried out.
Trade off between clinical benefits and harms	The GDG felt that in the absence of any evidence to support one treatment option over any other, it was important that patients had access to a full range of treatment options including systemic therapy, all of which may improve local control for this patient group. The GDG also felt that highlighting the specific treatment options would lead to an increased awareness of the available treatments. The GDG acknowledged that there may be potential adverse effects related to these treatments, but they felt that there was no evidence to suggest that one treatment was significantly worse than any of the others and that patient and clinicians should be free to choose what they consider to be the best option. The GDG feel that the benefits of treatment in relation to local control outweigh the potential adverse treatment effects that a minority of patients may suffer.
Trade off between net health benefits and resource use	No relevant cost effectiveness analyses were identified and this topic was not considered a priority area for the development of an economic model. No cost effectiveness analysis was conducted for this topic. The GDG felt that there would be no significant savings resulting from these recommendations as the GDG did not consider that it was likely that there would be a major change in clinical practice because isolated limb perfusion is a more complex procedure and available in only a few centres. The GDG agreed that recommendations may result in a small increase in the use of isolated limb perfusion (and therefore increased costs) but could not exclude this option on cost grounds as there is no strong evidence that it is less effective or more toxic.
Other considerations	No equalities issues were identified for this topic.

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7 Stage 4 melanoma

7.1 Localised treatments for metastatic stage 4 melanoma

A variety of different localised, non-drug, treatments have been used to treat metastatic melanoma - a tumour which has spread through the bloodstream to reach distant sites. The commonest metastatic sites are the skin and subcutaneous tissues, liver, lungs, brain and bone. These treatments are used to control symptoms and sometimes to treat oligometastatic disease (here defined as a small number of metastases which are surgically resectable) in the belief that this might prolong survival.

All the many local treatments which have been used, and several new techniques currently being evaluated, have in common the aim of removing the melanoma metastases completely, and so reducing the risk of recurrence at that particular site, while minimising the risks of harm. Surgical removal of melanoma metastases has been used for many years and recent advances in imaging and diagnostic techniques have allowed more precise surgical intervention, improving palliation with less morbidity. In addition there are new techniques such as laser therapy and electro-chemotherapy which are being increasingly used particularly for the palliation of multiple subcutaneous metastases.

Stereotactic radiosurgery, introduced in the last two decades, is able to deliver highly focused radiation treatment, in a few treatment fractions, to very precise target areas with much less radiation to surrounding normal tissues. This not only reduces the risk of treatment morbidity but also the number of patient visits for treatment. This is most often used for brain metastases (see section 7.2) for which the inevitable morbidity of surgery, might not justify the likely palliation, but may also have a role in managing pulmonary metastases.

Recent developments in the use of effective systemic therapy for selected patients with metastatic melanoma (see section 7.3), may mean that these palliative treatments may be needed less often in the future. However there will be patients who, for a number of reasons, are not suitable for systemic therapy, do not respond to it or develop progressive disease subsequently, for whom these localised treatments will be indicated.

Clinical question: How effective is surgery, ablative treatments or stereotactic radiotherapy for people with stage 4 melanoma with oligometastatic disease?

Clinical evidence

The evidence is summarised in Tables 41 to 51.

Overall survival

The effectiveness of surgery, ablative treatments or stereotactic radiotherapy for people with stage IV melanoma with oligometastatic disease is unclear from the evidence in the 14 included papers.

Surgery and/or stereotactic radiotherapy

Very low quality evidence suggests that patients who receive surgery and/or stereotactic radiotherapy have greater median length of survival compared to patients who do not receive these treatments but these studies are at high risk of selection bias.

Surgery versus no surgery

Very low to low quality evidence from a number of papers comparing survival in patients who received surgery compared to those who did have not surgery for a number of different metastases – brain, lung, adrenal, liver and abdominal. There were also two papers that examined this in patient cohorts with a range of different metastatic locations. All these papers demonstrated that patients having surgery survived longer than those who did not have surgery.

Surgery versus supportive care, chemotherapy, whole brain radiotherapy (WBRT) and chemotherapy and/or WBRT

These studies of the treatment of brain metastases showed that surgery gives better results with regards to overall survival than supportive care, chemotherapy, WBRT and chemotherapy and/or WBRT; STR resulted in longer median overall survival than chemotherapy and WBRT; treatment with STR or surgery resulted in longer median overall survival than WBRT and supportive care. There were two studies comparing surgery and STR and they demonstrated little difference in overall survival between these two treatments. One study found that surgery increased survival by 0.3 months compared to STR and the other study found that STR increased survival by 1.71 months compared to surgery.

Surgery + ablation versus ablation alone

A single study (Faries et al, 2014) reported on 58 patients undergoing surgery with ablation or ablation alone and reported a 5-year overall survival rate of 6.6% in the non-surgical group compared with 30% in the surgical group ($p<0.001$) though outcomes did not differ significantly by type of surgery (resection, ablation, resection with ablation).

To what extent the longer median survival associated with surgery and stereotactic radiotherapy is related to the treatment itself or to selection of patients with better performance status is unclear. All 14 studies are retrospective cohort studies and all have a high patient selection bias. Also the studies do not aim to compare treatment modalities but to show that the treatment investigated (usually surgery) in suitable patients can confer a survival advantage - many of the studies compare surgery vs. no surgery, but the no surgery group is made up of patients undergoing a range of different treatments or no treatment at all.

Adverse events

Two studies provided low quality evidence about adverse events. In Bushbaum et al, 2002 radiotherapy for brain metastases (either STR or WBRT) was associated with acute complications (swelling requiring steroid treatment or seizures) in 10/70 patients (14%) but no symptomatic radiation necrosis was reported. Surgery was associated with acute complications requiring hospitalization in 6/25 (24%) patients. These complications included infection, haemorrhage and central nervous system deficits. In Gutman et al, 2001 surgery for abdominal metastases was associated with a 14% rate of major complications (sepsis, evisceration or pulmonary embolism) and mortality rate of 3% within 30 days of surgery.

Metastases-free survival

In Bushbaum et al, 2002 brain metastases recurred locally in 2/10 patients (20%) treated with local therapy only (surgery or STR) and 4/24 patients (17%) treated with WBRT alone.

Health related quality of life

Health related quality of life was not reported although there was low quality evidence from one study (Gutman et al, 2001) that surgery provides better symptom relief in patients with

abdominal metastases. 23% of patients treated using surgery were symptom free for at least 1 year compared with a typical symptom free period of 1 month in those treated without surgery.

Table 41: GRADE profile: How effective is surgery versus no surgery for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	no surgery	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	163	292	-	Overall median survival was 5.4 - 7.7 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Serious adverse events: brain metastases											
1	observational study[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	6/25 (24%)	10/70 (15%)	-	90 fewer adverse events per 1000 treated in the non surgery group – but the types of adverse events were different.	VERY LOW
Overall survival: lung metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	26	96	-	Overall median survival was 27 months longer in patients that underwent surgery	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	no surgery	Relative (95% CI)	Absolute	Quality
										compared to those who did not have surgery.	
Overall survival: adrenal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	None	16	163	-	Overall median survival was 11 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Overall survival: liver metastases											
2	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	39	907	-	Overall median survival was 17 - 22 months longer in patients that underwent surgery compared to those who did not have surgery.	VERY LOW
Overall survival: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	96	155	-	Overall median survival was 6 months longer in	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	no surgery	Relative (95% CI)	Absolute	Quality
										patients that underwent surgery compared to those who did not have surgery.	
Serious adverse events: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	13/96 (14%)	-	-	Cannot calculate because adverse events were not reported for the non surgical patients.	VERY LOW
Symptom free at 1 year: abdominal metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	22/96 (23%)	-	-	Symptom free rate at 1 year not reported for non-surgical group – although authors state that such patients were rarely symptom free for more than a month.	VERY LOW
Overall survival: mixed metastases											
	observational	very	no serious	no serious	no serious	none	151	318	-	Overall median	VERY

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	no surgery	Relative (95% CI)	Absolute	Quality
	studies[1]	serious[2]	inconsistency	indirectness	imprecision					survival was 12.3 - 13 months longer in patients that underwent surgery compared to those who did not have surgery.	LOW

[1] *Retrospective cohort study;* [2] *High bias due to patient selection for surgery;* [3] *Low number of events or patients*

Table 42: GRADE profile: How effective is surgery versus chemotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	Chemo-therapy	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	42	55	-	Overall median survival was 4 - 7 months longer in patients treated with surgery compared to those treated with chemotherapy.	VERY LOW

[1] *Retrospective cohort study;* [2] *Serious risk of bias due to patient selection for treatment;* [3] *Low number of events or patients*

Table 43: How effective is surgery versus supportive care for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	supportive care	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	120	336	-	Overall median survival was 4 - 10 months longer in patients treated with surgery compared to those that had supportive care only.	VERY LOW

[1] Retrospective cohort studies; [2] Serious risk of bias due to patient selection for treatment

Table 44: How effective is surgery stereotactic radiotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	stereotactic radiotherapy	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	73	43	-	Overall median survival was -1.71 – 0.3 months longer in patients	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	stereotactic radiotherapy	Relative (95% CI)	Absolute	Quality
										treated with surgery compared to those treated with stereotactic radiotherapy.	

1 *[1] Retrospective cohort study; [2] High risk of bias due to patient selection for treatment; [3] Low number of events or patients*

2 **Table 45: How effective is surgery versus whole brain radiotherapy for people with stage IV melanoma with oligometastatic disease?**

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	WBRT	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
4	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	125	418	-	Overall median survival was 4.2 - 9 months longer in patients treated with surgery compared to those treated with WBRT.	VERY LOW

3 *[1] Retrospective cohort study; [2] High risk of bias due to patient selection for treatment*

Table 46: How effective is surgery versus chemotherapy and/or whole brain radiotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	chemotherapy and/or WBRT	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	32	75	-	Overall median survival was 2 months longer in patients treated with surgery compared to those treated with chemotherapy and/or WBRT.	VERY LOW

[1] Retrospective cohort study; [2] High risk of bias due to patient selection for treatment; 3 Low number of events or patients

Table 47: How effective is stereotactic radiotherapy versus chemotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	chemotherapy	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	17	38	-	Overall median survival was 3.7 months	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	chemotherapy	Relative (95% CI)	Absolute	Quality
										longer in patients treated with STR compared to those treated with chemotherapy	

[1] *Retrospective cohort study;* [2] *High risk of bias due to patient selection for treatment;* [3] *Low number of events or patients*

Table 48: How effective is stereotactic radiotherapy versus whole brain radiotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	WBRT	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	17	54	-	Overall median survival was 4.8 months longer in patients treated with STR compared to those treated with WBRT.	VERY LOW

[1] *Retrospective cohort study;* [2] *High risk of bias due to patient selection for treatment;* [3] *Low number of events or patients*

Table 49: How effective is stereotactic radiotherapy or surgery versus supportive care for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	supportive care	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	3	-	Overall median survival was 3.7 months longer in patients treated with STR or surgery compared to those that had supportive care only.	VERY LOW

[1] Retrospective cohort study; [2] High risk of bias due to patient selection for treatment; [3] Low number of events or patients

Table 50: How effective is stereotactic radiotherapy or surgery versus whole brain radiotherapy for people with stage IV melanoma with oligometastatic disease?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	WBRT	Relative (95% CI)	Absolute	Quality
Overall survival: brain metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	25	-	Overall median survival was 2.5 months longer in	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	WBRT	Relative (95% CI)	Absolute	Quality
										patients treated with STR or surgery compared to those treated with WBRT.	
Recurrence of metastasis at local site: brain metastases											
1	observational study[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	2/10 (20%)	4/24 (17%)	-	30 more recurrences per 1000 treated in the non surgery group	VERY LOW

1 *[1] Retrospective cohort study; [2] High bias due to patient treatment selection; [3] Low number of events or patients*

2 **Table 51: How effective is surgery with or without ablation for people with stage IV melanoma with oligometastatic disease?**

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery± Ablation	No Surgery	Relative (95% CI)	Absolute	Quality
Overall survival: any metastases											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported		Median overall survival was 8 months in the non surgical group compared with 24.8 months in the non-surgical group. 5 year overall survival was 6.6% in the non-surgical group compared with 30% in the surgical group	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery± Ablation	No Surgery	Relative (95% CI)	Absolute	Quality
										(p<0.001). Outcomes did not differ significantly by type of surgery (resection, ablation, resection with ablation)	

1 [1] *Retrospective cohort study;* [2] *High risk of bias due to treatment selection*

2

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

Recommendations	**Refer the care of people who appear to have oligometastatic melanoma to the specialist skin cancer multidisciplinary team (SSMDT) for recommendations about staging and management.** **Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms of the metastases.**
Relative value placed on the outcomes considered	The GDG considered symptom control to be the most important outcome when drafting the recommendations. This outcome is considered to be the most important to patients and for which recommendations could have a major impact. Overall survival was also considered important for patients but because of the poor quality evidence the GDG agreed that evidence for this outcome should not be used when drafting the recommendations and so recommendations were made on the basis of clinical experience and consensus.
Quality of the evidence	The quality of the evidence was assessed using GRADE methodology and appropriate NICE Checklists. Using these methods it was determined that the quality of the evidence for all reported outcomes was very low. All the studies included in the evidence review were retrospective cohort studies and all have a high degree of patient selection bias. As a result the GDG were limited when making their recommendations. In particular the GDG were unable to recommend any specific treatment to improve survival. Because of the very low quality evidence the GDG also used clinical experience and consensus to make these recommendations. Because of the lack of RCT evidence the GDG discussed whether a research recommendation should be made. However it was felt that the current emergence of new systemic therapies would make specific research recommendations become quickly out of date and inappropriate. The decision to refer the care of people with apparently oligometastatic melanoma to the SSMDT for recommendations about staging and management was based on GDG clinical consensus and similar advice already provided in the NICE Improving outcomes in people with skin tumours including melanoma.
Trade off between clinical benefits and harms	The GDG concluded that the recommendations made would provide patients with an opportunity to have access to treatment which may improve symptoms. The GDG acknowledged that there is a risk of adverse side

	effects and needless investigation associated with the treatments recommended. The GDG concluded that the benefits of symptom control outweigh the drawbacks of needless investigations and side effects.
Trade-off between net health benefits and resource use	The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. This topic was not considered a priority area for the development of an economic model. The GDG agreed that although there may be additional costs associated with using surgery or other ablative treatments there would be a benefit from preventing or controlling of symptoms in a small population of patients. Because of a lack of evidence of survival benefit from these treatments, there may be an overall reduction in costs if clinicians decide not to use them.
Other considerations	When discussing the evidence and making recommendation the GDG also discussed the role of treatment for oligometastatic disease in other epithelial tumours and in particular the role of ablative treatments for metastatic disease. The GDG felt that there may possibly be a small change in practice as a result of the recommendations. No equalities issues were identified for this topic.

