National Institute for Health and Care Excellence

Guideline version (Draft)

Prostate cancer: intervention comparisons

[G] Evidence reviews for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer

NICE guideline <number>

Evidence reviews

[April 2019]

Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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Active surveillance, radical prostatectomy or radical radiotherapy for localised prostate cancer

Review question

- What is the clinical and cost- effectiveness of active surveillance, radical prostatectomy or radical radiotherapy compared to each other for people with localised prostate cancer?

Introduction

The aim of the review was to determine the most clinically and cost-effective method of treating people with localised prostate cancer. The review compared the use of radical prostatectomy, radical radiotherapy and active surveillance. The effectiveness of each treatment was compared based on mortality, the development of distant metastasis, disease progression, treatment-related effects and quality of life.

Active surveillance is a form of monitoring people who are diagnosed with localised prostate cancer with regular testing such as PSA tests, digital rectal examination and prostate biopsies. Additional treatment, such as prostatectomy or radiotherapy, is only provided if test results indicate that the cancer is progressing. Watchful waiting is another form of monitoring people with localised prostate cancer which usually involves less regular testing than active surveillance. Any signs of disease progression are usually followed by treatment aimed at controlling the cancer rather than curing it. People offered watchful waiting are often older and have more comorbidities than those offered active surveillance. Although active surveillance and watchful waiting are different forms of monitoring, the two terms are often used interchangeably in the literature. Both types of monitoring will therefore be included within this review but the results will be presented separately.

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

Table 1: PICO table

Population	• People with localised prostate cancer
Interventions	• Active surveillance (also referred to as observation) • Radical radiotherapy (alone or in combination with brachytherapy) • Radical prostatectomy
Comparator	• Each other
Outcomes	• Prostate-cancer-specific mortality • Treatment-related mortality • Metastasis-free survival • Health-related quality of life - for example: – European Organisation for Research and Treatment of Cancer quality of life – EPIC instrument • Treatment-related morbidity for example -

- Late effects of radiation therapy (toxicity occurring or lasting more than 90 days after radiation therapy is completed) including bladder, bowel and sexual dysfunction and radiation-induced malignancy,
- Toxicity: acute radiation therapy toxicity. Acute effects of radiation therapy are those effects occurring during and within 90 days of starting radiation therapy. These may include bladder, bowel, skin and systemic effects.

- Number of severe adverse events
  - Incontinence
  - Erectile dysfunction
- Number of treatment discontinuations due to adverse events

Clinical evidence

Included studies

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews with no date limit yielded 8,377 references. These were screened on title and abstract, with 142 full-text papers ordered as potentially relevant systematic reviews or RCTs. Studies were further excluded at full text screening if they did not match any of the outcomes specified in the protocol.

Twenty one papers were identified for full text screening: there were 14 RCTs and 7 systematic reviews. Three RCTs were excluded because data was not in an extractable format. Six systematic reviews were excluded because they did not include any randomised control studies not already identified in the search. A reference from one systematic review was included that had not previously been identified in the literature search (see evidence tables for details – appendix E). Thirteen articles reporting on three trials were included in the final analysis.

Multiple papers reporting results of the same study were identified and collated, so that each study rather than individual reports was the unit of interest in the review;

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G.

Excluded studies

Details of the studies excluded at full-text review are given in appendix L along with a reason for their exclusion.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to both NICE's 2014 and 2018 conflicts of interest policies.

Summary of clinical studies included in the evidence review

Three randomised controlled trials, reported in 13 papers, were included in this review for localised prostate cancer. All 3 unique studies were directly applicable as they matched the protocol.

Table 1: Interventions used in the studies and details of follow-up and outcomes

Study	Study arms	Outcomes	Duration of follow-up
PROTECT TRIAL 2016 n = 1,643 (UK)	Active monitoring versus radical prostatectomy versus external-beam radiotherapy	Overall mortality Prostate cancer-specific mortality Distant metastasis EPIC domains	Follow-up 10 years
SCANDINAVIAN PROSTATE CANCER GROUP-4 RANDOMISED TRIAL 2002 n = 698 (Sweden, Finland, Iceland)	Radical prostatectomy versus watchful waiting	Overall mortality Prostate cancer-specific mortality Distant metastasis Urinary incontinence Erectile dysfunction Quality of life	Follow-up: 2014: 18 years (median 13.4 years)
PIVOT TRIAL 2012 n = 731 (USA)	Radical prostatectomy versus watchful waiting	Overall mortality Prostate cancer-specific mortality Distant metastasis Urinary incontinence Erectile dysfunction Quality of life	2012: median 10 years 2017: no median provided - range 12 - 19.5 years

Outcomes and sample sizes

The reported outcomes where data was extractable are detailed in Table 2. EPIC domains reported in some studies included the four domains of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. These include urinary function and effect on quality of life, sexual function and effect on quality of life, bowel function and effect on quality of life and health-related quality of life.

The sample sizes ranged from 698 to 1,643 participants across the studies.

No information was provided on treatment-related mortality or treatment discontinuation due to adverse events, therefore analysis could not be carried out.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

See appendix E for full evidence tables.

Economic evidence

Included studies

Standard health economics filters were applied to the clinical search strategy for this question. Details are provided in appendix C. In total, 4,671 references were returned, of which 4,654 could be confidently excluded on screening of titles and abstracts. The remaining 17 studies were reviewed in full text, and 10 were found not to be relevant. Selectively excluding further 4 non-European studies left 3 unique cost–utility analyses.

Excluded studies

Details of studies excluded after consideration at the full-text stage are provided in appendix H.

Summary of studies included in the economic evidence review

Ramsay et al. (2015) performed a UK economic evaluation based on a modified Markov modelling approach to predict lifetime costs and QALYs for patients with localised prostate cancer receiving brachytherapy (80 seeds with an average of 28 needles used per patient), external beam radiotherapy, using intensity modulated radiotherapy (IMRT: 74 - 78 Gy in 37 fractions) or radical prostatectomy. Additional comparators – cryotherapy and high-intensity focused ultrasound – are beyond the scope of this review question and excluded from consideration, here. Recurrence events were represented by health states where patients received further active or palliative treatments. Treatment-related acute and late toxicities (urinary incontinence, erectile dysfunction and bowel dysfunction) were modelled. The base case assumed identical efficacy in terms of biochemical recurrence. Utility values were drawn from multiple sources by literature review; when the authors found multiple values for particular parameters, median values were used, which were then calibrated to the EQ-5D. Costs adopted an NHS perspective. Short- and long-term toxicity rates were higher for IMRT for erectile and bowel dysfunction, and higher for brachytherapy for urinary incontinence. The authors found that brachytherapy is slightly more effective than IMRT (3.75 vs 3.69 QALYs), but also incurs higher costs (£24,456 vs £19,363), resulting in an ICER of around £85,000 per QALY gained. Radical prostatectomy was found dominated, less effective and incurring higher cost than brachytherapy and IMRT: 3.44 QALYs, £26,507. In sensitivity analysis, the finding that brachytherapy is more expensive than IMRT was maintained, but there was much greater uncertainty about whether it is more effective. The study was judged to be directly applicable with potentially serious limitations. The study was judged to be directly applicable with potentially serious limitations.

Lyth et al. (2012) developed a probabilistic Markov model using data of 695 participants in a randomised trial: Scandinavian Prostatic Cancer Group Study Number 4, SPCG-4 between October 1989 and February 1999 to compare watchful waiting (WW) with radical prostatectomy (RP) and investigate outcomes, e.g. survival, HRQoL and costs. Participants were aged less than 75 years, and tumours had to be newly diagnosed and localized to the prostate, the PSA value had to be below 50 ng/ml. the Markov model used symptomatic disease instead of hormonally controlled metastasis and refractory disease instead of refractory metastasis. The analysis took the perspective of the Swedish healthcare system, and costs were expressed in Swedish currency (SEK) at 2007 prices. Health outcomes were estimated in QALYs, derived from a 77-item questionnaire with a visual analogue scale (VAS). Both costs and QALYs were discounted by 3.5% per year. Sub-group analysis, based on age, Gleason score and PSA values was performed. The authors found that the age was the most important independent factor explaining the size of the incremental cost-effectiveness ratio (ICER) of RP vs WW, it costs more to gain an extra QALY in elderly age

groups. The value of the ICER varied from 21,026 SEK to 858,703 SEK. The group at age 70 and above with Gleason score less than 4 and PSA ≤10 generated an ICER above 200 000 SEK. The probability of RP being cost-effective at a threshold of 100 000 SEK increased with higher severity based on PSA value and Gleason score. The study was judged to be partially applicable with minor limitations.

Koerber at al. (2014) performed a cost-utility analysis by developing a three-monthly cycle Markov model to compare radical prostatectomy with active surveillance (AS), defined as 3-monthly determination of PSA and DRE for the first 2 years, then bi-annually thereafter plus biopsy at the 1st year then every 3 years. When a radical treatment was triggered for patients on AS, open radical prostatectomy was offered for those at age less than 72 year-old; older patients received radiotherapy (RT). The model was intended to estimate lifetime costs and health outcomes of 65-year old with low-risk localised prostate cancer (PSA value ≤10 ng/ml, Gleason score ≤6 and tumour stage ≤T2a). The analysis adopted the perspective of the citizen insured by German Statutory Health Insurance and included out of pocket payments. All costs (€) were adjusted to 2011 values. Both health outcomes and costs were discounted annually by 3%, and the half-cycle correction was applied. Health-related utility values of people with adverse events due to the radical treatment were obtained from an existing literature using the standard gamble technique. Prostate cancer specific mortality was obtained from SPCG4. However, as the SPCG included patients with more advanced disease and compared WW instead of AS with RP, based on existing literature, the authors assumed that only half the treatment benefit of RP would be maintained, and they obtained a modified death relative risk. Then, they calibrated the metastatic risk obtained from SPCG. The probability of developing treatment-related adverse events were obtained from an existing systematic review. The authors found that AS and RP were associated with 12.07 and 12.15 discounted lifer years and €9,585 and €16,468 discounted lifetime costs respectively, the ICER was €96,420/life year gained for people with low-risk localised prostate cancer. However, after adjusting for quality of life, effectiveness values of AS and RP were 7.60 and 7.56 QALYs respectively, resulting in the AS being more effective and cost saving. Probabilistic sensitivity analysis was performed and AS was more effective in 56% of the all 1000 iterations. The study was judged to be partially applicable with potentially serious limitations.

Economic model

Original health economic modelling was not prioritised for this review question

Evidence statements

Radical Prostatectomy versus Active Surveillance

Moderate to high-quality evidence from 1 RCT reporting data on 1,643 people with localised prostate cancer found there was reduced time to disease progression and fewer people developing distant metastases but a greater number of people reporting issues with urinary incontinence in thoseoffered prostatectomy compared to those offered active surveillance. Subgroup analysis found that there were more people reporting urinary and sexual dysfunction at up to 3 years follow-up in those people who were offered prostatectomy compared to those who were offered active surveillance.

Very-low to moderate-quality evidence from 1 RCT reporting data on 1,643 people with localised prostate cancer could not differentiate overall survival, prostate-cancer specific survival, erectile dysfunction, issues with bowel function, the effects of bowel function issues on quality of life, cancer-specific quality of life, anxiety or depression between people offered prostatectomy compared to those offered active surveillance.

Very-low to low-quality evidence from 1 RCT reporting data on 1,643 people with localised prostate cancer demonstrated there is no difference in urinary function (at 3 years and 6

years follow-up) or bowel function at 6 months, 3 years and 6 years follow-up between people offered active surveillance and those offered prostatectomy. Low to moderate-quality evidence from 1 RCT reporting data on 1,643 people with localised prostate cancer found no meaningful difference in erectile dysfunction at4 and 6 years follow-up between people offered active surveillance and those offered prostatectomy.

Radical Prostatectomy versus Watchful Waiting

Very-low to high-quality evidence from 2 RCTs reporting data on 1,429 people with localised prostate cancer found improved overall survival at 8 years follow-up, improved prostate-cancer specific survival at 6 years follow-up, fewer signs of disease progression and fewer people developing distant metastases for people offered prostatectomy compared to those offered watchful waiting. More people offered prostatectomy experienced issues with urinary incontinence and erectile dysfunction up to 8 years.

Moderate to high-quality evidence from 2 RCTs reporting data on 1,429 people with localised prostate cancer could not differentiate overall mortality up to 6 years, prostate-cancer specific mortality up to 4 years or erectile dysfunction at 18 years between people offered prostatectomy or watchful waiting.

Radical Radiotherapy versus Active Surveillance

Very-low to high-quality evidence from 1 RCT reporting data on 1,643 people found there was no meaningful difference in urinary function or in erectile dysfunction from 3 years onwards between people offered active surveillance and those offered radiotherapy .

Very-low to high-quality evidence from 1 RCT reporting data on 1,643 people found fewer signs of disease progression, fewer people developing distant metastases and lower anxiety and depression (at 6 years) for people offered radiotherapy compared to those offered active surveillance. Subgroup analysis found that at 6 months, there were more issues with erectile dysfunction, greater sexual and bowel function issues and a greater impact of sexual function issues on quality of life for people offered radiotherapy compared to those offered active surveillance.

Very-low to high-quality evidence from 1 RCT reporting data on 1,643 people could not differentiate overall survival, prostate cancer-specific survival, cancer-related quality of life or the effects of urinary or bowel function issues on quality of life between people offered radiotherapy compared to those offered active surveillance. From 3 years onwards evidence could not differentiate between the two groups for sexual function issues or impact of sexual function issues on quality of life.

Very-low to high-quality evidence from 1 RCT reporting data on 1,643 people demonstrates that, from 3 years onwards, there is no difference in sexual function or bowel function between people offered active surveillance or radiotherapy.

Radical Radiotherapy versus Radical Prostatectomy

Moderate to high-quality evidence from 1 RCT reporting data on up to 1,643 people with localised prostate cancer found that there was no meaningful difference for urinary function, erectile dysfunction or bowel function (from 3 years) between people offered radiotherapy and those offered prostatectomy.

Very-low to high-quality evidence from 1 RCT reporting data on up to 1,643 people with localised prostate cancer found more issues with bowel function at 6 months for people offered radiotherapy compared to those offered prostatectomy. Urinary function issues and sexual function issues (up to 3 years) had a greater impact on quality of life for people offered prostatectomy compared to those offered radiotherapy.

Very-low to high-quality evidence from 1 RCT reporting data on up to 1,643 people could not differentiate overall survival, prostate cancer-specific survival, the number of people developing distant metastases, disease progression, cancer-related quality of life, anxiety or depression between people offered radiotherapy compared to those offered prostatectomy. Subgroup analysis found that, from 3 years onwards, evidence could not differentiate between the two groups for the impact of sexual function issues on quality of life.

Recommendations

G1. Offer a choice between active surveillance, radical prostatectomy or radical radiotherapy to people with low-risk localised prostate cancer for whom radical treatment is suitable. Use Table 2 to discuss the benefits and harms with them.