7.2 Localised treatment for brain metastases

Whole brain radiotherapy has been used for many years to treat patients with symptomatic brain metastases from melanoma. It entails five to ten outpatient visits to hospital over one to two weeks and is associated with side effects of tiredness, headache and hair loss. Its effect is variable and often short-lived.

Stereotactic radiosurgery is now more frequently used in the treatment of those patients with small solitary or few brain metastases in whom long term local tumour control is considered to be important. Patients may also be considered for neurosurgical resection.

Clinical question: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma?

Clinical evidence

The evidence is summarised in Tables 52 to 64.

Overall survival

Very low quality evidence from two retrospective studies analysed the effect of treatment on patients with single or multiple metastases separately (Katz, 1981; Eigentler et al, 2011) and they both found surgery to be associated with a significantly longer survival compared with other treatment modalities for patients with a single brain metastasis. This benefit was no longer detectable when considering patients with multiple brain metastases.

Very low quality evidence showed there was no difference in overall survival between surgery and STR, however only one study compared these treatments (Meier et al., 2004).

Very low quality evidence showed STR resulted in longer overall survival than chemotherapy and WBRT (Meier et al., 2004).

Very low quality evidence showed WBRT resulted in increased survival compared to supportive care (Buchsbaum et al., 2002; Fife et al., 2004; Panagiotou et al., 2005). Whether WBRT gives better results than chemotherapy is uncertain as one study of 385 patients (Sampson et al., 1998) showed that WBRT did result in increased survival compared to chemotherapy, but 2 other studies with a total of 137 patients (Meier et al., 2004; Panagiotou et al., 2005) demonstrated longer survival with chemotherapy than WBRT.

Very low quality evidence from one retrospective study in 157 patients treated with stereotactic radiotherapy with and without WBRT (Dyer et al, 2014) showed that death occurred in 135 patients (92%) with a median overall survival of 7.3 months. On multivariate analysis extensive extracranial metastases [HR=1.78, 95% CI 1.25-2.53, p=0.001] and Karnofsky Performance status 50-80 (versus 90-100) [HR=1.52, 95% CI 1.08-2.15, p=0.02] were associated with poorer survival. The use of up front whole brain radiotherapy was associated with treatment centre (p<0.0001) and multiple brain metastases (p<0.0001).

To what extent the longer median survival associated with local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care is related to the treatment itself or to selection of patients with better performance status is unclear. All 12 studies are retrospective cohort studies and all have undergone patient selection that is likely to be biased toward treating patients with more favourable prognoses with local treatments such as surgery. Prospective studies are required to overcome selection bias and confirm the results observed by these retrospective studies.

Symptom control

There was very low quality evidence from two studies reporting improvement in neurological symptoms following surgery or radiotherapy. One study found similar rates of improvement in neurological symptoms with 50% of patients experiencing improvement in at least 1 neurological symptom following surgery and 54% of patients experiencing improvement after whole brain radiotherapy (Sampson, 1998). Another study found that surgery improved neurological symptoms in 70% patients compared to radiotherapy which improved symptoms in 42% of patients (Katz, 1981).

Adverse events

Very low quality evidence from two studies suggests that serious treatment related adverse events are more likely with surgery than radiotherapy. In Sampson et al, 1998) 12/139 (9%) patients treated with surgery had treatment-related serious complications (including death) compared with 2/180 (1%) treated with whole brain radiotherapy. In Katz et al, 1981 there was a serious adverse event rate of 1/10 (10%) with surgery compared with 0/52 (0%) in the whole brain radiotherapy group.

Table 52: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (surgery versus chemotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	Chemo-therapy	Relative (95% CI)	Absolute	Quality
Overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	94	260	-	Overall median survival was 4 - 7 months longer in patients treated with surgery compared to those treated with chemotherapy.	VERY LOW

[1] Retrospective cohort study; [2] Serious risk of bias due to patient selection for treatment; [3] Low event rate or low number of patients

Table 53: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (surgery versus supportive care)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	supportive care	Relative (95% CI)	Absolute	Quality
Overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	84	253	-	Overall median survival was 4 - 10 months longer in patients treated with surgery compared to those	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	supportive care	Relative (95% CI)	Absolute	Quality
										undergoing supportive care.	

[1] *Retrospective cohort studies;* [2] *Serious risk of bias due to patient selection for treatment;* [3] *Low event rate or low number of patients*

Table 54: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (surgery versus stereotactic radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	stereotactic radiotherapy	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	37	17	-	Overall median survival was 0.3 months longer in patients treated with surgery compared to those treated with STR.	VERY LOW

[1] *Retrospective cohort study;* [2] *High bias due to patient selection for treatment;* [3] *Low event rate or low number of patients*

Table 55: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (surgery versus whole brain radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	WBRT	Relative (95% CI)	Absolute	Quality
Overall survival											
5	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149	527	-	Overall median survival was 2.5 – 11.5 months longer in patients treated with surgery compared to those treated with WBRT.	VERY LOW
Symptom control (improvement in at least 1 neurological symptom)											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	149	232	-	Symptoms improved in 50 – 70% of patients treated with surgery compared to 42 -54% of patients treated with WBRT.	VERY LOW
Serious complications											
2	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	13/149 (9%)	2/232 (1%)	-	80 per 1000 more with surgery than with WBRT	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment; [3] Low event rate or low number of patients

Table 56: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (surgery versus chemotherapy and/or whole brain radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	surgery	chemotherapy and/or WBRT	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	32	75	-	Overall median survival was 2 months longer in patients treated with surgery compared to those treated with chemotherapy and/or WBRT.	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment; [3] Low event rate or low number of patients

Table 57: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (stereotactic radiotherapy versus chemotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	Chemo-therapy	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	17	38	-	Overall median survival was 3.7 months longer in patients treated with STR compared to those treated with chemotherapy.	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment; [3] Low event rate or low number of patients

Table 58: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (whole brain radiotherapy versus chemotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Chemo-therapy	Relative (95% CI)	Absolute	Quality
Overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	262	260	-	Overall median survival was 3.7 months longer in patients treated with WBRT compared to those treated with chemotherapy in one study. However, for 2 studies overall	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Chemo-therapy	Relative (95% CI)	Absolute	Quality
										median survival was 1.1 - 2 months longer in patients treated with chemotherapy compared to those treated with WBRT.	

[1] *Retrospective cohort studies;* [2] *High bias due to patient selection for treatment*

Table 59: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (whole brain radiotherapy versus supportive care)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	supportive care	Relative (95% CI)	Absolute	Quality
Overall survival											
3	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	289	227	-	Overall median survival was 1 – 1.3 months longer in patients treated with WBRT compared to those undergoing supportive care.	VERY LOW

[1] *Retrospective cohort study;* [2] *High bias due to patient selection for treatment*

Table 60: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (whole brain radiotherapy versus stereotactic radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	STR	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	54	17	-	Overall median survival was 4.8 months longer in patients treated with STR compared to those treated with WBRT.	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment; [3] Low event rate or low number of patients

Table 61: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (stereotactic radiotherapy or surgery versus supportive care)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	supportive care	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	3	-	Overall median survival was 3.7 months longer in patients treated with STR or	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	supportive care	Relative (95% CI)	Absolute	Quality
										surgery compared to those undergoing supportive care.	

[1] *Retrospective cohort study;* [2] *High bias due to patient selection for treatment;* [3] *Low event rate or low number of patients*

Table 62: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (stereotactic radiotherapy or surgery versus whole brain radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	WBRT	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	10	25	-	Overall median survival was 2.5 months longer in patients treated with STR or surgery compared to those treated with WBRT.	VERY LOW

[1] *Retrospective cohort study;* [2] *High bias due to patient treatment selection;* [3] *Low event rate or low number of patients*

Table 63: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (stereotactic radiotherapy or surgery versus chemotherapy and/or whole brain radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR or surgery	Chemo-therapy and/or WBRT	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	92	-	Overall median survival was 3 months longer in patients treated with STR or surgery compared to those treated with chemotherapy and/or WBRT.	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment

Table 64: GRADE profile: What is the effectiveness of local treatment using surgery or radiotherapy compared with systemic drug therapy or supportive care in the management of brain metastases in people with stage IV melanoma (stereotactic radiotherapy with or without whole brain radiotherapy)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	STR	STR+ WBRT	Relative (95% CI)	Absolute	Quality
Overall survival											
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	147 (numbers not reported for each treatment separately)			Death occurred in 92% of patients with a median overall survival was 7.3 months	VERY LOW

[1] Retrospective cohort study; [2] High bias due to patient selection for treatment

1 Cost effectiveness evidence

2 A literature review of published cost effectiveness analyses did not identify any relevant
3 studies for this topic. Although there were potential implications for resource use associated
4 with making recommendations in this area, other topics in the guideline were agreed as a
5 higher economic priority. Consequently, *de novo* modelling was not done for this topic.

6

Recommendations	**Discuss the care of people with melanoma and brain metastases with the SSMDT.** **Refer people with melanoma and brain metastases that might be suitable for surgery or stereotactic radiotherapy to the brain and other central nervous system tumours multidisciplinary team for a recommendation about treatment.**
Relative value placed on the outcomes considered	The GDG considered symptom control to be the most important outcome when drafting the recommendations for this topic. This outcome was considered to be the most important to patients and for which recommendations could have a significant impact on patient care. Overall survival was also considered important for patients but because of the poor quality evidence the GDG agreed that evidence for this outcome should not be considered when drafting the recommendations and so recommendations were made on the basis of clinical experience and consensus.
Quality of the evidence	The quality of the evidence was assessed using GRADE methodology and appropriate NICE Checklists. Using these methods it was determined that the quality of the evidence for all reported outcomes was very low. All the studies included in the evidence review were retrospective cohort studies and all have a high patient selection bias. As a result the GDG were limited when making recommendations. In particular the GDG were unable to recommend specific treatments to improve survival. Because of the very low quality evidence the GDG also used clinical experience and consensus to make appropriate recommendations. Because of the lack of RCT evidence the GDG discussed whether a research recommendation should be made. However it was felt that the current emergence of new systemic therapies would make specific research recommendations become quickly out of date and inappropriate.
Trade off between clinical benefits and harms	The recommendations made by the GDG to discuss management at the MDT should ensure that the treatment options for patients with stage 4 melanoma are fully explored and considered and that patients have access to appropriate treatment options. The GDG agreed that there were no harms associated with the recommendations and that that there was a net clinical benefit in favour of these recommendations.
Trade-off between net health benefits and resource use	The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. This topic was not considered a priority area for the development of an economic model.

	The GDG recommended that patients with brain metastases should be discussed at both melanoma and brain and CNS MDTs. This will only increase costs slightly as the GDG believed that this practice is already common in the UK. The recommendation also gives the option for either surgery or stereotactic radiotherapy to be used and the GDG did not anticipate significant changes in the proportion of patients receiving either treatment. So the GDG agreed that there would be no significant extra costs or savings as a result of these recommendations.
Other considerations	When discussing the evidence and making recommendations the GDG also discussed the treatment of oligometastatic disease in epithelial tumours and different treatment options for brain metastases. The GDG felt that any change in practice as a result of the recommendations is likely to be very small. No equalities issues were identified for this topic.

7.3 The role of systemic anticancer therapy

Treatment for metastatic melanoma is evolving rapidly. New effective systemic targeted treatments and immunotherapy offering a survival benefit is now available, and has replaced the traditional role of cytotoxic chemotherapy in most situations.

Targeted treatments, immunotherapy and chemotherapy differ in their response rates, onset and duration of action shown in Table 65. The selection and sequencing of the most appropriate class of systemic therapy depends on the tumour mutational status, tumour load, pace of disease progression and patient fitness.

Table 65: Characteristics of systemic treatment classes

	Mutation-dependent	Response rate	Onset of Action	Potential for long term response	Survival benefit
Targeted treatment(s)	yes	high	days	no	yes
Immunotherapy*	no	low	months	yes	yes
Chemotherapy	no	low	weeks	no	no

**anti-CTLA4 immunotherapy*

Although the role of cytotoxic chemotherapy has diminished, there remain situations where it is treatment option of choice. Intravenous dacarbazine has been the principle cytotoxic chemotherapy for melanoma for over 20 years. Temozolomide is an orally administered analogue of dacarbazine with better central nervous system penetration. Carboplatin and paclitaxel, alone or in combination with each other or other agents, are also occasionally used in the UK.

Clinical question: What is the effectiveness of systemic anticancer therapy compared with supportive care in the treatment (first and second line) of patients with stage 4 metastatic melanoma?

Clinical evidence

The evidence is summarised in Tables 66 to 67.

Systemic anticancer therapy versus best supportive care

From one Cochrane Review (Crosby et al, 2013) there was no evidence comparing the use of systemic anticancer therapy with best supportive care alone for any of the outcomes of interest.

Dacarbazine versus temozolomide

Moderate quality evidence from two randomised trials (Middleton et al, 2000 and Patel et al, 2010) suggests similar overall survival for patients treated with temozolomide when compared to those treated with dacarbazine. The pooled hazard ratio (HR) for death from any cause was 0.96 (95% CI: 0.84 to 1.09), translating to an absolute improvement in median overall survival of 0.33 months with temozolomide.

Moderate quality evidence from two randomised trials with a combined population of 1164 patients (Middleton et al, 2000 and Patel et al, 2010) that patients treated with temozolomide have better progression free survival (PFS) than those treated with dacarbazine. The pooled HR for disease progression was 0.87 (95% CI: 0.77 to 0.98) translating to an absolute improvement in median progression free survival of 0.28 months with temozolomide. This hazard ratio combined with the control arm PFS data from Patel et al, 2010 suggests 6 month progression free survival of 27% with temozolomide treatment compared to 22% with dacarbazine.

Moderate quality evidence from two randomised controlled trials with a combined population of 1164 patients (Middleton et al; 2000 & Patel et al, 2011) indicate that there is no significant difference in responses to treatment for patients treated with temozolomide compared with patients treated with dacarbazine (OR for complete response: 1.48 (0.59-3.70); OR for partial response: 1.39 (0.94-2.06)).

Moderate quality evidence from two randomised controlled trials with a combined population of 1164 patients (Middleton et al, 2000 & Patel et al, 2011) reported that the rate of Grade 3-4 adverse events ranged from 35%-38% in patients treated with temozolomide compared with 29%-36% for patients treated with dacarbazine. The authors did not report whether this difference was significant.

Thus there is some evidence for better disease-free survival for patients treated with temozolomide but more toxicity.

Paclitaxel versus paclitaxel plus carboplatin

Low quality evidence from one phase II randomised trial with 40 participants (Zimpfer-Rechner et al, 2003), the median overall survival time was 218 days for patients treated with paclitaxel versus 209 days for patients treated with paclitaxel + carboplatin.

Low quality evidence from one phase II randomised trial with 40 participants (Zimpfer-Rechner et al, 2003), the median progression free survival time was 54 days for patients treated with paclitaxel versus 57 days for patients treated with paclitaxel + carboplatin.

Table 66: GRADE profile: What is the effectiveness of systemic anticancer therapy compared with supportive care in the treatment (first and second line) of patients with stage IV metastatic melanoma (temozolomide versus dacarbazine)?

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Temozolo-mide	Dacarb-azine	Relative (95% CI)	Absolute	Quality
Overall Mortality (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	585[4]	579[4]	HR 0.96 (0.84-1.09)	Median overall survival 0.33 months longer with temozolomide (from 0.7 months shorter to 1.5 months longer	MODERATE
Disease Progression (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious [2]	no serious inconsistency	no serious indirectness[5]	no serious imprecision	none	508/585 (87%)	505/579 (87%)	HR 0.87 (0.77-0.98)	Median progression free survival was 0.28 months longer with temozolomide (from 1 months shorter to 0.04 months longer)	MODERATE
Partial Response (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/557 (12%)	48/537 (8.9%)	OR 1.39 (0.94 to	31 more per 1000 (from 5 fewer to 79 more)	MODERATE

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Temozolo-mide	Dacarb-azine	Relative (95% CI)	Absolute	Quality
								9.1%	2.06)	31 more per 1000 (from 5 fewer to 80 more)	
Complete Response (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/557 (2.2%)	8/547 (1.5%)	OR 1.48 (0.59 to 3.7)	7 more per 1000 (from 6 fewer to 37 more)	MODERATE
								2%		9 more per 1000 (from 8 fewer to 50 more)	
Health Related Quality of Life[3] (Kiebert et al 2003))											
1	randomised trials	serious[1], [2]	no serious inconsistency	no serious indirectness	no serious imprecision	none					MODERATE
Grade 3-4 Adverse Events (Patel et al, 2011; Middleton et al, 2000)											
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Rate ranged from 35%-38% in 585 patients	Rate ranged from 29%-36% in 579 patients			MODERATE

[1] There is a lack of information provided in the methodology to adequately assess factors such as allocation concealment or blinding; [2] Two randomised trials compared temozolomide with dacarbazine however it was not possible to conduct a meta-analysis of the results; [3] This study reports the Health Related Quality outcome measured as part of the Middleton et al, 2000 trial, in more detail. The quality assessment has been based on the information provided both in this publication and also in the original trial publication; [4] Number of deaths was not reported in Middleton, but hazard ratios were reported so meta-analysis was still possible; [5] Patel et al included patients with mucosal melanoma which is not covered by the scope of the guideline. However, as the rates of mucosal melanoma are lower than for other types of melanoma, it was considered that the numbers of patients in the trial with mucosal melanoma would be low enough as to not impact the results and so the evidence was not downgraded for indirectness

Table 67: GRADE profile: What is the effectiveness of systemic anticancer therapy compared with supportive care in the treatment (first and second line) of patients with stage IV metastatic melanoma (paclitaxel versus paclitaxel + carboplatin)?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Tumour Response							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Overall Survival							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Progression Free Survival							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW
Toxicity							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	LOW

[1] Phase II trial - small numbers with no details on method of randomisation; [2] A sample size of 242 patients was required to assure statistical significance however the study planned to initially recruit 40 patients in order to evaluate response and as the response rates were <10% in each arm, recruitment to the trial was stopped early

Cost effectiveness evidence

The following databases were searched for economic evidence relevant to the review question: MEDLINE, EMBASE, COCHRANE, NHS EED. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

303 possibly relevant papers were identified. Of these, 2 full papers relating to this topic were obtained for appraisal. A further 1 paper was excluded as it was not applicable to the review question. Therefore only one paper (Hillner et al, 2000) was included in the current review of published economic evidence for this topic.

The study was a cost effectiveness analysis of temozolomide (TEM) versus dacarbazine (DTIC) which reported the results in terms of incremental cost per life year gained. Typically papers which do not report quality of life based outcomes are excluded but given the paucity of economic evidence on this topic an exception was made.

Hillner et al. (2000) is deemed only partially applicable to the decision problem that we evaluated This is primarily because the study did not consider a UK setting (US healthcare setting) and did not express health outcomes in terms of quality adjusted life years (QALYs).

Very serious limitations were identified with Hillner et al (2000) Most notably, a potential conflict of interest was identified (as the study was funded by the manufacturer of temozolomide) and probabilistic sensitivity analysis (PSA) was not conducted.

The base case suggested that treating with TEM over DTIC would cost $36 990 per life-year gained although this varied from temozolomide being dominated (more costly, less effective) to $18 670 per life-year gained when the 2.5% and 97.5% confidence interval estimates for effectiveness were used. No analyses using quality adjusted life-years (QALYs) were presented.

1 **Table 68: Modified GRADE table: included economic studies**

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Hillner et al. 2000 (USA)	Patients with advanced, metastatic malignant melanoma who are previously untreated for metastatic disease with a WHO performance status of either 0, 1 or 2. Patients were randomised to a Phase III comparing DTIC to TEM (n=305)	Intravenous DTIC once a day for 5 days with a starting dose of 250mg/m2 repeated every 21 days.	$3,697	8.6 months mean survival	Reference			One-way Sensitivity Analysis One-way sensitivity analyses were conducted with incremental cost per life-year gained ranging from $15,600 to TEM being dominated compared to DTIC Threshold Sensitivity Analysis Threshold sensitivity analysis showed that TEM could be increased to $1,805 per course and still be cost-effective at a WTP of $50,000 per life-year gained.	Partially Applicable Not conducted from a UK health service perspective. QALY results not presented (life years only).	Very Serious Limitations. Study funded by manufacturer. PSA not conducted.
		Orally administered TEM once a day for 5 days with a starting dose of 200mg/m2 repeated every 28 days.	$6,902	9.6 months mean survival	$3,205	0.087 years survival	$36,990 per Life Year gained.			
	Comments: Papers which do not report quality of life based outcomes are typically excluded from the review of economic evidence. However, given the paucity of economic evidence on this topic an exception was made.									

2

Recommendations	**<u>Dabrafenib</u>** **Refer to NICE's technology appraisal guidance on dabrafenib[c] for treating unresectable or metastatic BRAF V600 mutation-positive melanoma for adults.** **<u>Dacarbazine</u>** **Consider dacarbazine[d] for people with stage 4 metastatic melanoma if immunotherapy or targeted therapy are not suitable.** **Do not offer further cytotoxic chemotherapy for stage 4 metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial.** **<u>Ipilimumab</u>** **For adults, 'Ipilimumab[e] is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.' [This recommendation is from NICE's technology appraisal guidance on ipilimumab for previously treated advanced (unresectable or metastatic) melanoma.]** **Refer to NICE's technology appraisal guidance on ipilimumab[e] for previously untreated advanced (unresectable or metastatic) melanoma for adults** **<u>Vemurafenib</u>** **For adults, 'Vemurafenib[f] is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme'. [This recommendation is from the NICE's technology appraisal guidance on vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma.]**
Relative value placed on the outcomes considered	The GDG considered overall survival to be the most important outcome for this topic. The reason for prioritising this outcome was because they believed that patients would be most interested in which treatment gave them the longest survival time, although good evidence of consequent quality of life data would have been very important. Of the outcomes of interest that were listed in the review question, no evidence was identified relating to adverse events.

c Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

d Although this use is common in UK clinical practice, at the time of consultation (January 2015), dacarbazine did not have a UK marketing authorisation for this indication or for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

e Ipilimumab has a UK marketing authorisation 'for the treatment of advanced (unresectable or metastatic) melanoma in adults'.

f Vemurafenib has a UK marketing authorisation for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'.

	No additional outcomes were reported in the evidence. HRQoL was reported in one trial but because the trial was not designed to assess this as a primary outcome and the quality of the data were very poor, the GDG agreed that the evidence for this outcome should not be used in drafting the recommendations.
Quality of the evidence	The quality of the evidence was assessed using GRADE and appropriate NICE checklists. The evidence for overall survival was assessed to be of high quality, while the evidence for all other outcomes was either low quality or was not available. It was brought to the attention of the GDG that one of the included studies (Patel et al, 2011) included patients who were not relevant to the population in the review question and so the results may not be directly applicable to the population of interest. The GDG however did not consider this to be a reason to exclude the study from the evidence base as the proportion of patients not relevant to the review question was small enough not to affect the applicability of the trial results. The low quality evidence or lack of evidence for the majority of outcomes did not influence the GDG's decision to make a recommendation on the use of dacarbazine for patients with stage 4 metastatic melanoma. In the absence of evidence for benefit from any other drugs, the GDG used clinical experience and consensus to make a recommendation not to routinely recommend the use of further cytotoxic chemotherapy following dacarbazine except in the context of a clinical trial. Despite the lack of evidence on this topic, the GDG did not consider it necessary to make a research recommendation. The GDG felt that this area of research was currently in a rapid state of change with a number of new treatment options now under investigation and so concluded that making a research recommendation would be irrelevant and soon out of date.
Trade off between clinical benefits and harms	Although the treatments recommended by the GDG carry a potential risk of toxic side effects and/or discomfort related to the mode of treatment delivery, the GDG considered that these would be short-term harms and were outweighed by the potential benefit of disease control. The recommendations made by the GDG also provide patients with an opportunity to have access to treatment which may improve symptoms and prolong survival. There was no evidence of a clinically or statistically significant increase in progression-free survival from the use of temozolamide compared to dacarbazine, however temozolamide was shown to have greater toxicity. Even including intravenous administration costs, dacarbazine is the cheaper option. However temozolomide is given orally without the need to attend hospital for intravenous treatment three weekly, and this might be preferable for some patients.
Trade off between net health	The topic of cytotoxic chemotherapy was not considered a priority

benefits and resource use	area for the development of an economic model. A systematic review identified a limited amount of evidence relating to the cost effectiveness of the treatments of interest. The evidence was only partially applicable to the UK as it considered a US setting and did not report quality adjusted life years (QALYs).Very serious methodological limitations were identified including a risk of bias (the study was funded by the manufacturer of temozolomide) and lack of probabilistic sensitivity analysis. As a result, the GDG did not feel it was appropriate to use the evidence identified. Instead, the GDG considered UK costings of temozolomide and dacarbazine using sources including BNF costs, NHS reference costs and BNF costs of health and social care. Drug costs were estimated as £33 per cycle for dacarbazine compared to £1,146 for temozolomide. The reduction in delivery costs (£50 per cycle) of using temozolomide did not recoup this additional cost. Dacarbazine was thought to be equally as effective but less expensive than temozolomide. As a result the use of temozolomide would lead to additional resource use with no, or limited, additional health benefits.
Other considerations	The licensed indications for dacarbazine do not include melanoma. Therefore a footnote has been added to the recommendation to explain this and the implications to the prescriber. No equalities issues were identified for this topic.

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8 Follow-up

8.1 Method, frequency and duration of follow-up

After a melanoma is treated, patients have regular check ups. The purpose is to support the patient and to detect recurrence or a new primary so that appropriate treatment can be given promptly. Recurrence may be local to the scar, in transit, nodal or distant. Evidence was sought to inform the most effective approaches to follow-up.

The standard UK follow-up system currently depends on the American Joint Committee on Cancer (AJCC) stage at diagnosis (see page 20) and is as follows

- Stage 0 - no follow-up after initial treatment, results and advice
- Stage 1A- 2-4 reviews over a 12 month period then discharge with advice
- Stage 1B to 2C, review every 3 months for 3 years then every 6 months for another 2 years
- Stage 3 and over every 3 months for five to ten years.

In addition, given the previous lack of effective treatment for stage 4 melanoma, regular imaging has not been generally practised, but as new more effective therapies are emerging, the GDG sought evidence that might suggest a change to this practice. In particular, the evident survival advantage reported for patients who respond to treatment with the T cell checkpoint inhibitor ipilimumab was thought to be of great importance. As published data and clinical experience suggest that responses to treatment to ipilimumab take time to develop, the concern was to address the issue of whether regular imaging would identify stage 4 disease early enough to allow treatment for a proportion of patients, who, in the absence of regular imaging might be too unwell to tolerate treatment for long enough to benefit once the symptomatic disease had occurred.

The GDG therefore considered both the frequency and setting of follow up and the role of regular imaging in asymptomatic patients.

Clinical question: In asymptomatic patients who have undergone treatment with curative intent for melanoma, what is the optimal method, frequency and duration of follow-up?

Clinical evidence

The evidence is summarised in Table 69.

Fourteen studies (1 RCT and 13 case series studies) were identified as relevant to this topic. The reported follow-up schedules and protocols were broadly similar across the individual studies in terms of timing of follow-up and components of follow-up, with variation in timing occurring mostly in year one of follow-up depending on the stage of melanoma at diagnosis.

Overall, the quality of the evidence for this topic was considered to be very low on GRADE assessment for all clinical outcomes of interest. For diagnostic outcomes, the quality of evidence was considered to be very low based on assessment using the QUADAS checklist.

Follow-up schedules

Follow-up schedules varied across the individual studies and within the individual studies depending on the stage at diagnosis of primary melanoma, though all follow-up protocols consisted of clinic visits or physician exams and some chest x-ray at regular intervals.

Follow-up setting

One randomised trial assessed the impact of GP led follow-up in primary compared with secondary care on patient satisfaction and guideline adherence. The overall findings from the trial suggested that GP lead follow-up in primary care improved patient satisfaction and was more guideline compliant than hospital based follow-up and that the health status and psychological well-being of patients was not adversely affected (Murchie et al, 2010).

Patient satisfaction was assessed using a 15 point questionnaire which had been developed for use in a randomised trial of GP-led follow-up for breast cancer patients and was administered at baseline, 3 months, 6 months and 12 months No significant difference in patient satisfaction was observed at baseline though at follow-up there were statistically significant differences between the groups on 6 of the 15 aspects assessed. Members followed up in primary care were significantly more likely to think that is was ‘easier to get through by phone if you need to’ and they felt that they could usually see a doctor on the same day if needed and that they would usually be seen by a doctor within 20 minutes of their appointment time. The intervention group also reported feeling that the doctor ‘examines you thoroughly when necessary’ and ‘always prescribes medication if you need it. In addition, patients in the intervention groups were more likely to report being seen by ‘a doctor that knows you well’ (Murchie et al, 2010).