Table 2 Factors to consider when discussing active surveillance, radical prostatectomy or radical radiotherapy for people with low – risk or intermediate – risk localised prostate cancer using evidence from a large UK trial

What are the treatment options for people with localised prostate cancer?	There are 3 options for treatment: active surveillance[1] radical prostatectomy radical radiotherapy
Effects on survival and disease progression at 10 years	
What effect does each treatment option have on survival?	The evidence does not show a difference in the number of deaths from prostate cancer from people offered active surveillance, prostatectomy or radical radiotherapy. 98 out of 100 patients offered active surveillance had not died of prostate cancer 99 out of 100 patients offered radical prostatectomy had not died of prostate cancer 99 out of 100 patients offered radical radiotherapy had not died of prostate cancer
What effect does each treatment option have on disease progression[2]?	There is good evidence that both prostatectomy and radiotherapy reduce disease progression compared to active surveillance. 21 out of 100 patients offered active surveillance had signs of disease progression 8 out of 100 patients offered radical prostatectomy had signs of disease progression 8 out of 100 patients offered radical radiotherapy had signs of disease progression
What effect does each treatment option have on the rate of development of distant metastases?	There is good evidence that both prostatectomy and radiotherapy reduce the rate of development of distant metastases compared to active surveillance. 8 out of 100 patients offered active surveillance had developed distant metastases 3 out of 100 patients offered radical prostatectomy had developed distant metastases 3 out of 100 patients offered radical radiotherapy had developed distant metastases

Potential side effects of treatment	
What effect does each treatment option have on urinary function?	There is some evidence that urinary function is better for people offered active surveillance or radiotherapy than those offered prostatectomy: At 6 months: 39 out of 100 patients offered active surveillance reported problems with urinary continence 71 out of 100patients offered radical prostatectomy reported problems with urinary continence 39 out of 100 patients offered radical radiotherapy reported problems with urinary continence At 6 years: 50 out of 100patients offered active surveillance reported problems with urinary continence 69 out of 100 patients offered radical prostatectomy reported problems with urinary continence 49 out of 100 patients offered radical radiotherapy reported problems with urinary continence
What effect does each treatment option have on erectile dysfunction?	There is some limited evidence that sexual function is better for people offered active surveillance or radiotherapy than those offered prostatectomy: At 6 months: 29 out of 100 patients offered active surveillance reported moderate or severe problems with erectile dysfunction 67 out of 100 patients offered radical prostatectomy reported moderate or severe problems with erectile dysfunction 48 out of 100 patients offered radical radiotherapy reported moderate or severe problems with erectile dysfunction At 6 years: 40 out of 100 patients offered active surveillance reported a moderate or severe problem with erectile dysfunction 50 out of 100 patients offered radical prostatectomy reported a moderate or severe problem with erectile dysfunction 36 out of 100 patients offered radical radiotherapy reported a moderate or severe problem with erectile dysfunction
What effect does each treatment option have on bowel function?	There is some limited evidence that bowel function is better for people offered active surveillance or prostatectomy than those offered radiotherapy: At 6 months: 2 out of 100 patients offered active surveillance reported faecal incontinence more than once per week 1 out of 100 patients offered radical prostatectomy reported faecal incontinence more than once per week 5 out of 100 patients offered radical radiotherapy reported faecal incontinence more than once per week At 6 years:

	3 out of 100 patients offered active surveillance reported faecal incontinence more than once per week 1 out of 100 patients offered radical prostatectomy reported faecal incontinence more than once per week 4 out of 100 patients offered radical radiotherapy reported faecal incontinence more than once per week
[1]The trial used the intention-to-treat method of analysis and some of the patients in the active surveillance arm may therefore have undergone prostatectomy or radiotherapy during the follow up period. [2] The trial defined disease progression as-: • any rise in prostate-specific antigen (PSA) >20% between consecutive measures at any time during follow-up or • any rise in PSA level of 50% or greater in any 12 month period confirmed by repeat tests or • any indication of the appearance of symptomatic systemic disease	

G2. If a person wishes to move from active surveillance to radical treatment at any stage in their care, make a shared decision to do so based on the person's preferences, comorbidities and life expectancy **[2019]**

G3. Offer radical treatment to people with localised prostate cancer who had chosen an active surveillance regimen and who now have evidence of disease progression **[2019]**

G4. For people with intermediate-risk localised prostate cancer

- offer radical prostatectomy or radical radiotherapy **and**
- consider active surveillance (in line with recommendation 1.3.10) for people who choose not to have immediate radical treatment.

Use Table 2 to discuss the benefits and harms of each option. **[2019]**

G5. Do not offer active surveillance to people with high-risk localised prostate cancer. **[2019]**

G6. Offer radical prostatectomy or radical radiotherapy to people with high-risk localised prostate cancer when it is likely the person's cancer can be controlled in the long term. [2019]

Rationale and impact

Why the committee made the recommendations

The committee agreed that the existing recommendations were in line with the good body of evidence available for the treatment of localised prostate cancer, and reflected the trade-off seen in the evidence between the clinical benefits of radical treatments and potential side effects in people with low to intermediate risk prostate cancer.

The committee also noted that active surveillance has often been offered as a non-preferred treatment rather than as an equal choice alongside prostatectomy and radiotherapy. It agreed that active surveillance was a safe option for people with low-risk localised prostate cancer because most people live with low risk cancer for many years with no disease progression. The lasting negative effects of radiotherapy or prostatectomy mean that many people may prefer active surveillance. It also agreed that active surveillance might be a safe option for some people with intermediate-risk localised prostate cancer, although for this group there was more risk that the cancer would have an impact on their lives and they are more likely to need radical treatment. Since the committee agreed that all 3 options may be suitable for different people, it included a preference decision table to assist both the clinician and the patient in making the right choice for them. The committee did not change the existing recommendations that active surveillance should not be offered to those people with high-risk localised prostate cancer because no new evidence suggested it was beneficial.

The committee saw no new evidence to suggest any changes was needed to the recommendation on radical prostatectomy and radical radiotherapy in people with high risk prostate cancer.

Impact of the recommendations on practice

The recommendations reflect current practice, so there will be minimal impact on resources.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the most important outcomes were survival, development of distant metastases, disease progression and quality of life. These outcomes were considered to be the most important to inform patients of the balance between the risk of disease and the development of potential side effects. The committee was particularly interested in some of the quality of life outcomes as they relate to living with an untreated cancer (active surveillance) and how people dealt with the anxiety that this could cause. It agreed that these outcomes are important to patients and that patients should get the clearest information possible to make the best decision for them.

The quality of the evidence

All 3 included studies were at moderate risk of bias as a result of the lack of blinding of participants. This may have had a limited impact on clinical outcomes such as mortality and disease progression but a greater impact on patient-reported outcomes such as quality of life. Although there were a small number of studies these had large sample sizes, ranging from 698 to 1,643 participants.

Only one study (ProtecT (Donovan et al., 2016)) included radiotherapy as a comparison in addition to active surveillance and prostatectomy. The ProtecT trial has the greatest number of participants and was the only UK-based study, making it directly applicable to current practice in the NHS. ProtecT was also the only trial to include active surveillance, with the other two (PIVOT (Wilt et al., 2012) and SPCG-4 (Holmberg et al., 2002)) using watchful waiting as an intervention rather than active surveillance. As the two terms are often used interchangeably in the literature it was decided that these studies would be included in the analysis. However, given the differences between the definitions of active surveillance and watchful waiting it was decided that the results of these studies should be presented

separately to the active surveillance results. When the evidence was assessed using GRADE, the majority of the evidence for mortality and disease progressions was of moderate to high quality but the quality of patient-reported outcome measures were low.

All 3 studies used an intention-to-treat method of analysis. The committee discussed how people who undergo active surveillance often defer to either radical prostatectomy or radical radiotherapy if they show signs of disease progression. It noted that some patients who were assigned to the active surveillance arm of each study may have changed treatment during the follow-up period and this may have had an impact on some of the outcomes. For instance, people offered active surveillance experienced fewer issues with sexual dysfunction during short-term follow-up than people offered radiotherapy (ProtecT (Donovan, 2016)). However, the evidence could not differentiate between the groups at 3 years. This could be an indication that the difference in side effects narrows between the treatment options over time, but could also be a consequence of some of the patients in the active surveillance group undergoing radiotherapy and experiencing the associated side effects.

The committee also discussed concerns that risk of disease could have been misclassified in the study if the results of the biopsy suggested that a patient had low-risk rather than high-risk prostate cancer. Although this could be examined and upstaged after prostatectomy this would not be possible for patients in the observation arm. However, it was accepted that this reflects the method of diagnosis in clinical practice and therefore should not affect the applicability of the results to treatment for localised prostate cancer.

Benefits and harms

Based on the evidence from the ProtecT trial (Donovan et al., 2016), the choice of active surveillance, prostatectomy or radiotherapy appears to be a trade-off between the benefits offered by prostatectomy and radiotherapy against their potential risk of side effects. Benefits of prostatectomy and radiotherapy over active surveillance included reduced risk of disease progression and metastatic disease. Harms associated with prostatectomy over active surveillance were increased issues with incontinence and issues with erectile dysfunction whilst harms associated with radiotherapy over active surveillance were increased issues with urinary and bowel function. Similar outcomes were reported for mortality and disease progression between prostatectomy and radiotherapy. Side effects associated with urinary and sexual function were worse following prostatectomy but effects relating to bowel function were worse following radiotherapy. Based on this evidence, the committee decided that all three treatment options may be suitable for different people and therefore agreed to keep the existing recommendation to offer active surveillance as an option to people with low-risk localised prostate cancer.

The committee agreed that the trade-off between risks and harms means that the choice of treatment method should be based on an informed discussion with the patient. This should involve the clinician explaining the benefits and harms of each of the three treatment options to arrive at a shared decision over the best approach for that particular patient. The committee stated that clinicians need to ensure that people understand that if they choose active surveillance they may still need to undergo prostatectomy or radiotherapy at some point in the future if they show signs of disease progression. As a result, the committee decided to make a recommendation that clinicians should discuss the benefits and harms of each treatment using a preference decision point table to help guide the discussion.

The committee discussed that the ProtecT trial included patients with both low-risk and intermediate-risk localised prostate cancer. However, as the two groups of patients were not separated in the analysis it is not yet possible to determine the difference between the three treatment options for patients with intermediate-risk prostate cancer. As a result, the committee decided to keep the existing recommendation to consider active surveillance for people with intermediate-risk disease who did not wish to have radical treatment. It also agreed to keep the recommendation that the progression to radical treatment should be based on the man's personal preferences.

The committee agreed that active surveillance is a particularly viable option for peeople with low-risk localised prostate cancer. However, it was highlighted that there are some uncertainties when advising a patient over the best treatment option as there is potential for a patient to be misclassified as low-risk rather than high-risk following a biopsy. As such, some people who undergo active surveillance may progress to radical treatment because they were mistakenly classified as low-risk patients. This issue was also raised by one of the expert witnesses. However, it was accepted that regular testing for patients under active surveillance should help to flag any further signs of disease progression.

Cost effectiveness and resource use

The committee reviewed the included economic evidence on the comparison between active surveillance, radical prostatectomy and radiotherapy and the economic evidence on the comparison between active surveillance and radical prostatectomy for low-risk localised prostate cancer performed by Ramsay et al. and Koerber et al. respectively. It agreed that the cost-utility analysis performed by Ramsay et al. provided directly applicable evidence and the analysis by Koerber et al. provided partially applicable evidence. The committee agreed that the evidence from these two studies was sufficient to support recommendations in favour of offering active surveillance to people with low-risk localised prostate cancer.

The committee reviewed the economic evidence on the comparison between watchful waiting and radical prostatectomy. It agreed that the cost-utility analysis performed by Lyth et al. provided partially applicable evidence. The committee noted that watchful waiting was a passive approach compared to active surveillance. The committee, therefore found that this evidence could not inform a decision about changes in the current practice.

Appendices

Appendix A – Review protocols

Review protocol for RQ2 – Active surveillance, radical prostatectomy or radical radiotherapy for localised prostate cancer

ID	Field (based on PRISMA-P	Content
I	Review question	What is the clinical and cost- effectiveness of active surveillance, radical prostatectomy or radical radiotherapy compared to each other for people with localised prostate cancer?
II	Type of review question	Intervention
III	Objective of the review	This area was identified as requiring updating during the 2016 exceptional surveillance review and the scoping phase of the update. It aims to determine the clinical and cost-effectiveness of active surveillance, radical prostatectomy or radical radiotherapy compared to each other for people with localised prostate cancer
IV	Eligibility criteria – population/disease/condition/issue/domain	People with localised prostate cancer
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Active surveillance (also referred to as observation) • Radical radiotherapy (alone or in combination with brachytherapy) • Radical prostatectomy

VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	• Each other Alternative protocols within the intervention class (e.g. different active surveillance approaches compared to each other)
VII	Outcomes and prioritisation	• Prostate-cancer-specific mortality • Treatment-related mortality • Metastasis-free survival • Health-related quality of life - for example: o European Organisation for Research and Treatment of Cancer quality of life, o EPIC instrument If *reported – psychological aspects of quality of life to be reported separately* • Treatment-related morbidity for example - o Late effects of radiation therapy (toxicity occurring or lasting more than 90 days after radiation therapy is completed) including bladder, bowel and sexual dysfunction and radiation-induced malignancy, o Toxicity: acute radiation therapy toxicity. Acute effects of radiation therapy are those effects occurring during and within 90 days of starting radiation therapy. These may include bladder, bowel, skin and systemic effects. • Number of severe adverse events

		○ Incontinence ○ Erectile dysfunction • Number of treatment discontinuations due to adverse events
VIII	Eligibility criteria – study design	• RCTs. • Systematic reviews of RCTs
IX	Other inclusion exclusion criteria	Non English- language papers
X	Proposed sensitivity/sub-group analysis, or meta-regression	• Active surveillance strategies • Radiotherapy schedules • Types of surgery • Severity of cancer – low/intermediate
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
XII	Data management (software)	See appendix B below – section 1.3

XIII	Information sources – databases and dates	See appendix C of relevant chapter. Searches conducted from 2007 on advice of guideline committee.
XIV	Identify if an update	This is a new question. Original questions linked to this question: • What is the most effective follow-up protocol for active surveillance? • Which people with localised prostate cancer should be offered active surveillance? • Which is the most effective radical prostatectomy method for prostate cancer: retropubic, transperineal, laparoscopic or robot-assisted laparoscopic radical prostatectomy? **Related recommendations:** 1.3.7 Offer active surveillance (in line with recommendation 1.3.8) as an option to peoplewith low-risk localised prostate cancer for whom radical prostatectomy or radical radiotherapy is suitable. [new 2014] 1.1.10 Tell men: • about treatment options and their risks and benefits in an objective, unbiased manner and • that there is limited evidence for some treatment options. [new 2014]

		1.3.11 Consider active surveillance (in line with recommendation 1.3.8) for men with intermediate-risk localised prostate cancer who do not wish to have immediate radical prostatectomy or radical radiotherapy. [new 2014] 1.3.12 Do not offer active surveillance to people with high-risk localised prostate cancer. [2014] 1.3.13 Offer radical prostatectomy or radical radiotherapy to people with intermediate-risk localised prostate cancer. [2008] 1.3.14 Offer radical prostatectomy or radical radiotherapy to people with high risk localised prostate cancer when there is a realistic prospect of long-term disease control. [2008] 1.3.22 Consider high-dose rate brachytherapy in combination with external beam radiotherapy for people with intermediate- and high-risk localised prostate cancer. [new 2014]
XV	Author contacts	Guideline updates team, National Institute for Health and Care Excellence (contact adam.okeefe@nice.org.uk)
XVI	Highlight if amendment to previous protocol	This is a new protocol.
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter. This is a new question so no date cut-off will be used.

XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.4.1
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.4.2
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.4.3 and 1.4.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.4.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.

XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline update. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

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Appendix B – Methods

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome/predictor. For mean differences, where change from baseline data were reported in the trials/studies and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These/All studies were assessed to ensure that baseline values were balanced across the treatment/comparison groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. The committee did not identify any specific minimal important difference thresholds relevant to this guideline.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). Where a range of MIDs was provided, the middle value of the range was selected; MIDs other than those using the threshold suggested by Cohen

et al. (1988) are presented in Table 2. For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. The line of no effect was specified by the committee as an MID for hazard ratios.

Table 3: Identified MIDs

Outcome	Recommended MID	Chosen MID	Source
EPIC Urinary function summary score	6 – 9	-7.5, 7.5	Skolarus, TA, Dunn, RL, Sanda MG et al. Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form. Urology. 2015; 85 (1): 101-106
EPIC Sexual function summary score	10 – 12	-11, 11	Skolarus, TA, Dunn, RL, Sanda MG et al. Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form. Urology. 2015; 85 (1): 101-106
EPIC Bowel function summary score	4 - 6	-5, 5	Skolarus, TA, Dunn, RL, Sanda MG et al. Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form. Urology. 2015; 85 (1): 101-106

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 4

Table 4: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.

GRADE criteria	Reasons for downgrading quality
	Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). 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 committee for a specific topic within the guideline. There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 5.

Table 5 Applicability criteria

Level	Explanation
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

Level	Explanation
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 (that is, methodological quality); see categorisation criteria in Table 6.

Table 6 Methodological criteria

Level	Explanation
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.

Appendix C – Literature search strategies

Search summary

The search strategies were based on the review protocol provided and the previous strategies used in CG175 *(active surveillance search - page 6).*
A date limit from 2007 was applied as stated on the review protocol.

Clinical searches

Source searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The clinical searches were conducted in March 2018.

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw.
4 PIN.tw.
5 or/1-4
6 Watchful Waiting/
7 ((active* or watch* or expect* or conservat*) adj (surveillan* or monitor* or observat* or wait* or manag*)).tw.
8 ((deferr* or delay*) adj1 (treat* or therap*)).tw.
9 or/6-8
10 exp Prostatic Neoplasms/su
11 exp Prostatectomy/
12 (radical adj4 prostatectom*).tw.
13 or/10-12
14 exp radiotherapy/
15 radiotherap*.tw.
16 (radiat* adj4 (therap* or treatment*)).tw.
17 ((external* or conformal*) adj4 (irradiat* or therap* or treat*)).tw.

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
18 ((interstitial* or intracavit* or implant* or surface* or internal*) adj4 (irradiat* or radiation*)).tw. 19 curietherap*.tw. 20 (radioisotope* adj4 (irradiat* or therap* or treat*)).tw. 21 ((seed* or permanent*) adj2 implant*).tw. 22 or/14-21 23 Brachytherapy/ 24 brachytherap*.tw. 25 exp radiotherapy dosage/ 26 exp dose-response relationship, radiation/ 27 (Hyperfraction* or Hyper-fraction* or Hyper fraction* or Hypofraction* or Hypo-fraction* or Hypo fraction*).tw. 28 ((optim* or fraction* or respons*) adj4 (dose* or dosage or schedule*)).tw. 29 ((high* or full* or maximum* or larg* or escalat* or supplement* or low* or minimum* or small*) adj4 (dose* or dosage* or schedule*)).tw. 30 (HDR or LDR).tw. 31 or/23-30 32 22 and 31 33 9 or 13 or 22 or 32 34 5 and 33

Study design filters and limit

The SIGN systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below for MEDLINE. They were translated for use in the MEDLINE In-Process and Embase databases.

The SIGN SR and RCT filters are presented below.
Systematic Review 1. Meta-Analysis as Topic/ 2. meta analy$.tw. 3. metaanaly$.tw. 4. Meta-Analysis/ 5. (systematic adj (review$1 or overview$1)).tw. 6. exp Review Literature as Topic/ 7. or/1-6 8. cochrane.ab. 9. embase.ab. 10. (psychlit or psyclit).ab. 11. (psychinfo or psycinfo).ab. 12. (cinahl or cinhal).ab. 13. science citation index.ab. 14. bids.ab.

The SIGN SR and RCT filters are presented below.
15. cancerlit.ab. 16. or/8-15 17. reference list$.ab. 18. bibliograph$.ab. 19. hand-search$.ab. 20. relevant journals.ab. 21. manual search$.ab. 22. or/17-21 23. selection criteria.ab. 24. data extraction.ab. 25. 23 or 24 26. Review/ 27. 25 and 26 28. Comment/ 29. Letter/ 30. Editorial/ 31. animal/ 32. human/ 33. 31 not (31 and 32) 34. or/28-30,33 35. 7 or 16 or 22 or 27 36. 35 not 34
RCT 1 Randomized Controlled Trials as Topic/ 2 randomized controlled trial/ 3 Random Allocation/ 4 Double Blind Method/ 5 Single Blind Method/ 6 clinical trial/ 7 clinical trial, phase i.pt 8 clinical trial, phase ii.pt 9 clinical trial, phase iii.pt 10 clinical trial, phase iv.pt 11 controlled clinical trial.pt 12 randomized controlled trial.pt 13 multicenter study.pt 14 clinical trial.pt 15 exp Clinical Trials as topic/ 16 or/1-15 17 (clinical adj trial$).tw 18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw 19 PLACEBOS/ 20 placebo$.tw 21 randomly allocated.tw 22 (allocated adj2 random$).tw 23 or/17-22

The SIGN SR and RCT filters are presented below.

24 16 or 23
25 case report.tw
26 letter/
27 historical article/
28 or/25-27
29 24 not 28

A date limit from 2007 to 2018 and English language limit was applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) were excluded.

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The SIGN economic evaluations filter and the NICE quality of life filter were appended to population search terms in MEDLINE, MEDLINE In-Process and EMBASE. The MEDLINE filters are presented below.

An English language limit was applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) were excluded.

The economic searches were conducted in March 2018.

Health Economics filters

The SIGN economic evaluations and NICE quality of life search filters are presented below.

SIGN Economic evaluations

1 Economics/
2 "costs and cost analysis"/
3 Cost allocation/
4 Cost-benefit analysis/
5 Cost control/
6 Cost savings/
7 Cost of illness/
8 Cost sharing/
9 "deductibles and coinsurance"/
10 Medical savings accounts/
11 Health care costs/
12 Direct service costs/

The SIGN economic evaluations and NICE quality of life search filters are presented below.
13 Drug costs/ 14 Employer health costs/ 15 Hospital costs/ 16 Health expenditures/ 17 Capital expenditures/ 18 Value of life/ 19 Exp economics, hospital/ 20 Exp economics, medical/ 21 Economics, nursing/ 22 Economics, pharmaceutical/ 23 Exp "fees and charges"/ 24 Exp budgets/ 25 (low adj cost).mp. 26 (high adj cost).mp. 27 (health?care adj cost$).mp. 28 (fiscal or funding or financial or finance).tw. 29 (cost adj estimate$).mp. 30 (cost adj variable).mp. 31 (unit adj cost$).mp. 32 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. 33 Or/1-32
Quality of life
1 "Quality of Life"/ 2 quality of life.tw. 3 "Value of Life"/ 4 Quality-Adjusted Life Years/ 5 quality adjusted life.tw. 6 (qaly$ or qald$ or qale$ or qtime$).tw. 7 disability adjusted life.tw. 8 daly$.tw. 9 Health Status Indicators/ 10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 15 (euroqol or euro qol or eq5d or eq 5d).tw. 16 (qol or hql or hqol or hrqol).tw. 17 (hye or hyes).tw. 18 health$ year$ equivalent$.tw. 19 utilit$.tw. 20 (hui or hui1 or hui2 or hui3).tw.

The SIGN economic evaluations and NICE quality of life search filters are presented below.	
21	disutili$.tw.
22	rosser.tw.
23	quality of wellbeing.tw.
24	quality of well-being.tw.
25	qwb.tw.
26	willingness to pay.tw.
27	standard gamble$.tw.
28	time trade off.tw.
29	time tradeoff.tw.
30	tto.tw.
31	or/1-30

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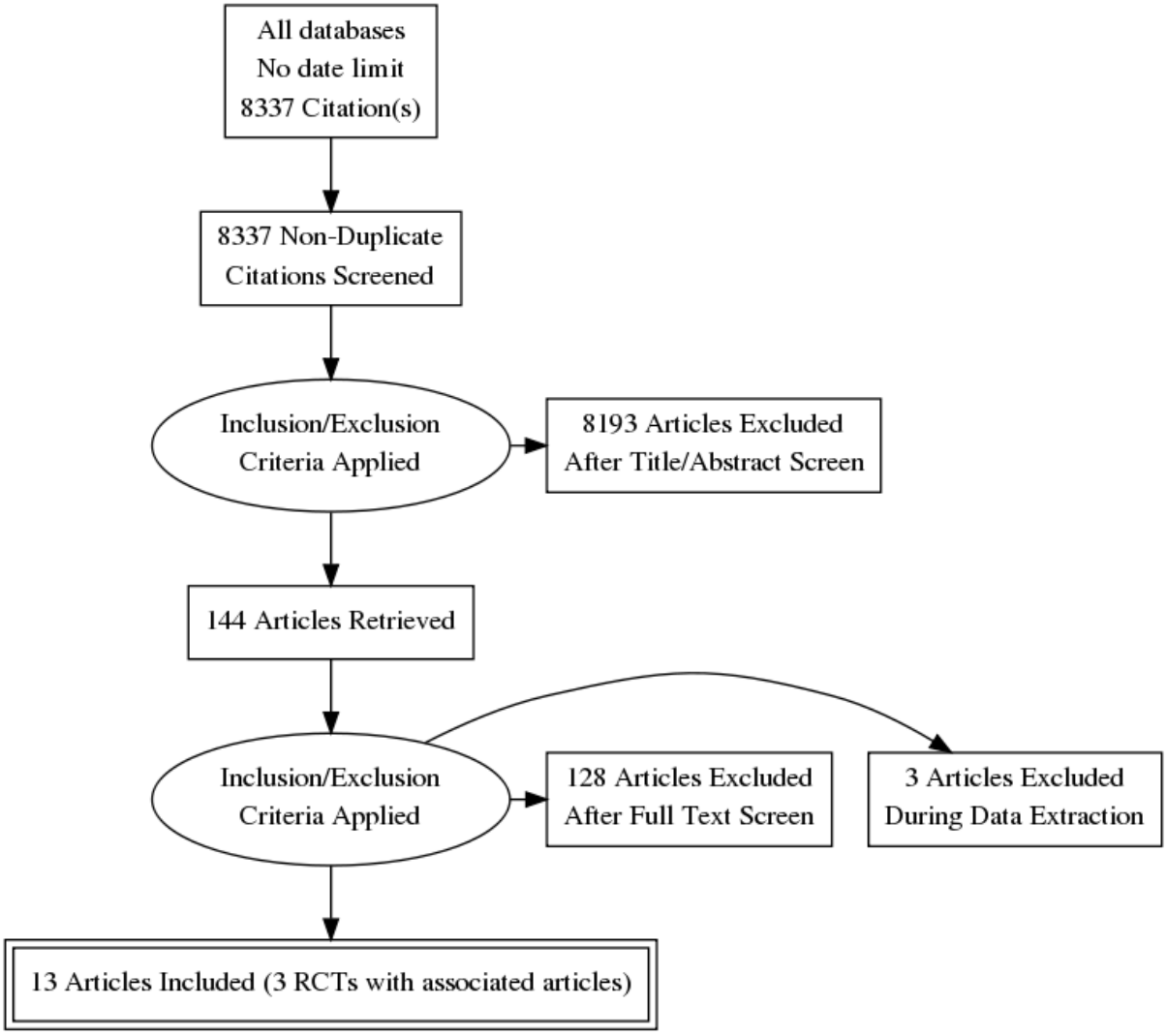
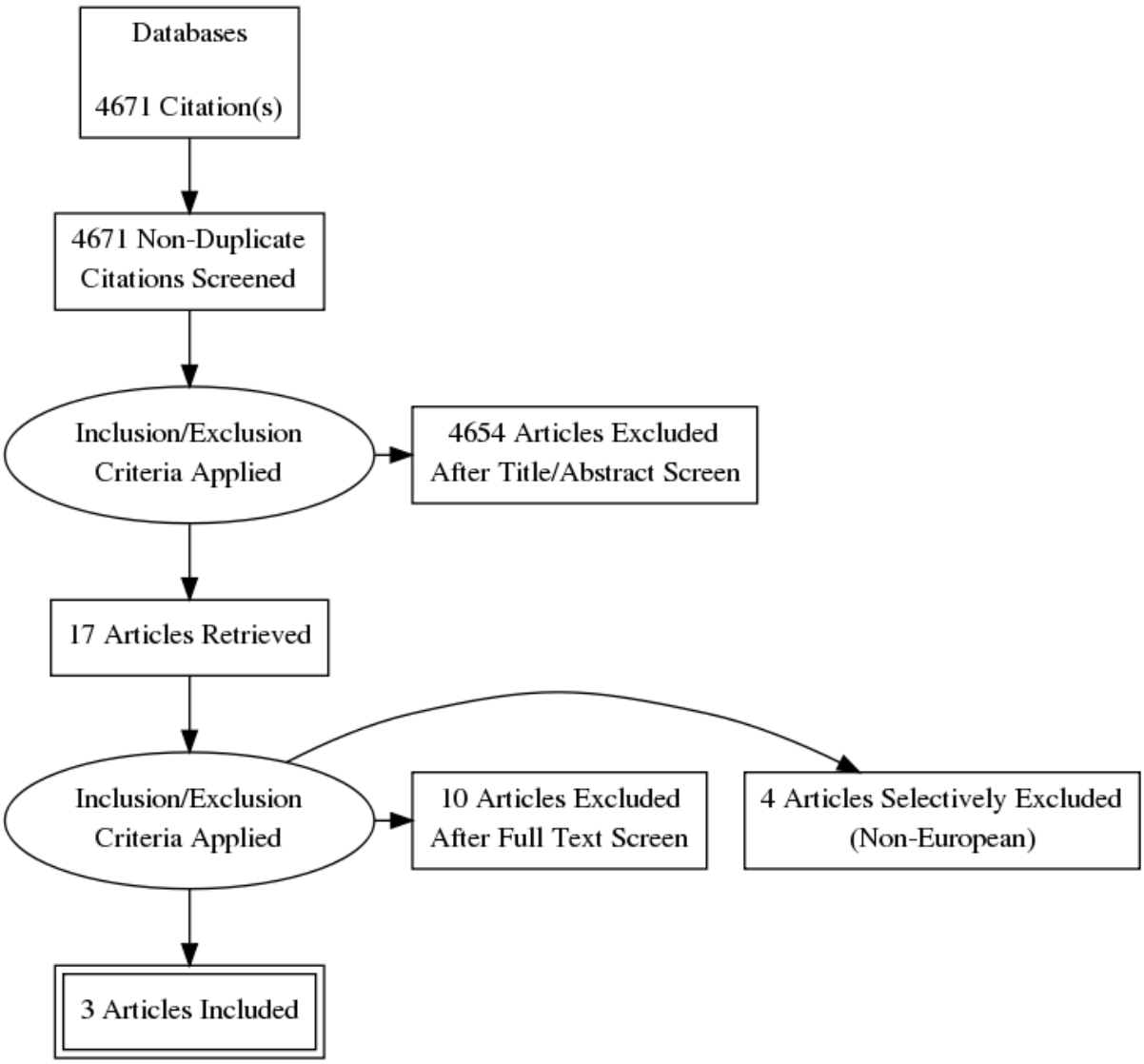
1 Appendix D - Study selection