Health status and psychological well being was assessed using a SF-36 and the HADS questionnaires and no significant differences were recorded between the groups at baseline or at follow-up (Murchie et al, 2010).

In the year before the study, adherence to local guidelines was 84.9% in the primary care group and 85.4% in the secondary care group. At follow-up however there was a significant difference in adherence to local guidelines (p=0.02); adherence had increased to 98.1% in the primary care group while adherence decreased in the secondary care group to 80.9% (Murchie et al, 2010).

Detection of recurrence

One retrospective study analysed how each first relapse was detected during follow-up in a total of 340 patients with stage III melanoma. 62% of local and in transit recurrences, 49% of nodal recurrences and 37% of systemic recurrences were patient detected. Physical examination (physician) detected 36% of local and in transit recurrences, 26% of nodal recurrences, 9% of systemic recurrences. 37% of patients detected systemic relapse by noticing a new tumour or new symptoms. 63% of patients had asymptomatic systemic relapse and radiological tests identified recurrence in 53% of these patients (CT scans 72%) (Romano et al, 2010). In a retrospective study following up 118 patients treated for melanoma, no statistically significant difference was observed between patients seeking care for symptomatic recurrence compared with patients whose recurrence was asymptomatic (patient-detected, physician-detected or detected by routine imaging). (Meyers et al, 2009).

Time to recurrence

In two retrospective case series studies (Mooney et al 1998 & Hoffmann et al, 2002) 71%-90.7% of recurrences were recorded in the first 5 years of follow-up. . In one retrospective study in 33,384 patients treated for stage I-III primary melanoma and undergoing follow-up, median recurrence-free survival time was 44 months (IQR 19-85) and median follow-up time to diagnosis of secondary melanoma was 21 months (IQR 4-61) (Leiter et al, 2012).

In a retrospective case series with a sample size of 108, there was no significant difference in median time to diagnosis for asymptomatic pulmonary metastases detected on chest x-ray and symptomatic pulmonary metastases detected during clinical visits (p=0.30). Median time to diagnosis of pulmonary metastasis was 24 months (95% CI 12-41 months) and median

time to the diagnosis of pulmonary disease by clinical follow-up was 16 months (95% CI 10-30 months) (Morton et al, 2009)

In one retrospective case series study in 118 patients, median time to recurrence was 14 months (2-88 months) and there was no significant difference in time to recurrence when comparing stage II and stage III patients (Meyers et al, 2009).

Survival

A number of studies have reported differences in survival in patients whose metastases were detected by screening compared with those in whom they were symptomatic. However all but one were retrospective observational studies. In the only prospective study in 2,008 patients treated for primary melanoma, early detection of recurrence was associated with a higher survival rate for patients with stage I-II melanoma, with a 76% overall survival rate at 3 years compared with 38% for late detection ($p<0.0001$). Early detection was similarly associated with an overall survival rate at 3 years for stage III patients (60% versus 18%; $p<0.0001$) (Garbe et al, 2003).

In one retrospective study in 340 stage III melanoma patients, overall 5-year survival from time of first relapse was 20%, in stage IIIA and IIIB patients and 11% in stage IIIC patients. Regional relapse was associated with longer overall survival than systemic relapse ($p<0.001$). Symptomatic relapse was associated with shorter survival compared with relapse discovered by physical exam or radiological imaging. RR=2.31, 95% CI=1.68-3.18, $p<0.001$ (Romano et al, 2010).

In one retrospective case series of 154 patients treated for stage I-II, no significant difference in disease-free survival interval was associated with asymptomatic disease compared with symptomatic disease (28 months and 23 months respectively, $p=0.15$) was seen. But there was a statistically significant difference in median disease-free survival: 12 months for symptomatic recurrences compared with 24 months for asymptomatic recurrences ($p=0.02$). Five-year overall survival was however similar for both groups: 46%±11% for any symptomatic recurrences and 47%±12% for any asymptomatic recurrences ($p=0.26$) (Mooney et al, 1998).

In one retrospective case series study in 419 patients treated for stage I-III melanoma, median survival was 27 months for patients with disease detected at routine examination compared with 14.5 months for patient detected (symptomatic) recurrences for patients with disease recurrence detected at routine examination (asymptomatic) ($p=0.02$ analysis controlled for stage, symptomatic versus asymptomatic and local versus distant recurrences) (Poo-Hwu et al, 1999).

Another retrospective case series study following up 118 patients treated for stage II or III melanoma, reported no statistically significant difference in survival for patients with a symptomatic recurrence compared with patients who had asymptomatic recurrence ($p=0.2$) (Meyers et al, 2009)

A retrospective case series, following up 118 patients treated for stage II or III melanoma reported no statistically significant different in survival for patients who detected recurrence themselves compared with patients whose recurrence was physician detected or detected on routine imaging ($p=0.6$) (Meyers et al, 2009)

Diagnostic efficacy of imaging

A number of studies have looked at the detection of recurrences using PET. A retrospective case series study reported a sensitivity of 100% for PET in the patient by patient analysis, compared with 84.6% for conventional imaging (chest radiograph, abdominal sonography, high resolution ultrasound of regional lymph nodes, X-ray, CT of thorax and abdomen, contrast MRI of the brain); overall specificity was 95.5% versus 68.2%. Accuracy of PET was

97.9% versus 77.1% for conventional imaging. In the lesion by lesion analysis, PET sensitivity was 91.8% compared with 57.5% for conventional imaging, specificity was 94.4% compared with 45% and accuracy was 92.1% compared with 55.7%for conventional imaging % (Rinne et al, 1998). In another retrospective case series study of 106 patients diagnosed with stage III-IV melanoma, PET successfully identified an additional 12 cases of asymptomatic recurrences which were amenable to complete surgical resection, representing an additional 25% of cases compared with patients whose follow-up did not include PET (Kottschade et al, 2009).

In a retrospective study of 30 stage IIB-IIIC patients, 6 out of 7 recurrences detected on standard follow-up were upstaged by FDG PET. One retrospective case series study including 30 patients with stage IIB-IIIC melanoma, PET sensitivity was 86%, specificity was 96%, positive predictive value was 86% and negative predictive value was 9% for melanoma recurrence (Koskivuo et al, 2007). The finding of recurrence influenced treatment plans in all cases; three patients underwent surgery with curative intent while four patients with inoperable recurrent disease received chemotherapy and/or interferon (Koskivuo et al, 2007).

From one case series study including 48 patients diagnosed with high risk melanoma and undergoing PET for re-staging; overall sensitivity of PET was 100% compared with 84.6% for conventional imaging, overall specificity was 95.5% versus 68.2%. Accuracy of PET was 97.9% versus 77.1% in the patient by patient analysis. While in the lesion by lesion analysis, PET sensitivity was 91.8% compared with 57.5% for conventional imaging, specificity was 94.4% compared with 45% and accuracy was 92.1% compared with 55.7%for conventional imaging (Rinne et al, 1998).

Table 69: GRADE profile: In asymptomatic patients who have undergone treatment with curative intent for melanoma, what is the optimal method, frequency and duration of follow-up?

Quality assessment							Summary of findings				Quality
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	what method, duration and frequency of follow-up	control	Relative (95% CI)	Absolute	
Time to Recurrence											
7	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	None of the studies were comparative and each study had variations in their follow-up protocols which made comparisons or meta-analysis of data inappropriate		not pooled		Very Low
Detection of recurrence											
10	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	None of the studies were comparative and each study had variations in their follow-up protocols which made comparisons or meta-analysis of data inappropriate		not pooled		Very Low
Overall Survival											

	8	observational studies	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	None of the studies were comparative and each study had variations in their follow-up protocols which made comparisons or meta-analysis of data inappropriate	not pooled	Very low

[1] *All studies were retrospective reviews;* [2] *Studies varied in their follow-up schedules, protocols and frequencies. Length of follow-up varied across the studies definitions of symptomatic and asymptomatic recurrences varied*

Cost effectiveness evidence (see also Appendix B)

After a melanoma is treated, patients have regular checkups to look for signs of:

- local recurrence
- nodal or distant metastases
- new primary melanomas

Current follow-up strategies were developed when effective systemic treatments for advanced disease were not available. Recently ipilimumab and vemurafenib have been licensed for use in the UK and showing significant survival benefits in phase 3 trials. Therefore the GDG postulated that it might be beneficial to have a more intensive follow-up regimen (including imaging which has not previously been the norm) to try and identify recurrent disease earlier, that may benefit from earlier systemic treatment. However, this would lead to an increase in resource use through increased imaging (CT, PET-CT, MRI etc) and staff time and an increased radiation dose for a significant proportion of patients who would never go on to develop stage IV disease.

Aim of analysis

The aim of the analysis was to estimate the cost effectiveness of adding routine imaging of asymptomatic patients to current standard follow-up in patients with stage III melanoma.

Economic evidence statement

A systematic literature review was performed to assess the current economic literature in this area. The review identified 303 possibly relevant economic papers relating to melanoma. Of these, eight full papers were obtained for appraisal. A further 4 papers were excluded as they only reported costs and 2 were excluded as they were not relevant to the PICO. Two papers (Mooney et al (1997) and Krug et al (2010)) were included in the current review of published economic evidence for this topic. The included studies are summarised in table 8

Mooney et al was a cost-utility analysis, conducted from a US healthcare payer perspective comparing usual follow-up to usual follow-up with life-long annual chest x-rays for local regional or metastatic recurrence in a hypothetical cohort of patents diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma. The study used a Markov model and a 20-year time horizon. The model estimated an additional cost per patient of $755 and an increase in Quality Adjusted Life Years (QALYs) of 0.035 resulting in an incremental cost effectiveness ratio (ICER) of $215,000. During deterministic sensitivity analyses screening was always more costly and effective with the ICER ranged from $109,000 to $765,000 per QALY for the lifetime (20 year) screening option. When also altering the frequency and total duration of the screening programme the ICER ranged from $143,000 to $240,000. Mooney et al was deemed to be only partially applicable with very serious limitations. The study also relatively old and treatment for identified metastatic recurrences has changed significantly since then.

Krug et al was a cost-utility analysis, conducted from a Belgian healthcare perspective. The authors developed a Markov model with a 10-year time horizon to compare whole body CT to FDG-PET CT for patients with suspected pulmonary metastases in a hypothetical cohort of patients with resected stage IIC and stage III malignant melanoma. In the base-case the model estimated that investigation with FDG-PET CT was both more effective and cost saving. During probabilistic sensitivity analysis FDG=PET had a 17.0% change of being both more effective and cost saving although whole body CT was more effective and less costly in 22.6% of iterations. The uncertainty was largely around the effectiveness of preventing unnecessary surgery. The study was deemed to be only partially applicable and have potentially serious limitations as a result of a lack of transparency around the model inputs.

As with Mooney et al the treatment after identification of recurrence has also changed significantly since publication of this analysis.

Table 70: Modified GRADE profile for included economic studies

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Mooney et al. 2000 (USA)	Hypothetical cohort of patients diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma. The cohort had an average age of 52 years and was 53% Male.	Usual follow-up.	Not reported	Not reported	Reference			One-way Sensitivity Analysis One-way sensitivity analyses were conducted with ICER ranging from $109,000/QALY to $765,000/QALY for the lifetime (20year) screening option. When altering the frequency and total duration of the screening program the ICER ranged from $143,000 to $240, 000. Screening was always more costly and effective.	Partially Applicable Not conducted from a UK perspective.	Very Serious Limitations. Lack of PSA Relevant costs not included in the analysis.
		Usual follow-up plus life-long annual CXR for local, regional or metastatic recurrence.	Not reported	Not Reported	$7557	0.035 QALYs8	$215 000			
	Comments:									
Krug et al 2010 (Belgium)	Patients with resected stage IIc and stage III malignant melanoma. Age, performance	Follow-up with suspected pulmonary metastases being examined with whole body CT.	$4 384	90.41 Life months	Reference			Probabilistic Sensitivity Analysis: PET-CT was dominant in 71.0% of iterations and dominated in 22.6% of iterations versus WB-CT.	Partially Applicable Not conducted from a UK health service perspective	Potentially serious limitations Lack of transparency around clinical inputs.
		Follow-up with	$3 438	90.61 Life	-€946	0.20	PET-CT			

8 Calculated by NCC-C health economist from reported data

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
	status and other demographic data was not reported for this cohort.	suspected pulmonary metastases being examined with fluorine-18 fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) with X-Ray computed tomography(CT)		Months			dominant (Both cost saving and health improving).		.	
	Comments:									

De novo economic model

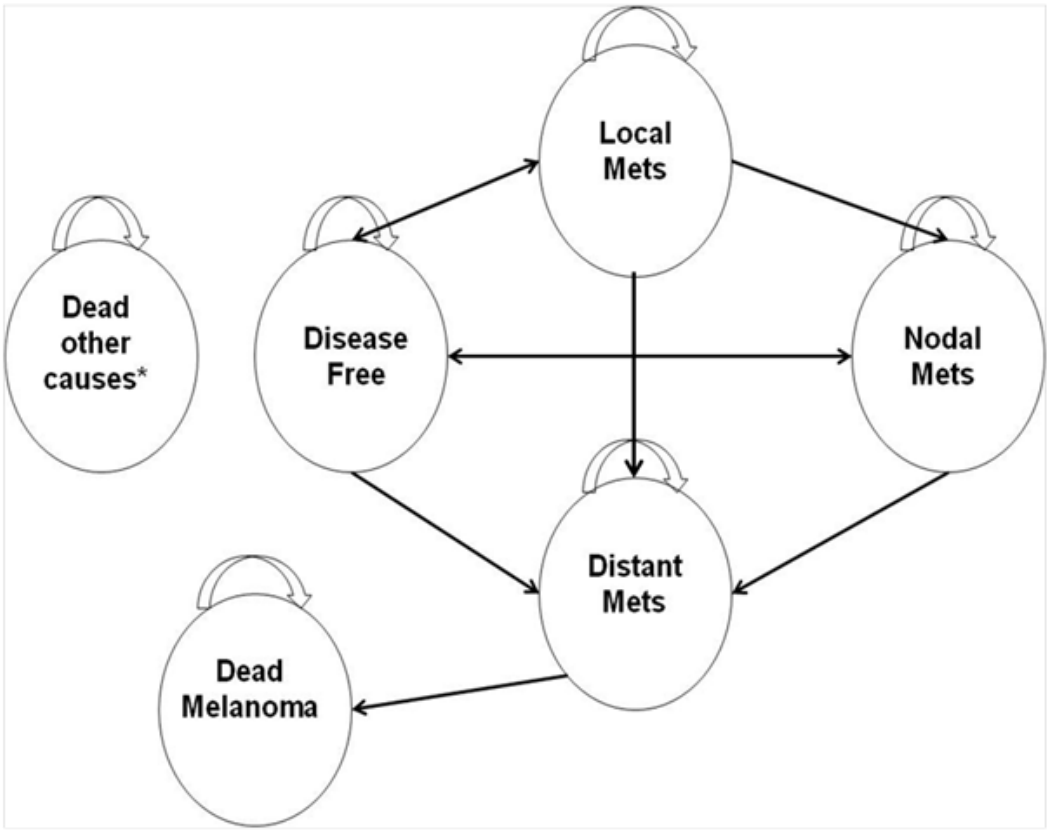
Since the current economic literature did not adequately address the decision problem, a *de novo* economic evaluation was undertaken to assess cost effectiveness.