2 Clinical evidence study selection



3

Economic evidence study selection



Appendix E – Evidence tables

Clinical Evidence

Observation versus Radical Radiotherapy versus Radical Prostatectomy

Short Title	Title	Study characteristics	Quality Assessment
Donovan (2016)	Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer (ProtecT study)	**Study type** Randomised controlled trial **Associated Articles** Hamdy Fc, Donovan Jl, Lane Ja, Mason M, Metcalfe C, Holding P, Davis M, Peters Tj, Turner El, Martin Rm, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario Dj, Rowe E, and Neal De (2016) 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England journal of medicine 375(15), 1415-1424 ProtecT study **Study details** Study location UK Study setting Primary care centres in 9 cities (England, Scotland, Wales) Study dates October 2001 - January 2009 Duration of follow up: Median 10 years 6 and 12 months in first year Annually after first year Duration of follow-up Median 10 years 6 and 12 months in first year Annually after first year Sources of funding UK National Institute for Health Research Health Technology	**Random sequence generation** Low risk of bias Computer generated random sequence allocation **Allocation concealment** Low risk of bias Central allocation of group assignment using telephone system **Blinding of participants and personnel** Unclear risk of bias Mortality and progression outcomes: Low risk - No blinding to participants but the outcomes should not have been influenced by this patient-reported QoL outcomes: High risk - No blinding to treatment group may have impacted on these outcomes **Blinding of outcome assessment** Unclear risk of bias Mortality and progression: Low risk - Independent committee classified cause of death and were blinded to interventions. Patient-reported QoL: High risk - participants knowledge of their treatment groups may have influenced outcomes

Short Title	Title	Study characteristics	Quality Assessment
		Assessment Programme **Inclusion criteria** Estimated life expectancy >10 years Localised prostate cancer Negative results for metastatic disease Age 50 - 69 **Exclusion criteria** Any previous malignancy apart from skin cancer Previous renal transplant or on renal dialysis Major cardiovascular or respiratory comorbidities Bilateral hip replacement PSA >20 **Sample characteristics** Sample size 2664 (1643 underwent randomisation) Split between study groups Active monitoring: 545 Radiotherapy: 545 Surgery: 553 Loss to follow-up 55 (3.3%) Mean age (SD) Median Age (range): Active monitoring - 62 (50-69) Radiotherapy - 62 (49-69) Radical prostatectomy - 62 (50-69) Mean PSA (ng/ml) Median PSA (range): Active monitoring - 4.6 (3.0-20.9) Radiotherapy - 4.6 (3.0-18.8) Radical prostatectomy - 4.7 (3.0-18.4) Tumour stage - no. (%) Active monitoring - T1c = 410 (75%); T2 = 135 (25%) Radiotherapy - T1c = 429 (79%); T2 = 116 (21%) Radical prostatectomy - T1c = 410 (74%); T2 = 143 (26%)	**Incomplete outcome data** Low risk of bias No missing outcome data **Selective reporting** Low risk of bias All expected outcomes are reported **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate **Directness** Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		Interventions Active Monitoring v Radiotherapy v Radical Prostatectomy **Outcome measure(s)** Overall mortality (death from any cause) Prostate cancer-specific mortality Distant metastases Urinary incontinence Erectile and sexual dysfunction Lower urinary tract symptoms Effect of urinary function on QoL Effect of sexual function on QoL Bowel function Effect of bowel function on QoL General health status Anxiety and depression Cancer-related QoL	

Prostatectomy versus Observation

Short Title	Title	Study characteristics	Quality Assessment
Holmberg (2002)	A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. (Scandinavian Prostate Cancer Group-4	**Study type** Randomised controlled trial **Associated Articles** Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, Busch C, Nordling S, Häggman M, Andersson So, Bratell S, Spångberg A, Palmgren J, Adami Ho, and Johansson Je (2008) Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. Journal of the national cancer institute 100(16), 1144-1154 Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark Jr, Busch C, Nordling S, Häggman M, Andersson So, Bratell S, Spångberg	**Random sequence generation** Low risk of bias Computer-generated random sequence allocation **Allocation concealment** Low risk of bias Central allocation of group assignment using telephone system **Blinding of participants and personnel** Low risk of bias

Short Title	Title	Study characteristics	Quality Assessment
	Randomized Clinical Trial)	A, Palmgren J, Steineck G, Adami Ho, and Johansson Je (2011) Radical prostatectomy versus watchful waiting in early prostate cancer. New England journal of medicine 364(18), 1708-1717 Bill-Axelson A, Garmo H, Holmberg L, Johansson Je, Adami Ho, Steineck G, Johansson E, and Rider Jr (2013) Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the Scandinavian Prostate Cancer Group-4 randomized clinical trial. European urology 64(6), 920-928 Bill-Axelson A, Holmberg L, Garmo H, Rider Jr, Taari K, Busch C, Nordling S, Häggman M, Andersson So, Spångberg A, Andrén O, Palmgren J, Steineck G, Adami Ho, and Johansson Je (2014) Radical prostatectomy or watchful waiting in early prostate cancer. New England journal of medicine 370(10), 932-942 Johansson E, Bill-Axelson A, Holmberg L, Onelöv E, Johansson Je, and Steineck G (2009) Time, symptom burden, androgen deprivation, and self-assessed quality of life after radical prostatectomy or watchful waiting: the Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) clinical trial. European urology 55(2), 422-430 Johansson E, Steineck G, Holmberg L, Johansson Je, Nyberg T, Ruutu M, and Bill-Axelson A (2011) Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. The lancet. Oncology 12(9), 891-899 Steineck G, Helgeson F, Adolfsson J, Dickman PW, Johansson J-E, Norlen BJ, and Holmberg L (2002) Quality of life after radical prostatectomy or watchful waiting. , Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Swen-Olofersson A, Bratell S, Spångberg A, Busch C, Nordling S, Garmo H, Palmgren J, Adami H, Norlén BJ, and Johansson Je (2005) Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. The New England Journal of Medicine , SPCGS number 4	Not possible to blind participants to intervention group but this should not have affected outcomes. **Blinding of outcome assessment** Unclear risk of bias Mortality-related outcomes = low. Independent committee classified cause of death and were blinded to interventions. Distant metastases = unclear. Limited information on whether the assessors were blinded to interventions. Participant-reported outcomes = high. These may have been influenced by knowledge of their treatment group **Incomplete outcome data** Low risk of bias No missing outcome data **Selective reporting** Low risk of bias All expected outcomes are reported **Other sources of bias** Low risk of bias QoL articles: Some patients excluded because of problems translating the questionnaire. But this was only 4 out of 400 patients. **Overall risk of bias** Moderate Mortality-related outcomes are low risk but patient-reported outcomes may be affected by

Short Title	Title	Study characteristics	Quality Assessment
		Study details Study location Sweden, Finland, Iceland Study setting 14 centres Study dates October 1989 - February 1999 Follow up until December 31 2000 Duration of follow-up First 2 years - every 6 months After 2 years - every 12 months 2002 article: FU until December 31 2000 (median FU 6.2 years) 2005 article: FU until December 31 2003 (median 8.2 years) 2008 article: FU until December 31 2006 (median 10.8 years) 2011 article: FU until December 31 2009 (median 12.8 years) 2014 article: FU until December 31 2012 (median 13.4 years) Sources of funding The Swedish Cancer Society National Institutes of Health (USA) **Inclusion criteria** Age <75 Primary, previously untreated adenocarcinoma of prostate Tumor in stage T0d, T1 or T2 T1c after 1994 Estimated life expectancy >10 years Localised prostate cancer PSA <50 ng/ml Negative results for metastatic disease **Exclusion criteria** None reported **Sample characteristics** Sample size 698 Split between study groups Radical Prostatectomy: 347 Watchful Waiting: 348	participant's knowledge of treatment groups **Directness** Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		Loss to follow-up 0 Mean age (SD) Prostatectomy group: 64.7 (5.1) Watchful Waiting group: 64.7 (5.1) Mean PSA (ng/ml) Prostatectomy group: 13.5 Watchful Waiting group: 12.3 Tumour stage - no. (%) Prostatectomy group: T1b = 33 (9.5); T1c = 43 (12.4); T2 = 270 (77.8); Unknown = 1 (0.3) Watchful Waiting group: T1b = 50 (14.4); T1c = 38 (10.9); T2 = 259 (74.4); Unknown = 1 (0.3) Intervention: Radical Prostatectomy v Watchful Waiting **Interventions** Radical Prostatectomy v Watchful Waiting **Outcome measure(s)** Overall mortality (death from any cause) Prostate cancer-specific mortality Distant metastases Urinary incontinence Erectile and sexual dysfunction Weak urinary stream Nocturia QoL	
Wilt (2012)	Radical prostatectomy versus observation for localized prostate cancer (PIVOT study)	**Study type** Randomised controlled trial **Associated Articles** Wilt Tj, Jones Km, Barry Mj, Andriole Gl, Culkin D, Wheeler T, Aronson Wj, and Brawer Mk (2017) Follow-up of prostatectomy versus observation for early prostate cancer. Journal of Clinical Outcomes Management 24(11), PIVOT study	**Random sequence generation** Unclear risk of bias No clear information on how random sequence was generated **Allocation concealment** Low risk of bias Central allocation using interactive telephone

Short Title	Title	Study characteristics	Quality Assessment
			service **Blinding of participants and personnel** Low risk of bias No blinding to participants but the outcomes should not have been influenced by this **Blinding of outcome assessment** Unclear risk of bias Mortality-related outcomes = unclear. No clear information on blinding of outcome assessment. Patient-reported outcomes = high. Participant-reported outcomes may have been influenced by knowledge of their treatment group **Incomplete outcome data** Low risk of bias No missing outcome data **Selective reporting** Low risk of bias All pre-specified primary outcomes are reported **Other sources of bias** Low risk of bias **Overall risk of bias** Moderate Limited information on random sequence allocation or blinding of outcome assessment **Directness** Directly applicable
		Study details Study location USA Study setting Department of Veterans Affairs and National Cancer Institute medical centers Study dates November 1994 - January 2002 Duration of follow-up Every 6 months for minimum 8 years and max 15 years or until patient died 2012 study: Follow up to January 2010 (median 10 years) 2017 study: Follow up to August 2014 (12 years - 19.5 years) Sources of funding Department of Veterans Affairs Cooperative Studies Program National Cancer Institute medical centers **Inclusion criteria** Age <75 Estimated life expectancy >10 years Localised prostate cancer Diagnosed within previous 12 months PSA <50 ng/ml Negative results for metastatic disease **Exclusion criteria** None reported **Sample characteristics** Sample size 731 Split between study groups	

Short Title	Title	Study characteristics	Quality Assessment
		Observation: 367 Radical Prostatectomy: 364 Mean age (SD) 67 Mean PSA (ng/ml) 7.8 **Interventions** Radical Prostatectomy v Observation **Outcome measure(s)** Overall mortality (death from any cause) Prostate cancer-specific mortality Distant metastases PSA progression Adverse events requiring treatment Urinary incontinence Erectile and sexual dysfunction Worry about health "Bother" due to PCa Physical discomfort Functional limitations Bowel function	

Economic evidence tables

Study, population, country and quality	Data sources	Other comments		Incremental			Authors' conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Ramsay et al. (2015) People with low-risk localised prostate cancer; mean age 70 years **Directly applicable** **Potentially serious limitations** [a, b]	**Effects:** Time to biochemical recurrence synthesised by met-analysis of 7 studies (majority are non-RCT) **Costs:** Adopting the NHS perspective estimated based on resource-use inputs and unit costs for the 2011–12 financial year, reported £. **Utilities:** From systematic search of multiple sources; when multiple values for particular parameters were found, median values were used, which were then calibrated to the EQ-5D	• Lifetime modified Markov model, 6-month cycle, 3.5% discount rate costs/QALYs • **BT, AS, IMRT** or **RP** alongside other comparators • Assuming biochemical recurrence is equal • Toxicity evidence synthesised with MA • Assumed 32% of patients on BT develop perioperative AEs causing additional 4 to 15 days in hospital • 0.84 of EBRT patients receive adjuvant HT • 0.58 of patients on RP receive pelvic lymphadenectomy; 0.38 would receive adjuvant EBRT and HT.					RP produced less health outcomes and was more expensive than IMRT and BT.	• One-way sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. • Marked uncertainty surrounding the analyses, different plausible data combinations may result in BT being cost-effective or IMRT may be more effective. • A sensitivity analysis included AS as a comparator; this showed AS more effective and less costly than the prompt use of active treatment
			IMRT	-	-	-		
			BT	5,093	0.06	84,883		
			RP			Dominated		

Study, population, country and quality	Data sources	Other comments		Incremental RP vs WW			Authors' conclusions	Uncertainty
				Cost (SEK)	Effect (QALYs)	ICER (SEK/QALY)		
Lyth et al. (2012) People ≤75 year old with localised prostate cancer, newly diagnosed, PSA<50 Swedish study **Partially applicable** [c, d, e] **Minor limitations**	**Effects:** Survival, HRQoL, time to progression and time to metastases sourced from SPCG4 **Costs:** Adopting the Swedish health care system perspective, 2007 prices expressed by Swedish currency (SEK)	• Probabilistic lifetime Markov model using data of 695 men randomly recruited in SPCG4 to compare the costs and health outcomes of RP vs WW; • Localised PCa patients at risk of symptomatic disease, controlled by HT. Then, they are at developing to refractory disease. PCa death is only	Age	Low-risk			RP was associated with higher health outcomes and more expensive than WW in all age groups and different disease severities	• Probabilistic sensitivity analysis was performed; • Results were more robust within younger age and more advanced disease
			65	49,784	0.86	58,045		
			70	63,864	0.42	150,274		
			75	72,439	0.15	472,327		
				Intermediate-risk				
			65	53,726	1.44	37,397		
			70	65,536	0.80	82,417		
			75	72,713	0.40	180,284		
				High-risk				
			65	74,314	1.50	49,643		
			70	76,986	1.02	75,302		
			75	78,164	0.61	127,529		

Study, population, country and quality	Data sources	Other comments		Incremental RP vs WW			Authors' conclusions	Uncertainty
				Cost (SEK)	Effect (QALYs)	ICER (SEK/QALY)		
	Utilities: Derived from 77-item questionnaire with visual analogue scale (VAS), completed by SPCG4 participants. Costs and QALYs discounted at 3.5% a year	possible from the last state; • Parameters of these transitions were estimated by finding best fit distributions for the SPCG4 data; • Mortality from other causes derived from Swedish life-tables, adjusted to exclude prostate-cancer specific mortality.						

Study, population, country and quality	Data sources	Other comments	Incremental RP vs AS			Authors' conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Koerber et al. (2014)	**Effects:** Survival, HRQoL, time to progression	• 3-monthly cycle lifetime Markov model to	RP was dominated by AS			AS is a cost saving strategy for	• Deterministic and probabilistic sensitivity

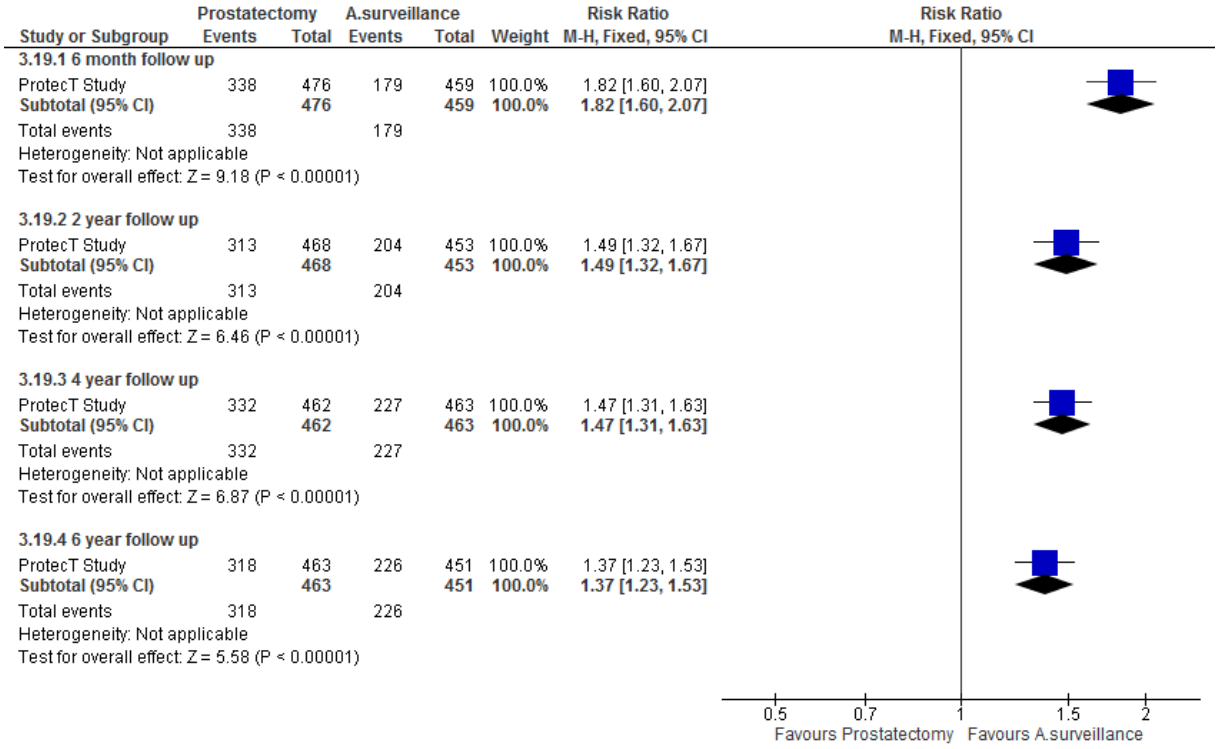
People with newly diagnosed low-risk (PSA≤10, Gleason≤6 and ≤T2a) localised PCa and life expectancy >15 years German Study **Partially applicable** [c, d] **Potentially serious limitations** [f, g, h]	and time to metastases, sourced mainly from PIVOT and SPCG4 **Costs:** Adopting the perspective of the statuary health insurance plus out of pocket expenses, 2011 prices expressed by (€) **Utilities:** Age-adjusted utility applied to baseline data. HRQoL reduced due to AEs of treatments were obtained from existing study used SG methods. Health outcomes and costs annually discounted by 3%	compare costs and outcomes of AS vs RP; • AS defined as PSA, DRE every 3 months for 2 years, then bi-annually; biopsy at 12 months and then every 3 years; once triggered: treatment can be RP ≤72 years or if older RT; • Assumed same PCa mortality for RT, RP; short and long-term AEs due to RP, RT were captured; • Local progression is prerequisite to move to metastases, from which PCa mortality is allowed;				people with low-risk prostate cancer newly diagnosed at age 65; AS produced more QALYS and was less expensive than RP	analyses performed; • Results showing the dominance of AS were relatively robust; • Increasing the probability of developing metastases under AS by almost 9% or decreasing the probability of recurrence after RP by almost 9% may change the conclusion.

Study, population, country and quality	Data sources	Other comments		Incremental RP vs WW			Authors' conclusions	Uncertainty
				Cost (SEK)	Effect (QALYs)	ICER (SEK/QALY)		
		• Mortality derived from SPCG4 (more advanced disease and less active WW), but adjusted to be more favourable towards WW.						
a) Assumed same efficacy for radiotherapy techniques b) Lack of long-term data in terms of recurrence and AEs c) Not a UK study d) Not EQ5D based utility e) Population with more advanced disease f) Assumed same prostate cancer mortality for radiotherapy and prostatectomy g) Authors modified risk of prostate cancer death estimated from an RCT h) Risk of metastases was calibrated based on the modified risk of prostate cancer death								

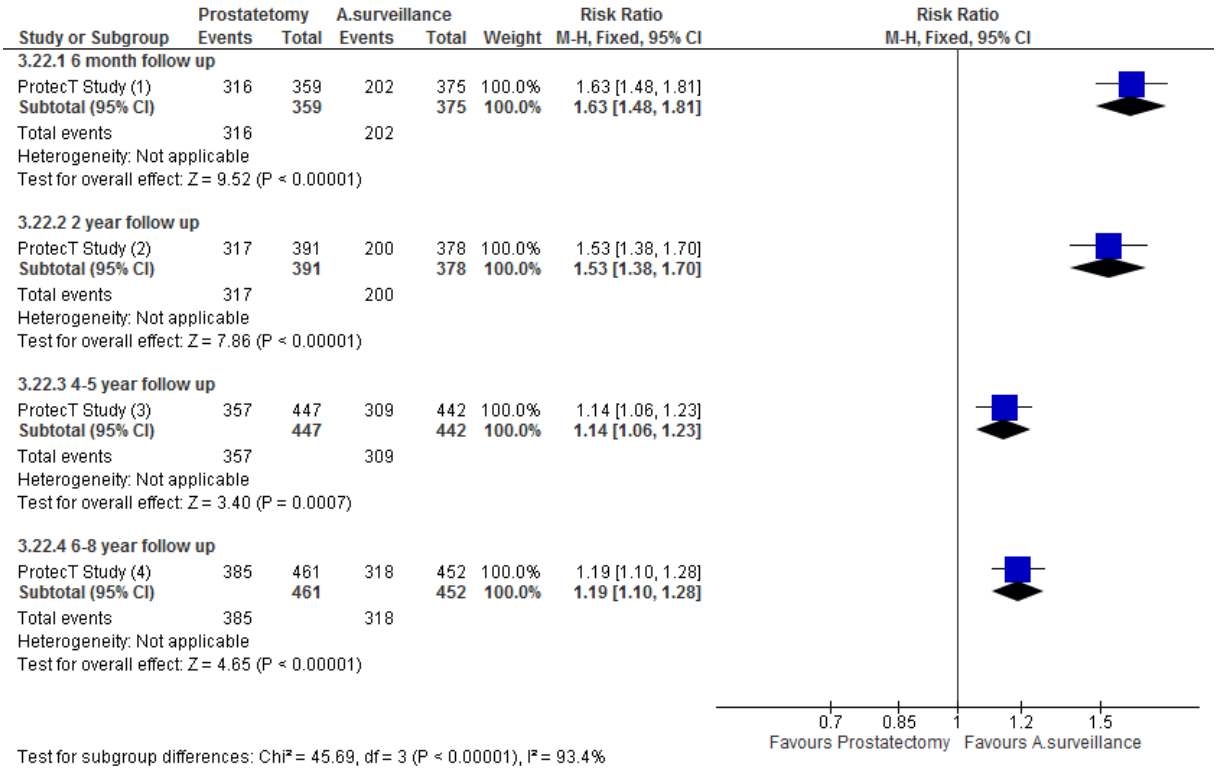
Appendix F – Forest plots

Radical prostatectomy versus active surveillance

Number of severe adverse events (incontinence)



Number of severe adverse events (erectile dysfunction)

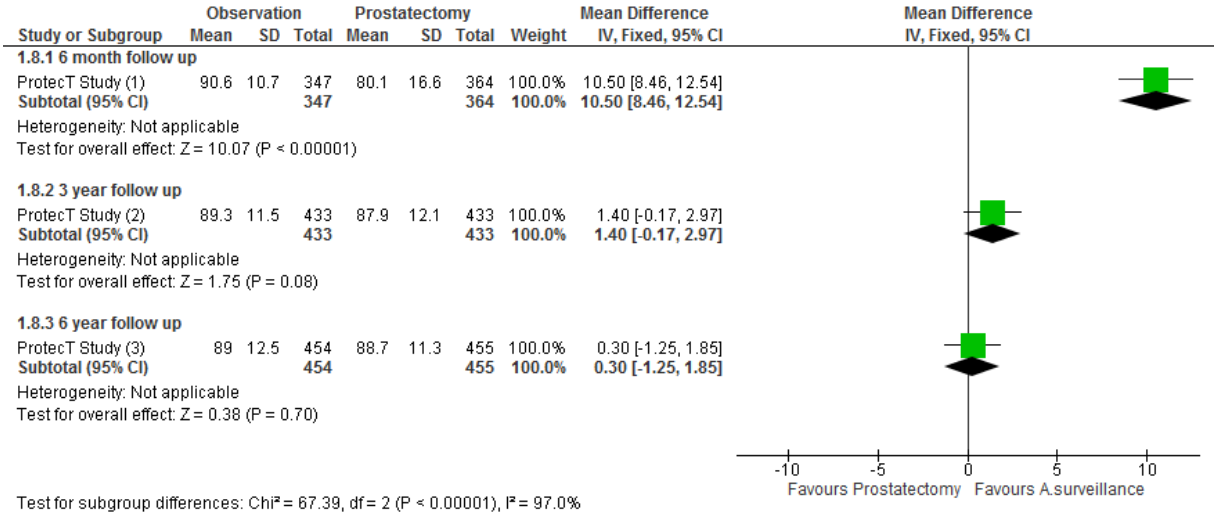


Test for subgroup differences: Chi² = 45.69, df = 3 (P < 0.00001), I² = 93.4%

Footnotes

(1) 2016 (6 month follow up)
(2) 2016 (24 month follow up)
(3) 2016 (48 month follow up)
(4) 2016 (72 month follow up)

Treatment-related morbidity (EPIC summary scores): Urinary function

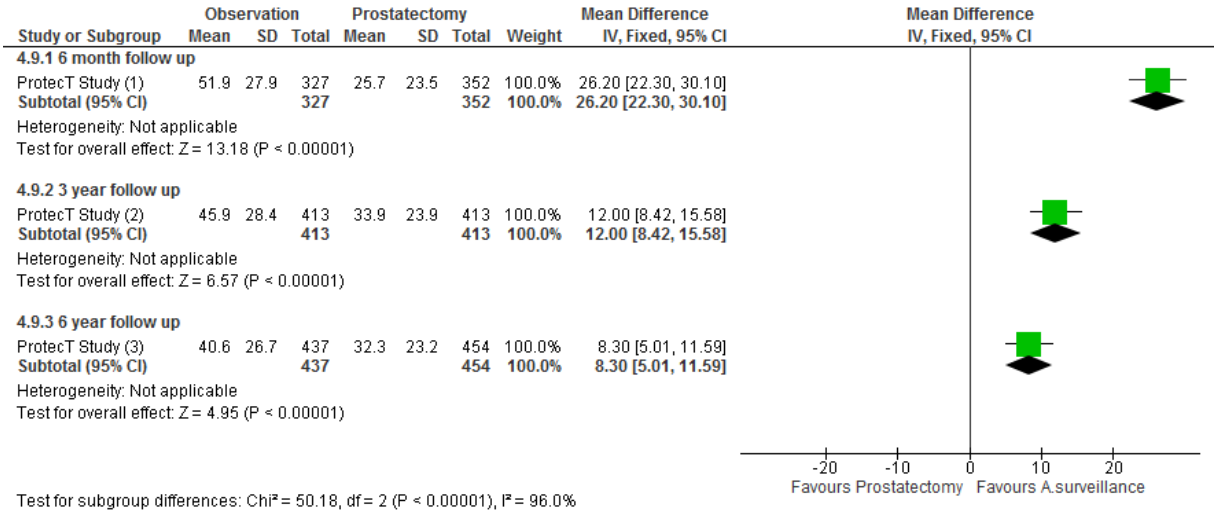


Test for subgroup differences: Chi² = 67.39, df = 2 (P < 0.00001), I² = 97.0%

Footnotes

(1) 6 months follow-up
(2) 36 months follow-up
(3) 72 months follow-up

Treatment-related morbidity (EPIC summary scores): Sexual dysfunction



Test for subgroup differences: Chi² = 50.18, df = 2 (P < 0.00001), I² = 96.0%

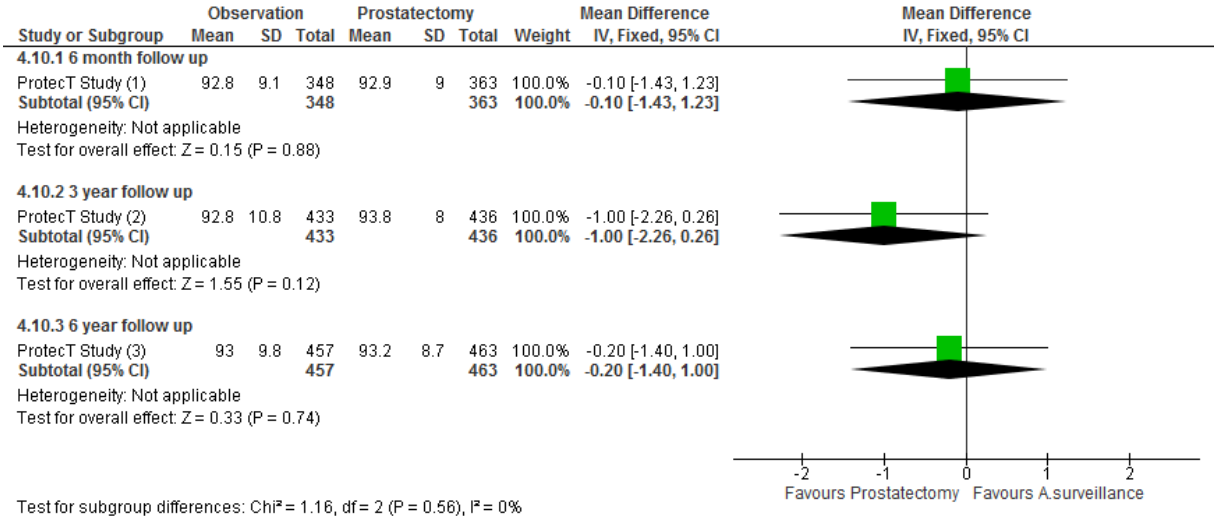
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Treatment-related morbidity (EPIC summary scores): Bowel function