Model structure

An economic model comparing follow-up with and without routine imaging was developed, in Microsoft Excel 2007, with a cycle length of 3 months and a time horizon of 20 years. Six mutually exclusive health states were included in the model:

- no evidence of disease
- loco-regional recurrence
- distant recurrence
- treatment for distant recurrence
- death from melanoma
- death from other causes.

Figure 42: Model structure



**Patients can transition to Death other Cause from any other non-dead health state*

In the model the following assumptions were made:

- Patients with stage IIIA, IIIB and IIIC disease, who have previously received treatment with curative intent and have no evidence of disease, are followed-up clinically to assess for recurrence of disease.

- Patients receive a clinical review every 3 months during the first 3 years, every 6 months in years 4-5 and then annually in years 5-10 following treatment.
- Patients receive imaging if either the patient or doctor identifies possible recurrence or there has been a change or progression in symptoms indicative of recurrence.
- Depending upon the arm of the model patients may also be given routine imaging, independent of this clinical assessment, by MRI head plus CT of the body.
- Patients identified as having a loco-regional recurrence receive surgery to remove the disease.
- If the surgery is successful then the patient returns to the 'no evidence of disease' state.
- If surgery is unsuccessful or the patient is not suitable for surgery or refuses surgery, they remain in the 'loco-regional recurrence' state.
- Patients in the 'loco-regional recurrence' state have an increased probability of moving to 'distant recurrence' or 'death from melanoma'.
- If recurrences are missed by the patient, doctor or routine imaging patients have an increased probability of moving to 'distant recurrence' or 'death from melanoma'.
- Patients identified as having distant recurrence are offered systemic treatment and remain in the 'treatment for distant recurrence' state until death.
- A hypothetical cohort of patients was modelled. The cohort had an age of 57 years and were 64% male (taken from one retrospective study described below). Lifetime total costs and QALYs were captured. The total costs included all costs associated with initial treatment, surveillance, further treatment and management. QALY were calculated by multiplying the life years that patients spend in each health state by the associated quality of life-weighting. QALYs and quality of life weights are discussed in more detail in later sections.

Clinical input data

Demographic data were taken from Romano et al (2010). The proportion in each stage of melanoma as staged before initial treatment was taken from the East of England Cancer Registry.

The 3-monthly risk of recurrence for stage IIIC melanoma was taken as the same as that calculated by Rueth et al (2014). Recurrence rates for stages IIIA and IIIB melanoma were calculated using recurrence data from Romano et al (2010) to adjust stage IIIC probabilities.(Table 67) Estimates for site of recurrence were taken from Romano et al (2010) who calculated that 49% of recurrences would be loco-regional and 51% would be distant.

Table 71: Three monthly probability of recurrence applied in the model

Disease stage	Year 0- 1	Year 1-2	Year 2-3	Year 3-5	Year 5-10
Stage IIIA	12.2%	2.8%	2.2%	1.5%	1.5%
Stage IIIB	13.5%	3.1%	2.5%	1.7%	1.7%
Stage IIIC	23.4%	5.6%	4.4%	2.9%	2.9%

It was assumed that loco-regional recurrence that is untreated or untreatable will have a probability of progressing to distant recurrence. From clinical experience, Rueth et al (2014) estimated that this would happen to all untreated loco-regional recurrences after 6 months. Progression for the *de novo* model was estimated by calculating a 3-monthly probability that would predict that 95% of the untreated recurrences would progress after 6 months for stage IIIC melanoma. This was reduced by 5% for stage IIIB melanoma and 10% for stage IIIA.

A 3-monthly probability of death for patients with no evidence of disease was taken from Office of National Statistics Life Tables. The probabilities of death following unidentified,

untreatable, unsuccessfully treated or missed loco-regional recurrence and distant recurrence were calculated from the median survival reported in Meyers et al (2009) for patients who refused or were unsuitable for surgical treatment.

Romano et al (2010) estimated that there was a probability of 68% that a recurrence would be identified without routine imaging i.e. by patient self-examination, through physician examination during follow-up or through new or changing symptoms. This figure was used in the base case model.

No directly applicable evidence was identified on the diagnostic accuracy of a strategy involving CT imaging of the body and MRI imaging of the head. Therefore, it was assumed that the diagnostic accuracy would be equivalent to the strategy of imaging with FDG PET and so sensitivity and specificity values of 86% and 96% were applied based on the Koskivuo et al (2007).

No evidence was identified on the proportion of recurrences going on to surgery or the effectiveness of surgery in rendering patients free of disease and therefore an estimate by the GDG was used for this variable. It was estimated that 90% of patients with a loco-regional recurrence would be suitable for surgery and that of these 70% would become disease free.

The proportion of patients starting each type of systemic treatment was also based on an estimate by the GDG because of uncertainties resulting from recent changes in access to ipilimumab. The GDG decided there were three treatments; dacarbazine (15%), ipilimumab (50%) and vemurafenib (35%) which would be considered in the model.

Survival following treatment for distant recurrence was taken from the DeQuen et al (2012) systematic review and meta-analysis of randomised controlled trials, comparing alternative treatments in the management of unresectable stage III or IV melanoma. The study did not identify any studies which allowed vemurafenib to be included in the meta-analysis. Therefore it was assumed to result in identical survival to ipilimumab. Although it is possible for patients to recover from distant disease and return to the no evidence of disease state, this transition was not included in the model structure to avoid double counting of survival from DeQuen et al. (2012).

Costs and utilities

Costs were taken from NHS Reference Costs 2012-2013 unless otherwise stated. (Table 72) Costs were inflated to 2013 prices, using the hospital and community health services (HCHS) index, where appropriate.

The lifetime costs of ipilimumab (£90,688) and dacarbazine (£11,469) for treatment of distant recurrence was taken from revised estimates for the lifetime costs reported by Dickson et al (2011) which includes all associated costs including additional imaging and follow-up during treatment. No estimates of the cost of vemurafenib were identified and so it was assumed to be identical to that of ipilimumab.

A terminal care cost (£5,527), taken from NICE TA319, was therefore added for patients in their final years of life.

Table 72: Key costs applied to the model

Parameter	Value	Reference
CT scan	£125	NHS Reference Cost 2012-2013
MRI scan	£169	NHS Reference Cost 2012-2013
BRAF test	£97	NICE (2012)

Parameter	Value	Reference
Surgical removal localised metastases	£835	NHS Reference Cost 2012-2013
Follow-up appointment	£139	NHS Reference Cost 2012-2013
Consultant outpatient oncology visit	£139	NHS Reference Cost 2012-2013
Ipilimumab (lifetime)	£90,688	Dickson et al 2011
Dacarbazine (lifetime)	£11,469	Dickson et al 2011
Vemurafenib (lifetime)	£90,688	Dickson et al 2011

Quality of life data were taken from Kilbridge et al (2001). (Table 73)

Table 73: 3-Monthly utilities applied to the model

Parameter	Value	Reference
NED	0.24	Kilbridge et al (2001)
Loco-regional recurrence	0.20	Kilbridge et al (2001)
Distant recurrence	0.15	Kilbridge et al (2001)
Dead	0	

All costs and health outcomes were discounted at a rate of 3.5% as recommended by the NICE Guidelines Manual (2012)

Base case results

The deterministic base case results (Table 68) of the model are shown in the table 68. The addition of routine imaging during follow-up lead to an increase in lifetime costs of £2,281 and an increase in QALYs of 0.12. This equates to an incremental cost effectiveness ratio (ICER) of £18,806 per QALY below the NICE threshold of £20,000 per QALY. Under the assumption of a long term survival benefit of 15% the addition of routine imaging lead to an increase in lifetime QALYs of 0.2159.

Table 74: Deterministic base case results

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£52,150	£49,869	£2,281
Quality adjusted life years (QALYs)	5.8777	5.7564	0.1213
Cost per QALY gained			£18,806

The stochastic base case results of the model calculated from the means of the PSA are shown in table 75. The addition of routine imaging during follow-up lead to an increase in lifetime costs of £2,782 and an increase in QALY of 0.09. This equates to an incremental cost effectiveness ratio (ICER) of £30,301 per QALY above the NICE threshold of £20,000 per QALY. Under the assumption of a long-term survival benefit of 15% the cost per QALY was £15,322 again below the NICE threshold. The base case results differ considerably from the deterministic base-case results. This is as a result of none symmetrical distributions around a number of key parameters.

Table 75: Stochastic base case results

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£49,652	£46,870	£2,782
Quality adjusted life years (QALYs)	6.0492	5.9574	0.0918
Cost per QALY gained			£30,301

Sensitivity analyses

A series of deterministic sensitivity analyses were also conducted around our base case, whereby an input parameter was changed to assess its influence on the overall result. The results of the deterministic sensitivity analysis are shown in Table 69.

Table 76: Deterministic sensitivity analysis results

Change made	Incremental cost	Incremental QALYs	ICER
Identified outside routine imaging (=80%)	£1,630	0.0747	£21,818
Perfect diagnostic accuracy	£2,473	0.1415	£17,469
Sensitivity CT=70%	£2,024	0.0983	£20,587
3 monthly probability of transition from loco-regional to distant halved	£2,504	0.0899	£27,848
3 monthly probability of transition from loco-regional disease identical to those with no evidence of disease	£2,567	0.0530	£48,419
Cost of CT scan doubled	£3,251	0.1213	£26,809
Distant recurrence drug costs increased by 50%	£2,592	0.1213	£21,375
Life years instead of QALYs	£2,281	0.1255	£18,169

It can be seen from the results of the deterministic sensitivity analysis that the ICER was sensitive to the probability of moving from 'loco-regional recurrence' to 'distant recurrence' if the recurrence is not identified. Under the conservative assumption that moving to 'distant disease' has the same probability in this group to that of the 'no disease' group, the resultant ICER is £48,419 and when the probability was halved (i.e. fewer patients with unidentified recurrence would progress to distant recurrence) the ICER value increased to £27,848. This was a parameter for which no evidence was identified and for which there was difficulty in obtaining a consensus in the GDG. The higher this probability and thus the greater the benefit of identifying local recurrence, the more cost-effective the addition of 'routine-imaging' would be with the ICER lower than the NICE threshold for probabilities at the higher end of

the range. The resulting ICER was less sensitive to other GDG assumptions (e.g. the proportion of patients starting each systemic treatment, diagnostic accuracy of CT etc).

The evidence around quality of life was weak but it made no difference to cost effectiveness when life-years were used instead of QALYs resulting in a cost per life-year gained of under £20,000 although again there was large uncertainty around this estimate. The ICER was also sensitive to both the additional benefit from being identified through imaging and the cost of the imaging modality. The ICER was above £20,000 per QALY in the majority of the sensitivity analyses.

Despite being below the threshold the cost effectiveness plane shows there is considerable uncertainty around the base-case estimate. The majority of iterations of the probabilistic sensitivity analysis resulted in routine imaging being more effective and more costly: 99.8% of iterations in the north-west quadrant of the cost effectiveness plane (Figure 43). Usual follow-up was preferred in 74.5% of iterations compared to usual follow-up with the addition of routine imaging at NICE's threshold of £20,000 per QALY. Usual care with the addition of routine imaging was cost effective over 50% of the time, compared to usual care, only when the threshold was above £34,000 per QALY (Figure 44).

Figure 43: Cost effectiveness plane

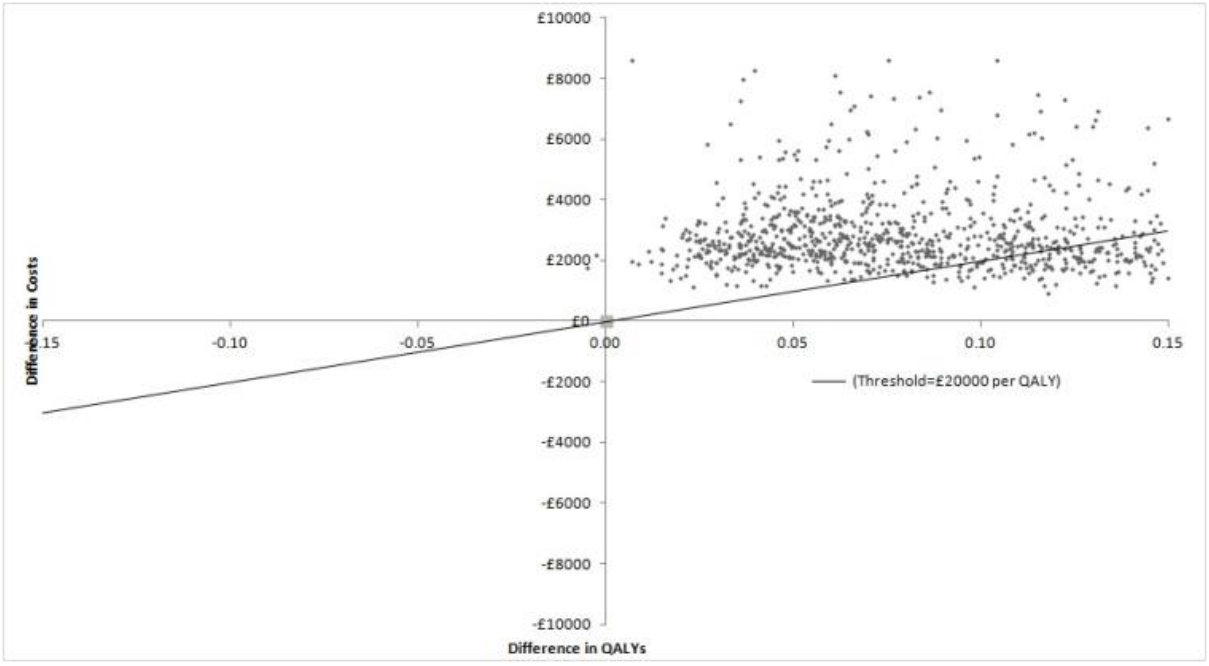
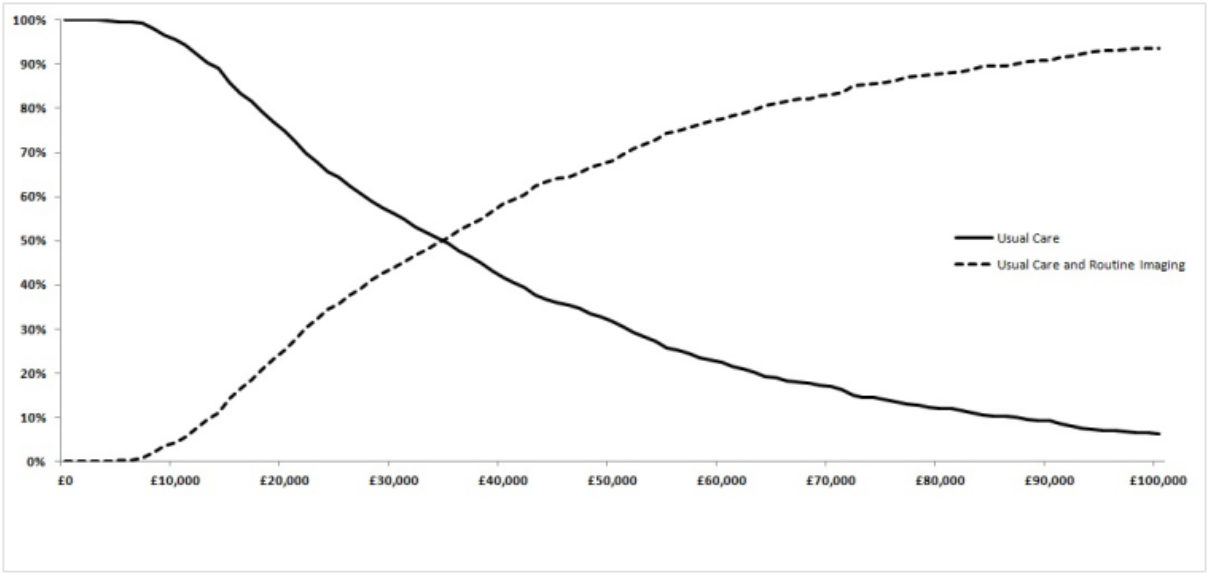