Test for subgroup differences: Chi² = 1.16, df = 2 (P = 0.56), I² = 0%

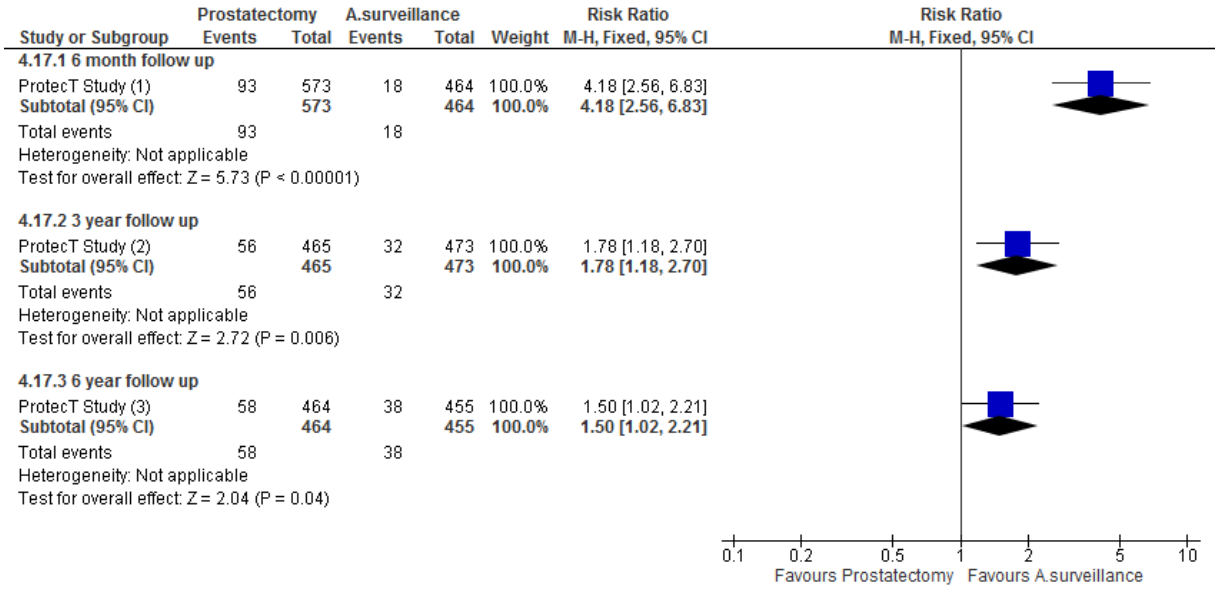
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

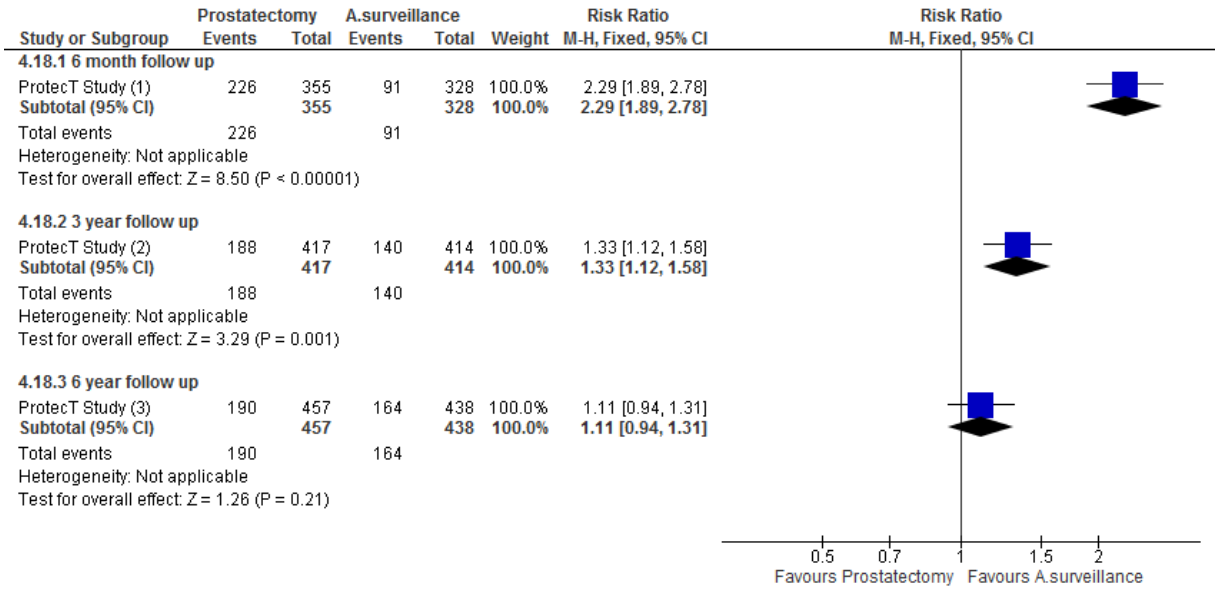
(3) 72 months follow-up

Moderate/severe impact of treatment on quality of life (incontinence)



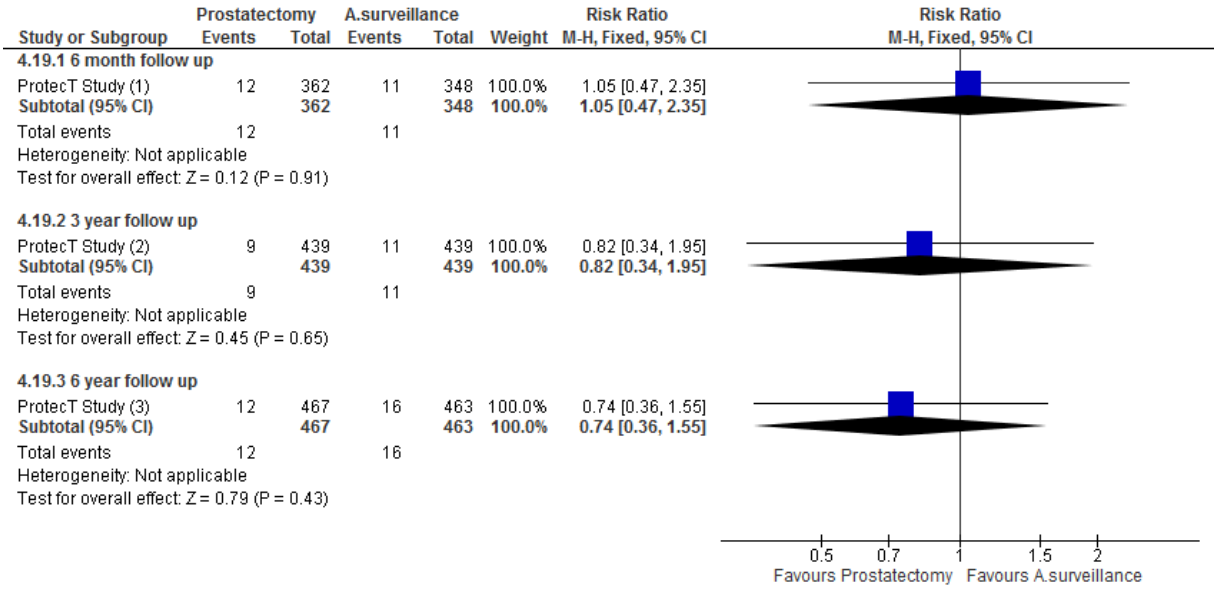
Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Moderate/severe impact of treatment on quality of life (sexual dysfunction)



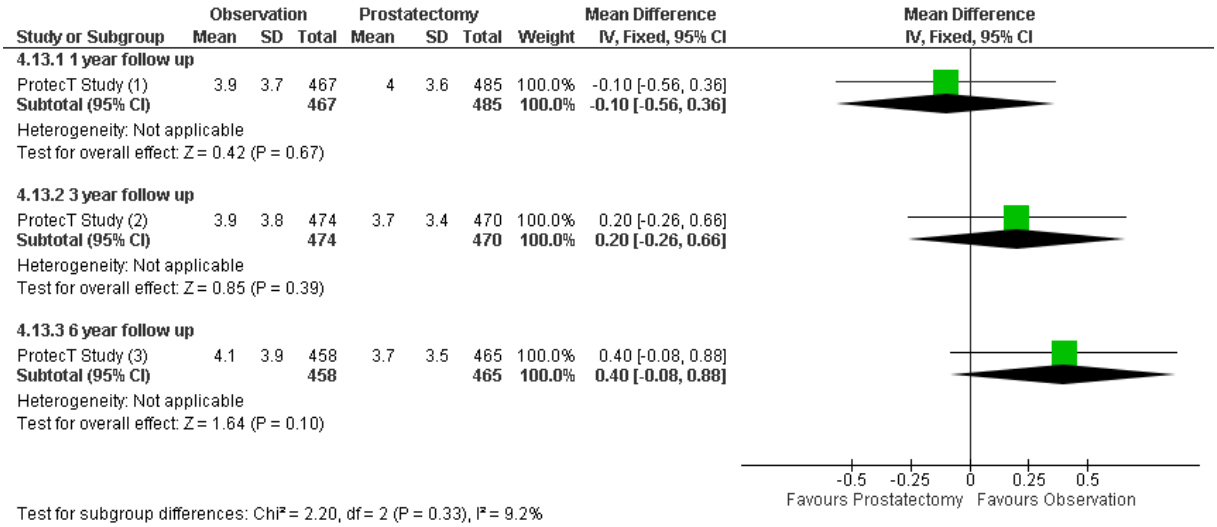
Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Moderate/severe impact of treatment on quality of life (bowel habits)



Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

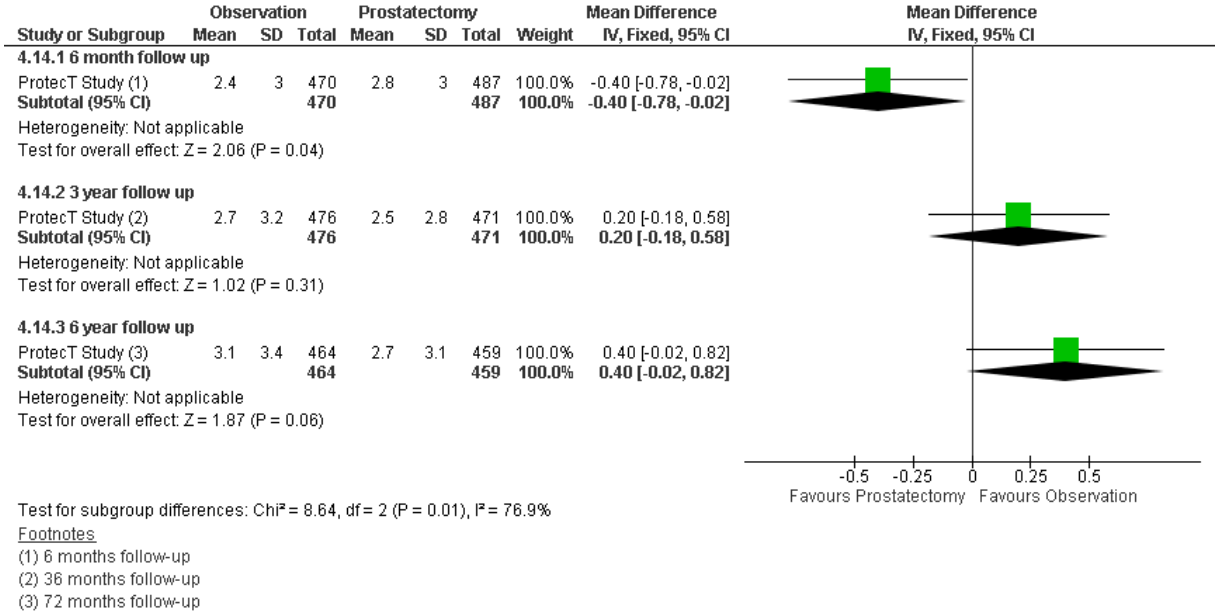
Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Anxiety



Test for subgroup differences: Chi² = 2.20, df = 2 (P = 0.33), I² = 9.2%

Footnotes
(1) 6 months follow-up
(2) 36 months follow-up
(3) 72 months follow-up

Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Depression



Test for subgroup differences: $Chi^2 = 8.64$, df = 2 (P = 0.01), $I^2 = 76.9\%$

Footnotes

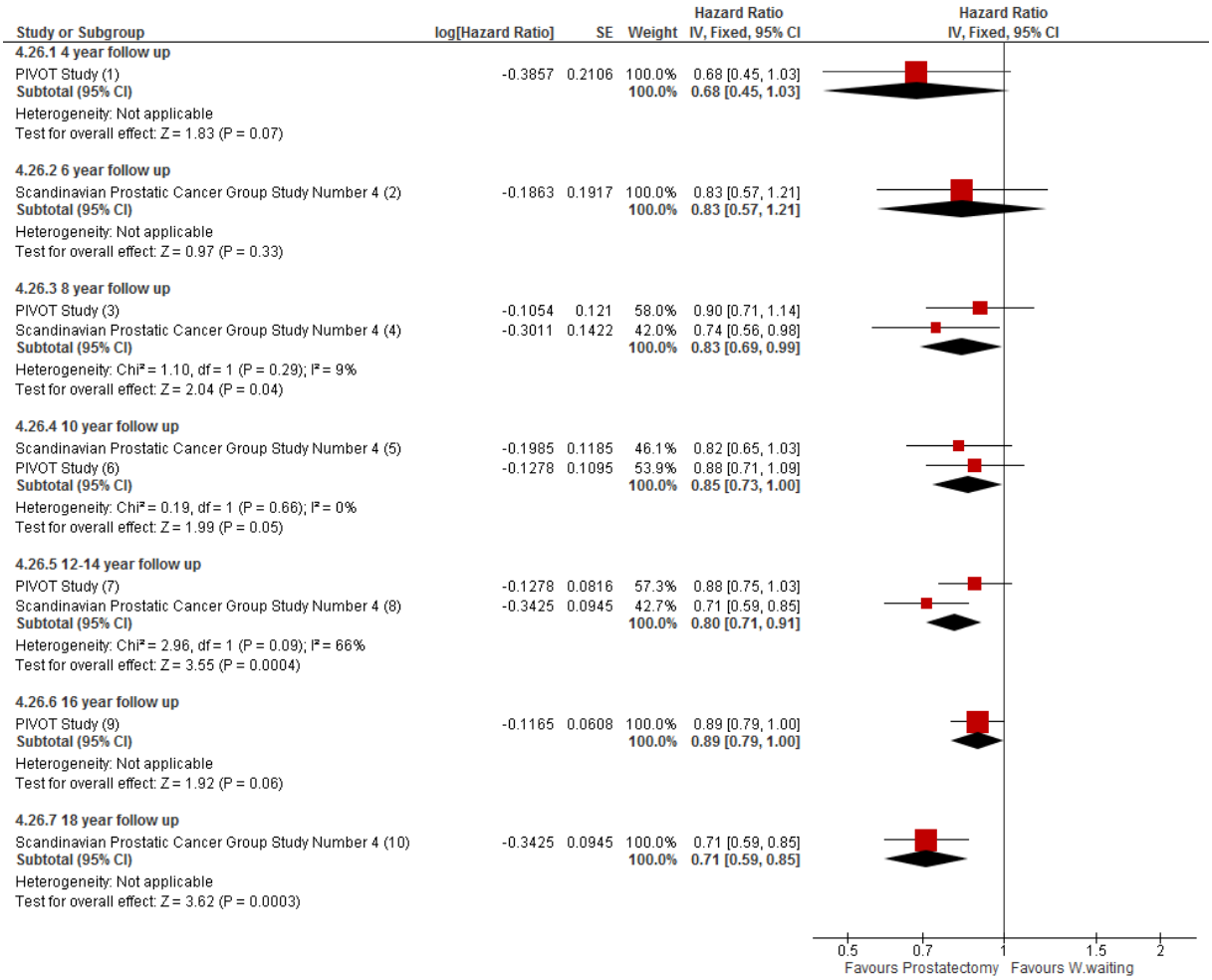
(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

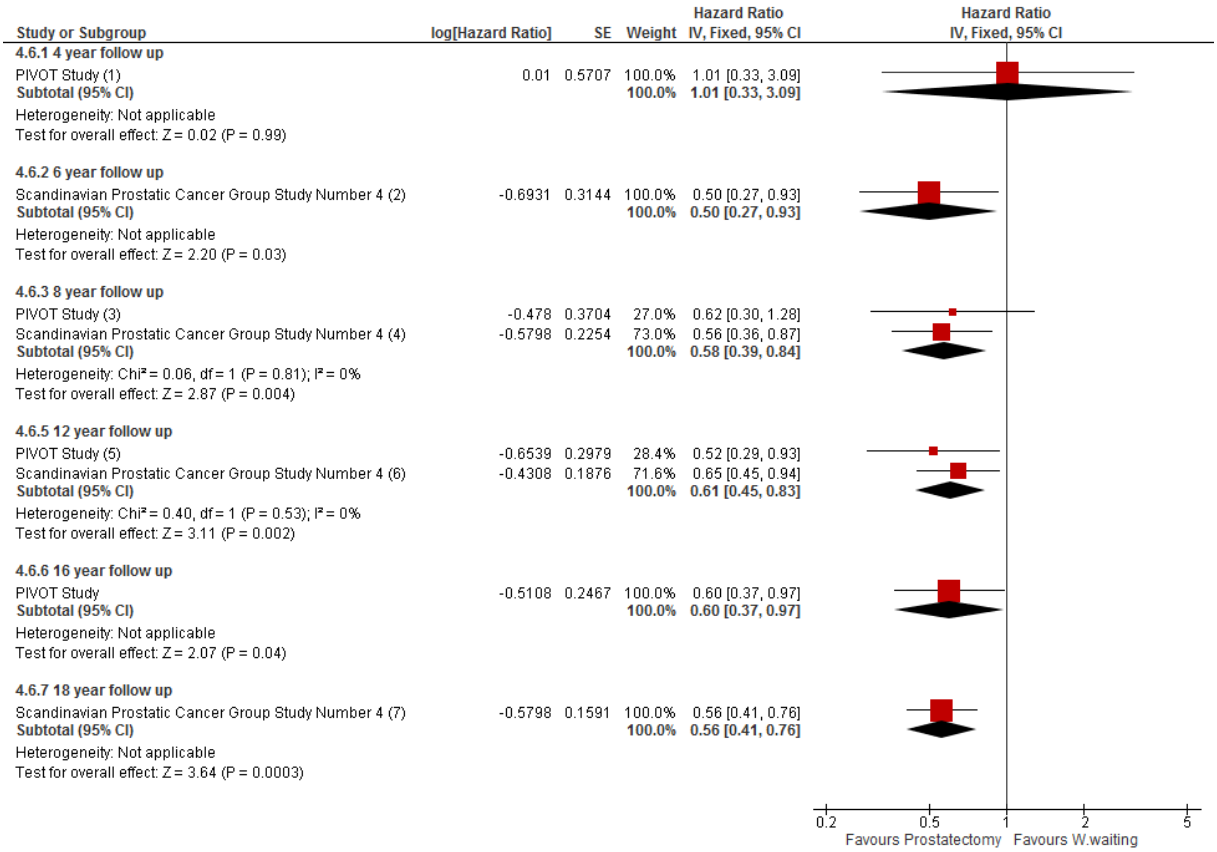
Radical prostatectomy versus watchful waiting

Overall mortality



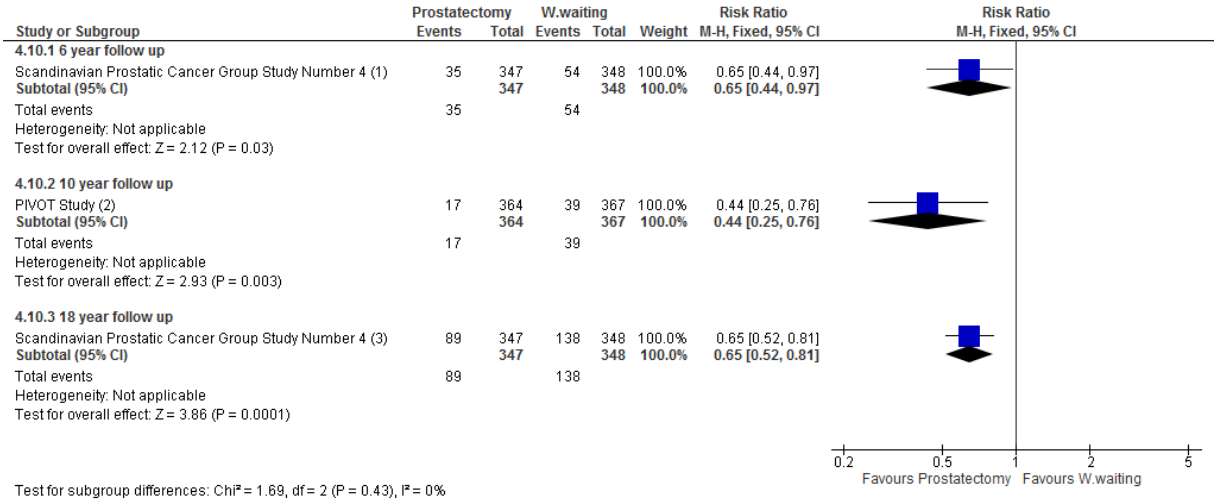
Footnotes
(1) 2012 (4 year follow-up)
(2) 2002 (6.2 year follow up)
(3) 2012 (8 year follow-up)
(4) 2005 (8.2 year follow up)
(5) 2008 (10.8 year follow up)
(6) 2012 (10 year follow up)
(7) 2017 (12 year follow-up)
(8) 2014 (13.4 year follow up)
(9) 2017 (16 year follow-up)
(10) 2014 (18 year follow up)

Prostate-cancer specific mortality



Footnotes
(1) 2012 (4 year follow up)
(2) 2002 (6.2 year follow up)
(3) 2012 (8 year follow up)
(4) 2005 (8.2 year follow up)
(5) 2017 (12 year follow up)
(6) 2008 (12 year follow up)
(7) 2014 (18 year follow up)

Number of people who developed distant metastasis

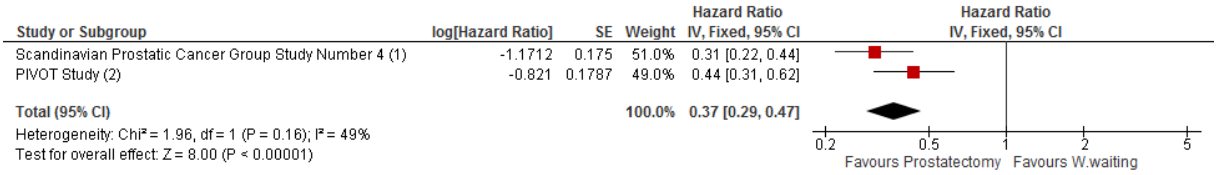


Test for subgroup differences: Chi² = 1.69, df = 2 (P = 0.43), I² = 0%

Footnotes

(1) 2002 (6.2 year follow up)
(2) 2012 (10 year follow up)
(3) 2014 (18 year follow up)

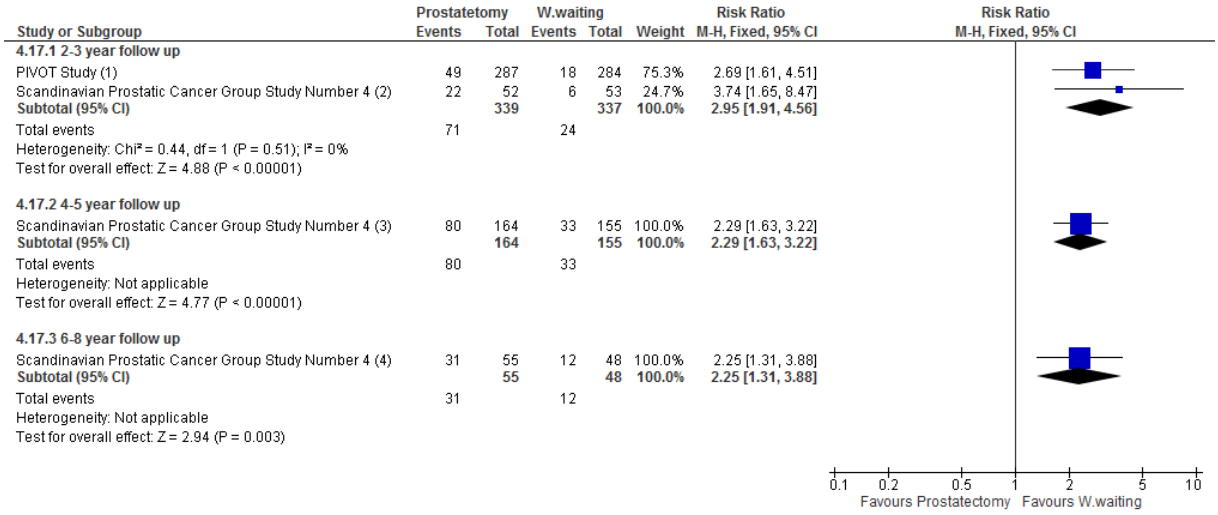
Disease Progression



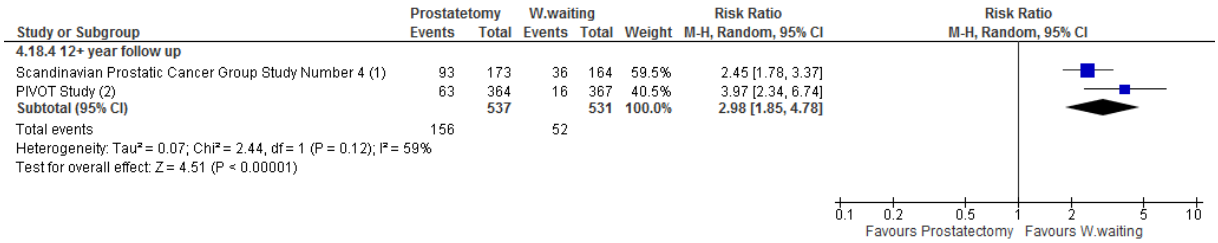
Footnotes

(1) 2002 (6.2 year follow up)
(2) 2017 (12-19.5 year follow up)

Number of severe adverse events (incontinence)

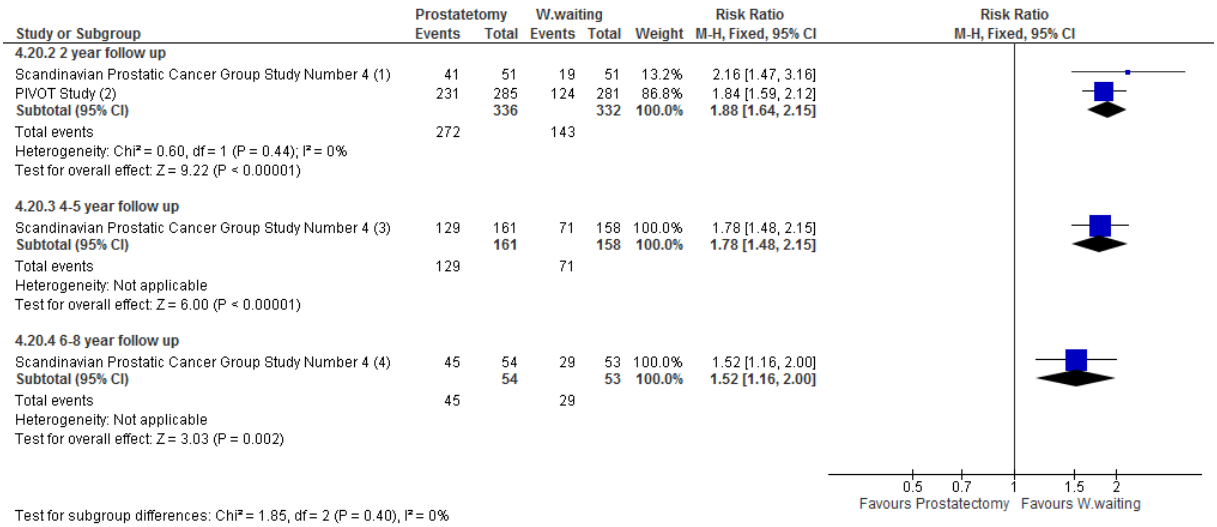


Footnotes
(1) 2012 (2 year follow up)
(2) Johansson 2008 (2-3 year follow up)
(3) Steineck 2002 (4 years follow up)
(4) Johansson 2008 (6-8 year follow up)



Footnotes
(1) Johansson 2011 (12.2 years follow up)
(2) 2017 (12-19.5 year follow up)

Number of severe adverse events (erectile dysfunction)