Figure 44: Cost effectiveness acceptability curve



When a fixed additional 15% survival benefit is added for those patients identified through imaging and treated with ipilimumab, all 1000 iterations are both more effective and costly (Figure 45). During probabilistic sensitivity analysis there was estimated to be a 77.1% probability that the addition of routine imaging was cost effective at a threshold of £20,000 per QALY (Figure 46).

Figure 45: Cost effectiveness plane under 15% survival benefit assumption

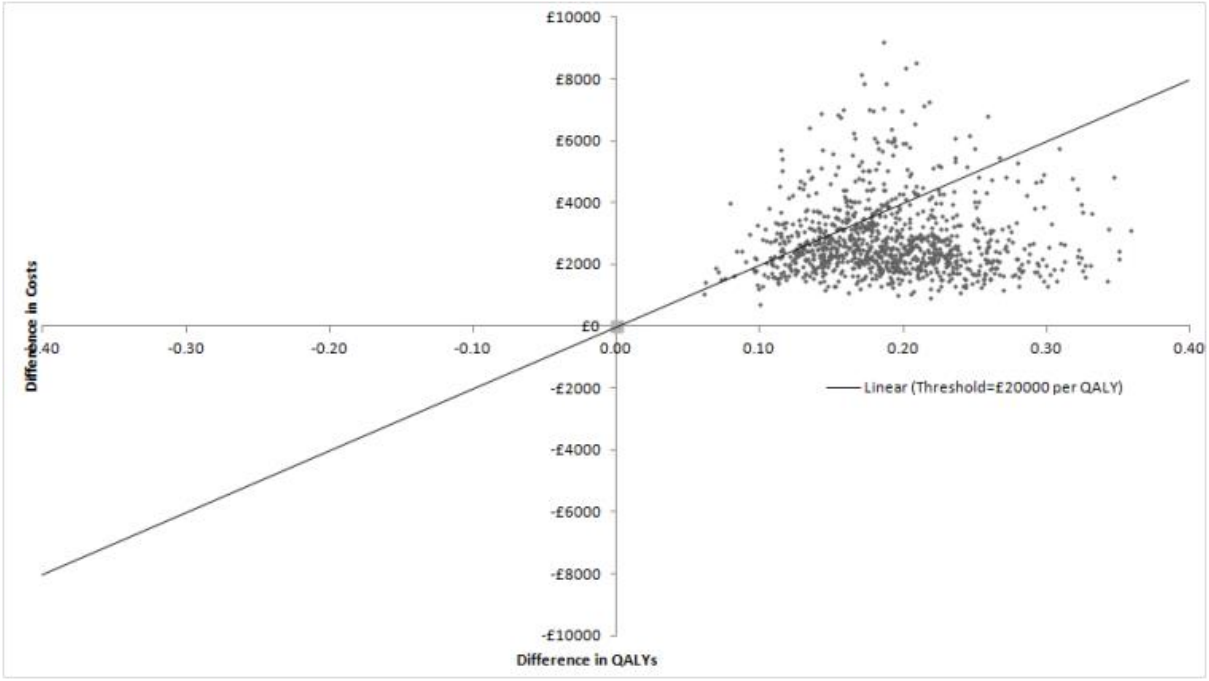
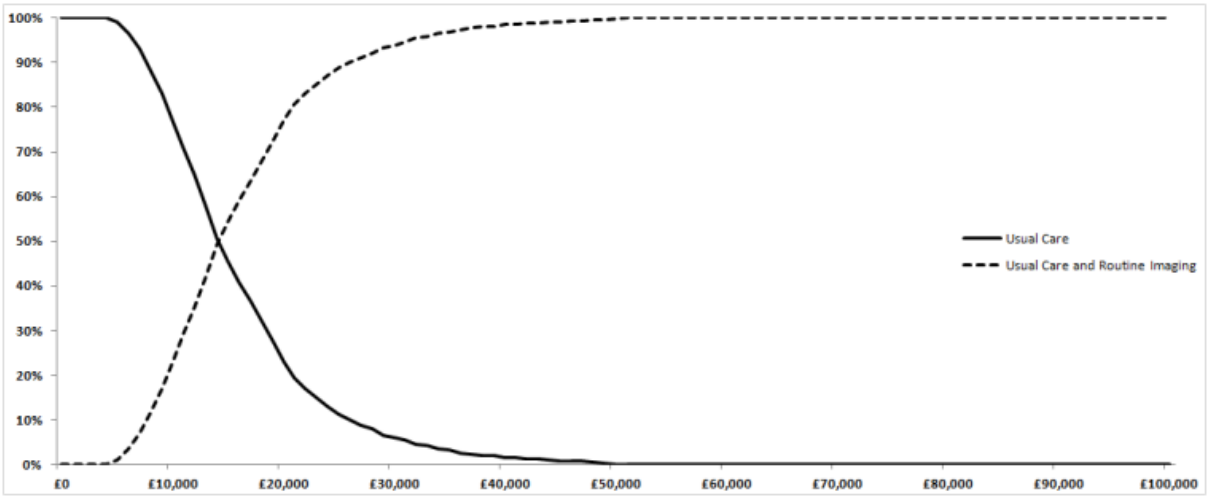


Figure 46: Cost effectiveness acceptability curve under 15% survival benefit assumption



Conclusion

Under the base case assumptions standard follow-up was cost effective at the NICE threshold of £20,000 per QALY. However there is uncertainty around the estimate with nearly three quarters of iterations in the probabilistic sensitivity analysis being above the NICE threshold of £20,000 per QALY. There is a stronger case that the addition of routine imaging to standard follow-up is cost effective if patients identified by routine imaging when asymptomatic are assumed to have a lower volume of disease and improved outcomes from treatment as a result. However, further research is needed to investigate this hypothesis.

1

Recommendations	**Perform a full examination of the skin and regional lymph nodes at all follow-up appointments.** **Consider personalised follow-up for people who are at increased risk of further primary melanomas (for example people with atypical mole syndrome, previous melanoma, or a history of melanoma in first-degree relatives or other relevant familial cancer syndromes).** **Provide psychosocial support for the person with melanoma and their family or carers at all follow-up appointments.** **All local follow-up policies should include reinforcing advice about self-examination (in line with recommendations in chapter 2), and health promotion for people with melanoma and their families, including sun awareness and vitamin D (in line with recommendations in chapter 2), and NICE guidance on smoking cessation.** **Continue to manage concurrent drug treatment in line with recommendations in section 9.2.** **<u>Stage 0 melanoma</u>** **Discharge people who have had stage 0 melanoma after completion of treatment and provide advice in line with recommendations in section 8.1.** **<u>Stage 1A melanoma</u>** **For people who have had stage 1A melanoma, consider follow-up 2–4 times during the first year after completion of treatment and discharge at the end of that year.** **Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up to people who have had stage 1A melanoma.** **<u>Stages 1B-2B melanoma or stage 2C melanoma (fully staged using sentinel node biopsy)</u>** **For people who have had stages 1B–2B melanoma or stage 2C melanoma with a negative sentinel lymph node biopsy, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years.** **Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up to people who have had stages 1B-2B melanoma or stage 2C melanoma with a negative sentinel lymph node biopsy.** **<u>Stage 2C melanoma with no sentinel lymph node biopsy or stage 3 melanoma</u>** **For people who have had stage 2C melanoma with no sentinel lymph node biopsy, or stage 3 melanoma, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years.**

	Consider surveillance imaging as part of follow-up for people who have had stage 2C melanoma with no sentinel lymph node biopsy or stage 3 melanoma and who would become eligible for systemic therapy as a result of early detection of metastatic disease if: • **the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging is identified or** • **there is a clinical trial of the value of regular imaging.** **<u>Stage 4 melanoma</u>** **Offer personalised follow-up to people who have had stage 4 melanoma.**
Relative value placed on the outcomes considered	The GDG considered the early detection of relapse or melanoma recurrence to be the most important outcome for this topic. Overall survival was also considered to be of importance by the group. Other outcomes originally considered by the GDG to be potentially informative included patient preference and adverse events, but there was no evidence available to inform these outcomes. Although not listed in the review question as a specific outcome, there was some evidence on the detection of new primaries which the GDG subsequently felt to be of relevance to this topic. The GDG felt that it was very important to compare the healthcare setting in which follow-up was carried out, particularly in relation to patient satisfaction and preference. Another aspect of the topic considered to be of importance was the diagnostic effectiveness of imaging as part of follow-up protocols. The recommendations differentiate between advice for patients with stage 2C melanoma (on the basis of the primary histology only) and stage 2C melanoma with a negative SLNB. In the absence of a SLNB, 20-30% of patients with thick tumours indicative of stage 2C would have had a positive SLNB and would therefore have been upstaged to stage 3. Although this may also occur in patients of stage 1B-2B, the proportions likely to be upstaged would be much smaller.
Quality of the evidence	The quality of the available evidence for this topic was considered to be very low on GRADE assessment. For diagnostic outcomes, QUADAS-2 was used and again the quality of available evidence was considered to be very low. In relation to the diagnostic evidence, the GDG were made aware of the high risk of bias. This was because the populations included in the imaging studies were thought probably to be highly selected and already considered likely to have suffered a relapse or recurrence, thus potentially overestimating the efficacy of any imaging modalities.

	The GDG discussed the applicability of the single published randomised trial comparing follow-up settings (Murchie et al. 2010) and concluded that there were some serious concerns, particularly in relation to the very short follow-up time, which meant it was not possible to make recommendations about where follow-up should take place. There was no high quality data identified which addressed whether treating stage 4 melanoma earlier was more likely to result in prolonged survival. Although some evidence supported the view that earlier stage disease was associated with better survival it was felt that this may reflect biological differences between tumours rather than the effect of different treatments. As a result of the poor quality of available evidence, the GDG did not feel that it was appropriate or possible to make strong recommendations and therefore all recommendations for this topic (including stratifying the recommendations by stage) are supported the GDGs clinical expertise and their epidemiological knowledge of melanoma survival curves. The GDG were keen to reinforce the important message of providing information on health promotion to people with melanoma (and their families) and the need for regular self examination, and this was based solely on clinical expertise and their epidemiological knowledge of melanoma survival curves. The decision to discharge people with stage 0 melanoma following treatment was also based on clinical expertise and published epidemiological data that shows a very low risk of recurrence for this patient group. The GDG also agreed to not routinely offer screening investigations to people with stage 1A and 1B-2C melanoma because of the low probability of identifying treatable disease in these groups. This decision was also balanced against the cost of increased imaging and the risks of increased exposure to radiation.
Trade off between clinical benefits and harms	Despite the lack of high quality evidence, the GDG felt that this was an area in which making recommendations for the follow-up of patients treated for melanoma was important. The group agreed that the early detection of relapse resulting from review in clinic, as well the ability to meet education and support needs of patients, their families and carers outweighed the potential risk of increased anxiety in patients being regularly followed up or finding an untreatable relapse.
Trade off between net health benefits and resource use	Two previous cost-effective analyses were identified for this topic. The evidence was considered low quality and neither considered a NHS or personal social services perspective. The evidence also considered interventions, during follow-up, that were no longer widely used in the NHS. The evidence was also superseded by a *de novo* health economic model. Therefore, the GDG did not consider this evidence in making their recommendations. A *de novo* health economic model was developed for this topic: specifically to address the cost-effectiveness of the addition of routine imaging to usual follow-up for asymptomatic patients with stage 3 melanoma who have previously received treatment with curative intent and have no evidence of disease. The results of the economic model were used to inform the recommendations on the use of routine imaging in follow-up.

	The economic model compared routine imaging to no routine imaging during follow-up in people with stage 3 melanoma. The model showed that at the NICE threshold of £20,000 per QALY there was a 25% chance that routine imaging would be cost-effective. The results of the model were sensitive to the poorly quantified transition probability of moving from unidentified loco-regional disease to distant disease and the additional benefit of identifying recurrences through imaging (i.e. being picked up earlier leading to possibly greater treatment effectiveness). There was a higher probability of the addition of routine imaging being cost-effective (>75%) when a higher additional benefit of identifying recurrences earlier through imaging was assumed. The GDG considered there were a number of uncertainties around parameters used in the model especially around capturing all the benefits of routine imaging in stage 3 melanoma. The GDG nonetheless made a recommendation because of the possibility that a small proportion of these high risk patients might benefit from early detection of recurrent disease. However, the GDG was aware of the cost implications and agreed that the decision to provide this would have to depend on the availability of local resources.
Other considerations	It was judged by the GDG that these recommendations would lead to a reasonably minor change in current UK practice affecting a relatively small number of patients and was noted that there may be a reduction in variation of follow up. A consensus recommendation was made to consider tailored follow-up for patients at increased risk of further primary melanomas which may be detected earlier as part of follow-up. The GDG were aware of the potential effects of increased radiation exposure from CT scanning and in particular the possible increased risk of second tumours and felt that this was an additional reason for being cautious about making recommendations for routine imaging. The GDG were also concerned about the finding of a false positive in around 25% of CT scans which might lead to unnecessary and, sometimes invasive investigation, and anxiety. Although the evidence did not present by stage, the GDG felt that important for clarity that specific recommendations were made for each stage separately. The recommendation to not offer imaging was made on the basis of clinical experience and consensus. No equalities issues were identified for this topic. The treatment of patients with advanced melanoma is a rapidly changing area, with the emergence of new agents whose benefits will become clearer in the relatively near future. Because this may result in greater benefit for patients with low-volume metastatic disease, these recommendations should be reviewed

Research recommendation	**In people treated for high-risk stage 2 and 3 melanoma, does regular surveillance imaging improve melanoma-specific survival compared with routine clinical follow-up alone? This should be investigated in a randomised controlled trial. Secondary outcomes should include time to recurrence, site of recurrence, proportion of people receiving active therapy at recurrence, cost effectiveness and quality of life.**
Why is this important	Until recently there have been no effective therapies for metastatic melanoma and no strong rationale for early detection of relapse through surveillance imaging. However, new, effective targeted treatments and immunotherapy agents are now available and further treatments are likely to become available in the near future. In particular, immunotherapy can offer long-term disease-free survival but takes a number of months to take effect. In this situation, early detection of relapse may identify people likely to be fit enough to receive the treatment for long enough to benefit. Although early detection of relapse through surveillance imaging might appear likely to improve outcomes, there is no evidence to confirm this. In addition routine imaging has resource implications and involves more hospital visits and increased radiation exposure for the person.

8.2 Brain imaging

Patients with Stage 3 and 4 melanoma are at risk of developing metastases in the brain. The probability of a patient having brain metastases increases with increasing stage of disease. Some centres routinely image the brain when carrying out body CT while others do not. Detecting asymptomatic brain metastases may lead to earlier treatment either with radiotherapy or chemotherapy. In particular the efficacy of stereotactic radiotherapy for small brain metastases is such that detection of brain metastases at a size amenable to treatment with this technique might mean that early detection is important. Furthermore, because treatment with ipilimumab is reported to have some effect on brain metastases and response takes some time, there might be an advantage in detecting brain metastases when they are small.

Clinical questions:

- **In patients with melanoma who are undergoing body imaging as part of follow-up and who have no neurological signs or symptoms, should brain imaging be included?**
- **Where imaging is indicated, is CT or MRI the most appropriate method of imaging for brain metastasis as part of follow-up for asymptomatic patients?**

Clinical evidence

None of the studies indentified for this topic included brain imaging as part of the follow-up protocols for asymptomatic patients.

No evidence was identified comparing CT scans to MRI scans for the identification of brain metastases in asymptomatic patients treated for melanoma.

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated

with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Include the brain for people having imaging as part of follow-up or when metastatic disease is suspected.** **Consider CT rather than MRI of the brain for adults having imaging as part of follow-up or when metastatic disease is suspected.** **Consider MRI rather than CT of the brain for children and young people (from birth to 24 years) having imaging as part of follow-up or when metastatic disease is suspected.**
Relative value placed on the outcomes considered	The GDG considered the early detection of brain metastases to be the most important outcome for this topic. Overall survival was also considered to be important. The only other outcome considered by the GDG to be important for this topic was HRQoL because the identification of small, asymptomatic brain metastases can adversely affect the patient's quality of life. Although not listed in the review question as a specific outcome, there was some evidence on the risk of brain metastases as site of first relapse in stage 3 patients which the GDG felt was important to consider when drafting recommendations on whether to image the brain as part of follow-up.
Quality of the evidence	The quality of the available evidence for this topic was considered to be low on GRADE assessment. Because of the poor quality of evidence available, the GDG did not feel it was appropriate or possible to make strong recommendations. Therefore all recommendations for this topic are mostly based on GDG consensus with the group drawing on their clinical expertise and their epidemiological knowledge of melanoma survival curves.
Trade off between clinical benefits and harms	Despite the lack of high quality evidence, the GDG felt that this was an area in which making recommendations for the follow-up of patients treated for melanoma was important. The group considered that the early detection of brain metastases as well as the ability to meet education and support needs of patients, their families and carers outweighed the potential risk of increased anxiety in patients undergoing brain imaging and the possibility of identifying non-significant abnormalities or benign lesions.
Trade off between net health benefits and resource use	The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. This topic was not considered a priority area for the development of an economic model. The GDG felt that there would be a modest cost increase through increased imaging and radiological reporting costs. The GDG acknowledged that MRI is more sensitive than CT in detecting small volume metastases. However, they recognised that MRI is more expensive and would involve the patient in a second visit to hospital, whereas CT brain could be carried out at

	the same time as imaging the rest of the body. Therefore the GDG agreed that the additional cost would not justify the relatively small benefits of finding brain metastases earlier. This is likely to be balanced out by increase in QALYs as a result of earlier identification and subsequently earlier treatment of disease.
Other considerations	It was judged by the group that these recommendations would lead to a minor change in current UK practice and it was noted that there would a reduction in variation of follow-up. No equalities issues were identified for this topic.

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9 Other management issues during follow-up

9.1 Managing suboptimal Vitamin D levels

The relationship between vitamin D, sun exposure, cancer and melanoma is complicated and not well understood. Vitamin D is needed to ensure healthy bones. The main natural source of vitamin D in the body is sunlight on skin. When patients are diagnosed with melanoma, they will be given advice to avoid excess sunshine because of concerns about a link between exposure to the sun and the development of skin cancer in general and further melanoma primaries in particular. Some studies have suggested that low levels of vitamin D are associated with a worse melanoma prognosis. It is currently not clear whether vitamin D levels should be measured at the time of diagnosis of melanoma and whether patients with suboptimal levels should take supplements. It is also not clear what the optimal levels of vitamin D are, the amount of sunshine that is needed to ensure the right amount of vitamin D is made in the body and how best to give vitamin D supplements to people who are short of this vitamin. The issue was recognised to be a cause of uncertainty in melanoma management and should therefore be addressed. The Vitamin D Working Group of the Scientific Advisory Committee on Nutrition (SACN) is currently considering a series of very relevant issues such as the optimal blood levels and this guideline should be read in conjunction with the advice issued by them, expected in March 2015.

The level of uncertainty around the advice necessary to promote health by avoidance of sunburn to reduce melanoma risk and yet synthesise sufficient vitamin D was reflected in the draft NICE Sunlight exposure guideline in February 2015. This stated that 'It is not possible to provide a simple definitive message on the optimal frequency and duration of exposure for different groups for the best ratio of benefits to risks. The only consistent message is that the risks can be reduced if people never expose their skin long enough for it to redden or burn. One reason why it is difficult to provide a simple message is that the amount of UV someone gets from sunlight depends on a range of biological, environmental and behavioural factors'.

Clinical question: How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)?

Clinical evidence

The evidence is summarised in Table 77.

One very low quality case-control study reported that patients who had serum vitamin levels <10ng/ml had earlier distant disease compared with patients serum levels >20ng/ml though the difference was not statistically significant (24.37 months versus 29.47; p=0.641) (Nurnberg et al. 2009).

Moderate quality evidence from a prospective cohort study including 872 patients, reported that, after adjusting for age, sex, Townsend score, tumour site, Breslow thickness and BMI on multivariate analysis, higher serum vitamin D levels showed a protective effect for relapse free survival (HR=0.79, 95% CI 0.64-0.96) and overall survival (HR=0.83, 95% CI 0.68-1.02) per 20nmol/L increase in serum vitamin D levels (Newton-Bishop et al, 2009). Moderate quality evidence from the same prospective cohort study indicates uncertainty over whether reported Vitamin D supplementation affects relapse free survival (HR=0.81, 95% CI 0.56-1.17) or overall survival (HR=0.71; 95% CI 0.47-1.09) (Newton-Bishop et al, 2009). In this study there was no evidence of a harmful effect of high serum levels of vitamin D with no adverse events observed at the highest levels of vitamin D (Newton-Bishop et al, 2009).

Moderate quality evidence from one prospective cohort study reported that inheritance of the BsmI A allele was associated with a poorer outcome from melanoma in patients with low

vitamin D levels but not in those with high vitamin D levels (p for interaction=0.02) (Newton-Bishop et al, 2009).

Moderate quality evidence from a systematic review and meta-analysis indicates a possible protective effect for cutaneous melanoma when comparing the highest versus lowest intake of vitamin D supplements (Summary relative risk 0.63; 95% CI 0.42-0.94) (Gandini et al, 2009).

Table 77: GRADE profile: How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)?

Quality assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Distant disease (Nurnberg et al. 2009).							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Relapse free survival (Newton-Bishop et al, 2009)							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	MODERATE
Adverse events (Newton-Bishop et al (2009)							
1	observational studies	serious[1]	No serious inconsistency	no serious indirectness	no serious imprecision	none	MODERATE

[1] *All studies were retrospective reviews*

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Measure vitamin D levels at diagnosis in all people with melanoma.** **Give people whose vitamin D levels are thought to be suboptimal advice on vitamin D supplementation and monitoring in line with local policies and NICE's guideline on vitamin D.**
Relative value placed on the outcomes considered	The GDG considered overall survival, bone health and cardiovascular disease to be the outcomes of most importance for this topic. However no evidence was found on the effect of reported lower levels of vitamin D in melanoma patients on bone health or cardiovascular disease. Additional outcomes reported in the evidence but not listed in the review question included metastasis-free survival and Breslow thickness at presentation.
Quality of the evidence	The quality of the evidence was considered to be moderate to very low on assessment using GRADE and NICE checklists. Issues highlighted by the reviewer were mainly about the quality of the evidence, specifically around what the optimal levels of vitamin D are for health in the general population and melanoma patients specifically and the possibility of a dose-response relationship between vitamin D levels and the outcomes in the review question. Data from one of the most relevant studies (Newton-Bishop et al., 2009) was carried out in a small part of the UK and there were concerns about the wider applicability of the results. These issues were considered by the group and as a result of the uncertainty around the effect of vitamin D supplementation on long term survival the group felt that the only recommendation that could be made was to provide advice on supplementation in accordance with local policies and current NICE guidance. The GDG were aware of theoretical concerns about the use of intermittent high dose supplementation on immune responses, but there was no evidence to support a recommendation. Also, no specific recommendation on monitoring was made because of the lack of evidence to balance the possible benefits from monitoring and consequent better control of long term serum vitamin D levels, against the increased laboratory costs.
Trade off between clinical benefits and harms	The GDG agreed that the evidence suggested suboptimal levels of vitamin D were common in melanoma patients in the North of England at diagnosis, and that there was also an association between low levels of vitamin D and poorer melanoma-specific

	survival. However the GDG recognised that this association did not establish causality and that there was therefore no evidence about whether supplementation would affect survival. There is however evidence to show that low levels of vitamin D are associated with a number of other medical conditions and a meta-analysis of a number of randomised clinical trials for any outcome showed a survival benefit from vitamin D supplementation. Melanoma patients are usually advised to avoid sunburn after diagnosis in order to reduce their risk of further primary tumours. The GDG considered therefore that if a recommendation was not made on vitamin D, then the potential was for the patients' low levels of vitamin D to become even lower after diagnosis with possible adverse effects. So the GDG considered that a possible benefit of this recommendation might be increased overall survival. Melanoma patients represent a specific cohort who have been recognised as having low levels of vitamin D. Measuring levels allows healthcare professionals to effectively manage the vitamin D supplementation. There is however, a risk of vitamin D overdose as well as the possibility of increased anxiety for patients about the possible link between vitamin D levels and prognosis. The GDG felt that the low risk of vitamin D overdose was outweighed by the benefits for long-term health (for example, bone health) as well as theoretical concerns on immune suppression. Current recommendations from NICE and the Department of Health are that measuring vitamin D levels should be avoided and that patients who are sun-avoidant should take a daily supplement of 10µg vitamin D. In melanoma patients however the GDG had concerns about the theoretical risks of vitamin D related immunosuppression in patients with high levels of vitamin D and therefore took the view that universal supplementation might be unwise and should be limited to patients with a demonstrably low level at diagnosis. Research is currently underway to explore whether the theoretical risk of immunosuppresion is substantiated in melanoma patients and this could be incorporated in any future review of this guideline. The recommendation to give people whose vitamin D levels are thought to be suboptimal advice on vitamin D supplementation and monitoring in line with local policies and NICE guidance was included to address the fact that both NICE and the Scientific Advisory Committee on Nutrition (SACN) are currently considering these issues. In particular, the vitamin D committee of SACN is currently considering what levels of measured 25-hydroxyvitamin D_3 in the blood should indicate a need for supplementation, how that supplementation should be given and whether there is evidence for an adverse effect of high levels.
Trade off between net health benefits and resource use	The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. This topic was not considered a priority area for the development of an economic model.

	There are likely to be increased costs associated with vitamin D testing and monitoring. However, the GDG felt it was important to only give vitamin D supplementation to those patients that require it to avoid the potential problems of overtreatment. The GDG did not consider that the costs of vitamin D supplementation would be too great because vitamin D supplementation has been shown to be cost effective in other areas (e.g. NICE osteoporosis guideline) as described in the NICE PH56.
Other considerations	The GDG felt that the recommendations may lead to a large change in practice as current practice was not to test or monitor vitamin D levels as standard. The GDG were concerned about the impact on GPs of advice to measure levels but believed that most of the monitoring and advice would take place in secondary care. In relation to the paediatric population specifically, these recommendations were also consistent with the RCPCH position statement on vitamin D. There is currently no recommended preparation containing vitamin D_3 only listed in the BNF but the supplements are relatively cheap. This might however be a problem for patients with limited income. No other equalities issues were identified for this topic.

Research recommendation	**In people with stage 1–3 melanoma does vitamin D supplementation improve overall survival? This should be investigated in a placebo-controlled randomised trial. Secondary outcomes should include disease-specific survival and toxicity, including the development of renal stones and hypercalcaemia.**
Why is this important	It has been reported that suboptimal levels of vitamin D at diagnosis are common in people with melanoma from the north of England and that higher levels protect against melanoma-related death. However, vitamin D levels are higher in leaner, fitter people and the nature of the relationship between vitamin D levels and melanoma survival is unclear.

9.2 Concurrent drug therapies

Melanoma patients may take a number of drugs to treat intercurrent medical conditions. These may have effects which might promote or inhibit the growth and spread of melanoma. For instance the use of immune-suppressants for auto-immune disease or following organ transplantation is clearly important but may adversely affect the survival of people with melanoma. MacKie et al (MacKie et al NEJM 2003) provided evidence suggesting that exposure to immune-suppressants may lead to melanoma relapse. Other drugs that might have an adverse effect on melanoma patients include levodopa and metformin, and also, possibly female hormone replacement therapy and the combined oral contraceptive pill. It is not clear how best to advise patients and how to manage the use of such concurrent medications.

Clinical question: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (for example, immunosuppressants, levadopa, metformin, HRT, COCP)?

Clinical evidence

There is some evidence about the relationship between exposure to a number of drugs and melanoma risk, but none on the effect of exposure to the drug after a diagnosis of melanoma on survival. The evidence is summarised in Tables 78 to 86.

Hormone replacement therapy (HRT)

Low quality evidence from an observational study of 206 patients with melanoma followed up for a median of 10.6 years (MacKie and Bray, 2004) suggests a lower overall mortality rate in those receiving HRT than in those not receiving HRT (mortality rate 1.2% versus 3.3%; HR=0.17, 95% CI 0.05 to 0.62). No evidence was found about the effect of hormone replacement therapy on progression-free survival, quality of life, melanoma-specific survival or concurrent disease-specific survival in patients with melanoma.

Indirect evidence comes from studies comparing the incidence rates of melanoma in women receiving hormone therapy to those not receiving such therapy:

- Low quality evidence from 8 case control and 2 cohort studies including 110113 patients (Gandini et al, 2011) suggests uncertainty over whether hormone replacement therapy is associated with an increased risk of melanoma, OR 1.16 (95% CI 0.93 to 1.44).
- Moderate quality evidence from a randomised trial of hormone replacement therapy (Tang et al, 2011) suggests uncertainty about the relative rates of melanoma, HR = 0.92 (95% CI 0.61 to 1.37; HRT versus no HRT).
- The evidence from these studies suggests that, even at the upper limit of the effect confidence interval, the absolute increase in melanoma risk is likely to be small.

Oral contraceptives

No evidence was found about the effect of oral contraceptives with respect to survival from melanoma.

Indirect evidence comes from studies comparing the incidence rates of melanoma in women taking oral contraceptives therapy to those not taking oral contraceptives. Low quality evidence from 4 cohort and 16 case control studies including 301347 women (Gandini et al, 2011) suggests that oral contraceptive use is not associated with an increased risk of melanoma, OR 1.04 (95% CI 0.92 to 1.18).

β-blockers

Low quality evidence comes from three cohort studies (De Giorgi et al, 2013; Livingston et al, 2013; Lemeshow et al, 2011) including 4641 patients with melanoma, 557 of whom had received treatment with β-blockers. Pooling the adjusted hazards ratios suggests better overall survival in those treated with β-blockers (HR = 0.80, 95%CI 0.67 to 0.94). One study (De Giorgi et al, 2013) also reported better disease free survival (defined as the time to melanoma recurrence or death from any cause) in the group taking β-blockers (rate of recurrence or death was 2.5% versus 8%; HR = 0.03, 95% CI 0.01 to 0.17).

Immunosuppressive therapy

No evidence was found about the use of immunosuppressive therapy in transplant patients with respect to survival from melanoma.

One systematic review of low quality, retrospective studies reported that transplant recipients had a pooled estimate of 2.4 times (95% CI 2.0-2.9) the risk of melanoma when compared with the general population (I2=46%, p=0.04). Adjusting for type of organ graft and most recent year of transplant in the cohort reduced the I2 to 0%. (Dahlke et al (2014).

Low quality indirect evidence comes from the rates of melanoma in two observational studies including 3686 kidney or heart transplant patients receiving immunosuppressive therapy (Jensen et al, 1999; Bastiaannet et al, 2007). The standardized incidence ratio (SIR) ranged from 1.7 to 3.4 suggesting an increased risk of melanoma in this population. The evidence from these studies suggests that if 1000 patients were treated for a year with immunosuppressive therapy we would expect one additional melanoma (assuming an incidence rate of 0.5 per 1000 in the untreated population).

Metformin for type 2 diabetes

No evidence was found about the use of metformin therapy with respect to survival from melanoma in diabetics.

Low quality indirect evidence comes from a systematic review of 2 randomised trials of meformin for type 2 diabetes (Franciosi et al 2013), including 6576 patients followed over 4 to 5 years of treatment. There was uncertainty over whether metformin increased or decreased the rate of melanoma compared to other treatments (0.08% versus 0.15%; OR = 0.87, 95%CI 0.36 to 2.66).

Levadopa

No evidence was found about the use of levadopa therapy in patients with respect to survival from melanoma.

Very low quality indirect evidence comes from a screening study of 2106 patients with Parkinson's disease (Bertoni et al, 2010), 1786 of whom had previously been treated with levadopa. There was uncertainty over whether levadopa treatment was associated with an increased or decreased prevalence of melanoma compared to other treatments (4.3% versus 5%; OR = 0.84, 95%CI 0.48 to 1.47).

Methotrexate

No evidence was found about the use of treatments for rheumatoid arthritis with respect to survival from melanoma.

Very low quality indirect evidence comes from an observational study of 459 patients treated with methotrexate (Buchbinder et al, 2008). The SIR for melanoma was 3.0 (95%CI 1.2 to 6.2) suggesting an increased relative risk of melanoma in this group, although the absolute increased risk is likely to be of the order of one additional melanoma per 1000 patient-years of treatment.

Non steroidal anti-inflammatory drugs (NSAIDs)

No evidence was found about the use of NSAIDs with respect to survival from melanoma.

Low quality indirect evidence comes from a meta-analysis of 10 case-control and observational studies, including 6999 patients with melanoma and 490332 controls (Hu et al, 2014). There was no increased risk of melanoma in patients treated with aspirin (RR=0.96, 95%CI 0.89 to 1.03) or with non-aspirin NSAIDs (RR=1.05, 95%CI 0.96 to 1.14).

Very low quality evidence from one case control study (Siiskonen, 2013) including 11318 patients with melanoma and 6786 controls suggest that propionic acid derivative NSAIDs are associated with an increased risk of melanoma (OR=1.33, 95%CI 1.14 to 1.54).

Quinolones

No evidence was found about the use of quinolones in patients with melanoma. Very low quality indirect evidence comes from one case control study (Siiskonen, 2013) including 11318 patients with melanoma and 6786 controls which observed an increased risk of melamona in people treated with quinolones (OR=1.33, 95%CI 1.01 to 1.76).

Table 78: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (hormone replacement therapy)?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exogenous hormones	No exogenous hormones	Relative (95% CI)	Absolute	Quality
Melanoma											
20	observational studies[1]	no serious risk of bias	no serious inconsistency	serious indirectness	no serious imprecision	none	2548 cases 30922 controls and 7642 patients from cohort studies	0.51%[2]	OR 1.16 (0.93 to 1.44)	1 more per 1000 (from 0 fewer to 2 more)	VERY LOW
Melanoma (in RCTs of HRT)											
1	randomized trials	no serious risk of bias	no serious inconsistency	serious indirectness	no serious imprecision[3]	none	46/13816 (0.33%)	49/13531 (0.36%)	HR 0.92 (0.61 to 1.37)	0 fewer per 1000 (from 1 fewer to 1 more)	MODERATE
Overall mortality (in melanoma patients) (follow-up median 10.6 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/83 (1.2%)	4/123 (3.3%)	HR 0.173 (0.048 to 0.621)	27 fewer per 1000 (from 12 fewer to 31 fewer)	LOW

[1] Case-control; [2] Control risk from large UK cohort study included in Gandini et al (2011) (Hannaford, 2007); [3] Although the confidence interval for the relative effect is large the difference in the absolute event rate is very small – so the study was not downgraded for imprecision

Table 79: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (oral contraceptive use)?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral contraceptives	Control	Relative (95% CI)	Absolute	Quality
Melanoma											
20	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	4171 cases 13644 controls and 283532 women from cohort studies	0.51% 3	OR 1.04 (0.92 to 1.18)	0 more per 1000 (from 0 fewer to 1 more)	VERY LOW

[1] Case-control and other study designs together; [2] Most of the included women did not have melanoma; 3 Rate reported in Hannaford (2007) UK cohort study

Table 80: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (immunosuppressive therapy in kidney or heart transplant patients)?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunosuppression	Control	Relative (95% CI)	Absolute	Quality
Melanoma (follow-up 7.3 years)											
2	observational studies	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	13/23288 (0.06%)[1]	0.017 9%[2]	SIR ranged from 1.7 to 3.4	-	LOW
1	systematic review[4]	no serious risk of bias	no serious inconsistency	no serious imprecision	serious	none					LOW

[1] Rate per person-years (the total number of patients was 3686); [2] Based on the reported expected rates of melanoma from the included studies (0.00007 to 0.00023 per person-year); [3] The included patients did not all have melanoma; [4] This was a systematic review of a number of poor quality retrospective observational studies

Table 81: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (beta blockers for hypertension)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blockers	No beta-blockers	Relative (95% CI)	Absolute	
Melanoma recurrence or mortality (follow-up median 4.2)											
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious	none	2/79 (2.5%)	53/662 (8%)	HR 0.03 (0.01 to 0.17)	78 fewer per 1000 (from 66 fewer to 79 fewer)	VERY LOW
Overall mortality											
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	194/557 (34.8%)	1113/4084 (27.3%)	HR 0.80 (0.67 to 0.94)	48 fewer per 1000 (from 14 fewer to 81 fewer)	LOW

[1] *Significant difference in the baseline characteristics of the two groups*

Table 82: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (metformin for type 2 diabetes)?

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	Control	Relative (95% CI)	Absolute	
Melanoma (follow-up 4-6 years)											
2	randomized trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[1]	none	2/2576 (0.78%)	6/4000 (0.15%)	OR 0.87 (0.36 to 2.66)	0 fewer per 1000 (from 1 fewer to 2 more)	LOW

[1] *Low event rate;* [2] *This study was not done in melanoma patients*

Table 83: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (methotrexate for rheumatoid arthritis)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Control	Relative (95% CI)	Absolute	Quality
Melanoma (follow-up median 9.3 years)											
1	observational studies	no serious risk of bias	no serious inconsistency	serious indirectness[3]	serious[1]	none	7/4145 (0.17%)[2]	(0.06%)	SIR 3.0 (1.2 to 6.2)	1 more per 1000 patient-years (0 more to 3 more)	VERY LOW

[1] Low number of events; [2] There were 4145 person years of follow-up in 459 patients; [3] This study was not done in melanoma patients

Table 84: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (levadopa for Parkinson's disease)?

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levadopa	Control	Relative (95% CI)	Absolute	Quality
Melanoma											
1	observational studies	no serious risk of bias	no serious inconsistency	serious indirectness[1]	no serious imprecision	none	76/1786 (4.3%)	16/320 (5%)	OR 0.84 (0.48 to 1.47)	8 fewer per 1000 (from 25 fewer to 22 more)	VERY LOW

[1] This study was not done in melanoma patients

Table 85: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (NSAIDs)

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Control	Relative (95% CI)	Absolute	
Melanoma (in studies of aspirin)											
8	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	-[3]		RR 0.96 (0.89 to 1.03)	-	VERY LOW
Melanoma (in non-aspirin NSAIDs)											
5	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	-[3]		RR 1.05 (0.96 to 1.14)	-	VERY LOW
Melanoma (in propionic acid derivative (phototoxic) NSAIDs)											
1	observational studies	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	1318 cases 6786 controls		OR 1.33 (1.14 to 1.54)	-	VERY LOW

[1] Case-control and other study designs together; [2] Most participants in the included studies did not have melanoma; [3] Numbers of patients not reported for subgroup analyses

Table 86: GRADE profile: What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (quinolones)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolones	Control	Relative (95% CI)	Absolute	Quality
Melanoma											
1	observational studies[1]	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	1318 cases 6786 controls	-	OR 1.33 (1.01 to 1.76)	-	VERY LOW

[1] *Case-control;* [2] *Not all patients had melanoma in this study*

Cost effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, *de novo* modelling was not done for this topic.

Recommendations	**Do not withhold or change drug treatment for other conditions, except immunosuppressants, on the basis of a diagnosis of melanoma.** **Consider minimising or avoiding immunosuppressants for people with melanoma.**
Relative value placed on the outcomes considered	The GDG considered melanoma-specific survival and overall survival to be the most important outcomes for this topic. Other outcomes of interest included progression-free survival, HRQoL and concurrent disease specific survival however no evidence was found to inform any of these.
Quality of the evidence	The quality of the evidence was assessed using GRADE and considered to be very low to low in quality. One of the main issues highlighted by the reviewer was that the included studies were not specifically designed to answer the review question and for this reason the GDG decided that it was necessary to make a research recommendation. The group also felt that in light of the poor evidence, no strong recommendations could be made on this topic and so all recommendations were consensus-based, with the group drawing on clinical knowledge and scientific (laboratory-based) evidence that immunosuppressant's may affect the outcome for patients with melanoma. Despite theoretical concerns, there is no strong evidence to support modification of concurrent drug therapies in melanoma patients. The group felt that it was important to make a specific recommendation about immunosuppressants in light of the theoretical knowledge and laboratory- based evidence.
Trade off between clinical benefits and harms	The group felt that the recommendations would reduce the risk of melanoma progression as a result of immune suppression as well as reducing anxiety about the use of concurrent medication. The group acknowledged that there could be a risk of sub-optimal control of conditions requiring immunosuppressants. For this reason, the GDG suggested that the balance of harms should be considered by the patient and the medical team as appropriate.
Trade off between net health benefits and resource use	The GDG noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. This topic was not however considered a priority area for the development of an economic model. Although there was uncertainty about the costs and savings associated with these recommendations the GDG felt that costs

	for treatment of melanoma progression could be reduced by minimising use of immunosuppressants.
Other considerations	The GDG felt that the recommendations would lead to a limited change in practice. The group gave particular consideration to immunosuppressants as this is a complex area involving relatively few patients requiring individualised decisions. No equalities issues were identified for this topic.

Research recommendation	**In people diagnosed with melanoma what is the effect of drug therapy to treat concurrent conditions on disease-specific survival? This should be investigated in a national prospective cohort study. Secondary outcomes should include overall survival and quality of life.**
Why is this important	Drugs such as immunosuppressants and those used to treat conditions such as diabetes have effects that may affect survival in people with melanoma. For example metformin, the most frequently prescribed drug for type 2 diabetes, is thought to reduce overall cancer rates in people with diabetes but to increase mortality from melanoma in the approximately 40% of these people who have a somatic *BRAF* mutation. There is a need to balance the risk of melanoma deaths with the benefits from the most effective treatment of the concurrent conditions. But there is currently no evidence to inform this decision.

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