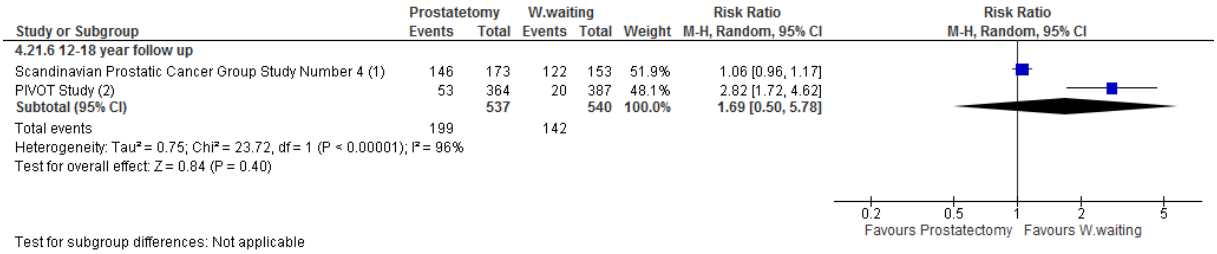


Study or Subgroup	Prostatetomy Events	Total	W.waiting Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.20.2 2 year follow up						
Scandinavian Prostatic Cancer Group Study Number 4 (1)	41	51	19	51	13.2%	2.16 [1.47, 3.16]
PIVOT Study (2)	231	285	124	281	86.8%	1.84 [1.59, 2.12]
Subtotal (95% CI)		**336**		**332**	**100.0%**	**1.88 [1.64, 2.15]**
Total events	272		143			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 9.22 (P < 0.00001)						
4.20.3 4-5 year follow up						
Scandinavian Prostatic Cancer Group Study Number 4 (3)	129	161	71	158	100.0%	1.78 [1.48, 2.15]
Subtotal (95% CI)		**161**		**158**	**100.0%**	**1.78 [1.48, 2.15]**
Total events	129		71			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.00 (P < 0.00001)						
4.20.4 6-8 year follow up						
Scandinavian Prostatic Cancer Group Study Number 4 (4)	45	54	29	53	100.0%	1.52 [1.16, 2.00]
Subtotal (95% CI)		**54**		**53**	**100.0%**	**1.52 [1.16, 2.00]**
Total events	45		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						

Test for subgroup differences: Chi² = 1.85, df = 2 (P = 0.40), I² = 0%

Footnotes

(1) Johansson 2008 (2-3 year follow up)
(2) 2012 (2 year follow up)
(3) Steineck 2002 (4 years follow up)
(4) Johansson 2008 (6-8 year follow up)



Study or Subgroup	Prostatetomy Events	Total	W.waiting Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.21.6 12-18 year follow up						
Scandinavian Prostatic Cancer Group Study Number 4 (1)	146	173	122	153	51.9%	1.06 [0.96, 1.17]
PIVOT Study (2)	53	364	20	387	48.1%	2.82 [1.72, 4.62]
Subtotal (95% CI)		**537**		**540**	**100.0%**	**1.69 [0.50, 5.78]**
Total events	199		142			
Heterogeneity: Tau² = 0.75; Chi² = 23.72, df = 1 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.84 (P = 0.40)						

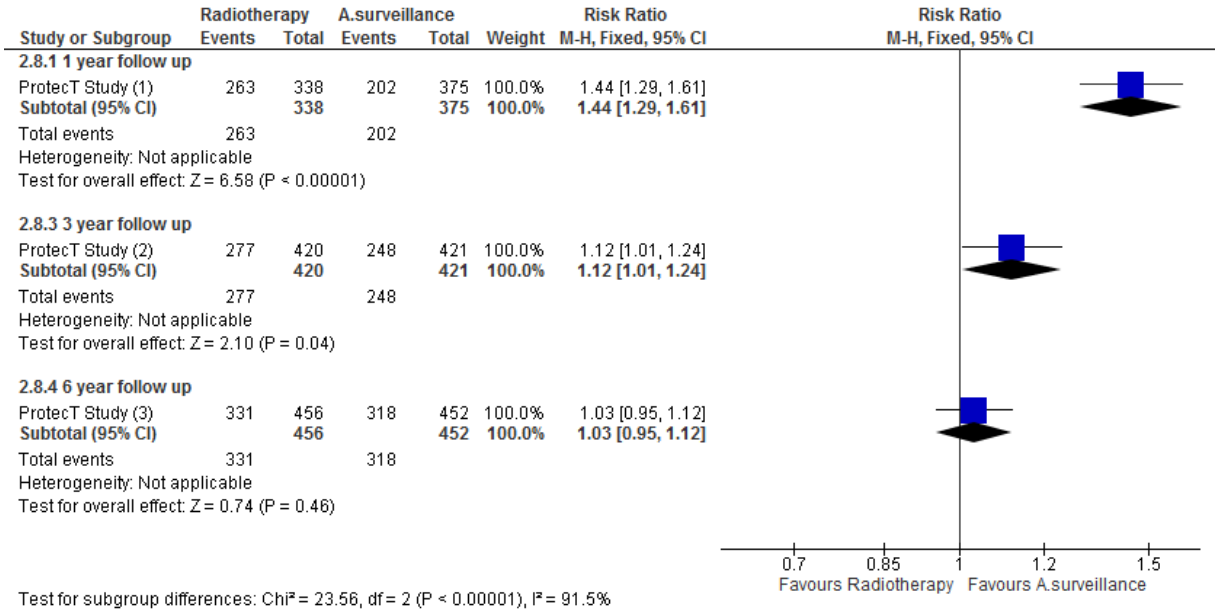
Test for subgroup differences: Not applicable

Footnotes

(1) Johansson 2011 (12.2 years follow up)
(2) 2017 (12-19.5 year follow up)

Radical radiotherapy versus Active surveillance

Severe adverse events (erectile dysfunction)

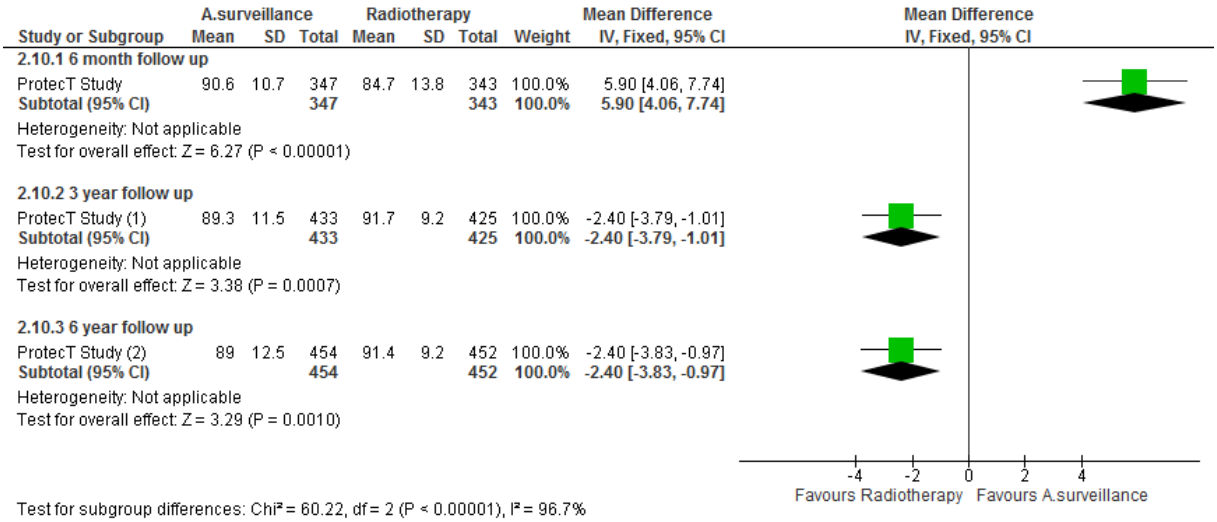


Test for subgroup differences: $Chi^2 = 23.56$, df = 2 (P < 0.00001), $I^2 = 91.5\%$

Footnotes

(1) 2016 (6 month follow up)
(2) 2016 (36 month follow up)
(3) 2016 (72 month follow up)

Treatment-related morbidity (EPIC summary scores): Urinary function



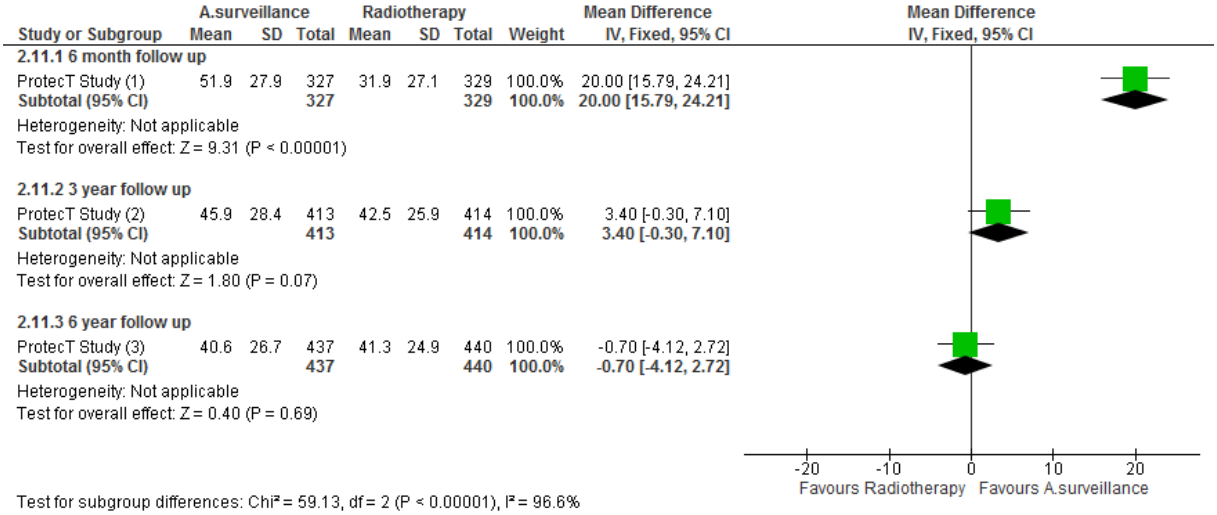
Test for subgroup differences: Chi² = 60.22, df = 2 (P < 0.00001), I² = 96.7%

Footnotes

(1) 36 months follow-up

(2) 72 months follow-up

Treatment-related morbidity (EPIC summary scores): Sexual dysfunction



Test for subgroup differences: Chi² = 59.13, df = 2 (P < 0.00001), I² = 96.6%

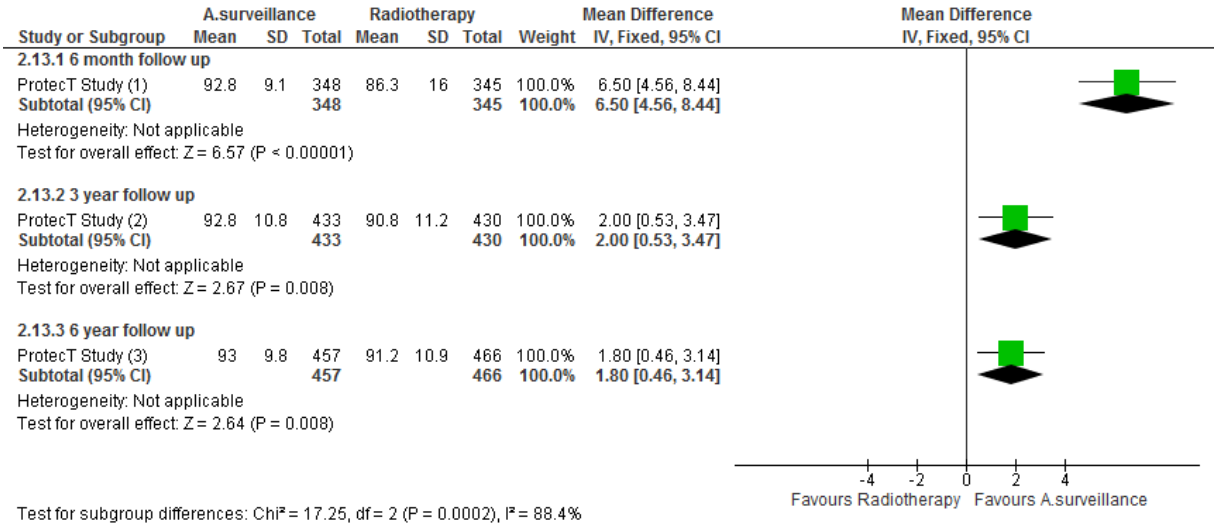
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

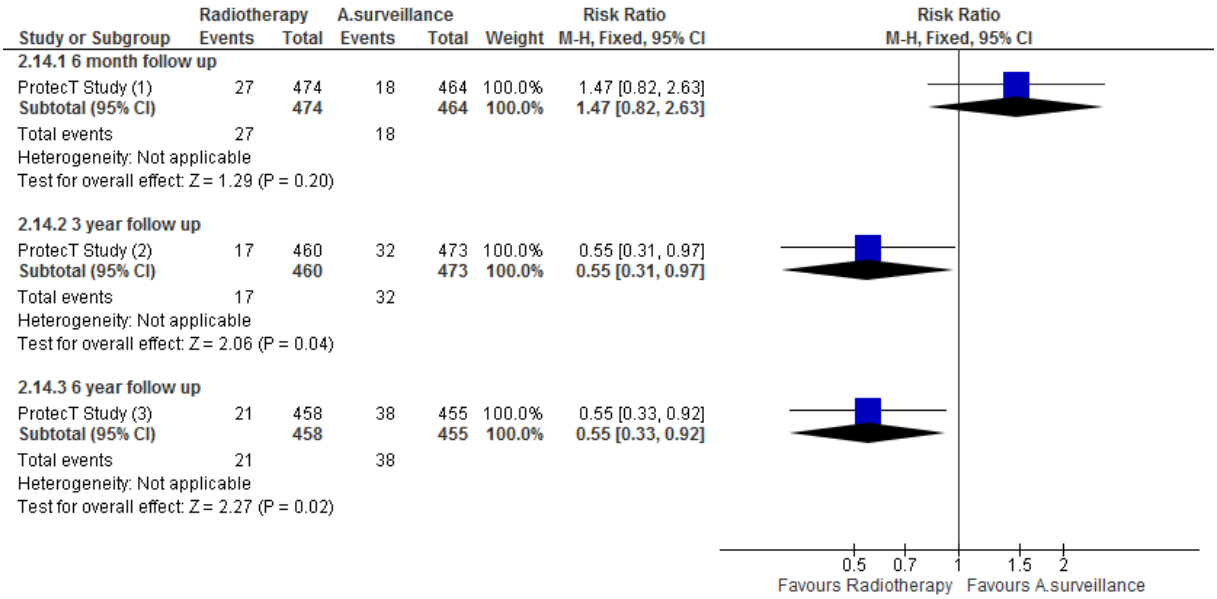
Treatment-related morbidity (EPIC summary scores): Bowel function



Test for subgroup differences: $Chi^2 = 17.25$, df = 2 (P = 0.0002), $I^2 = 88.4\%$

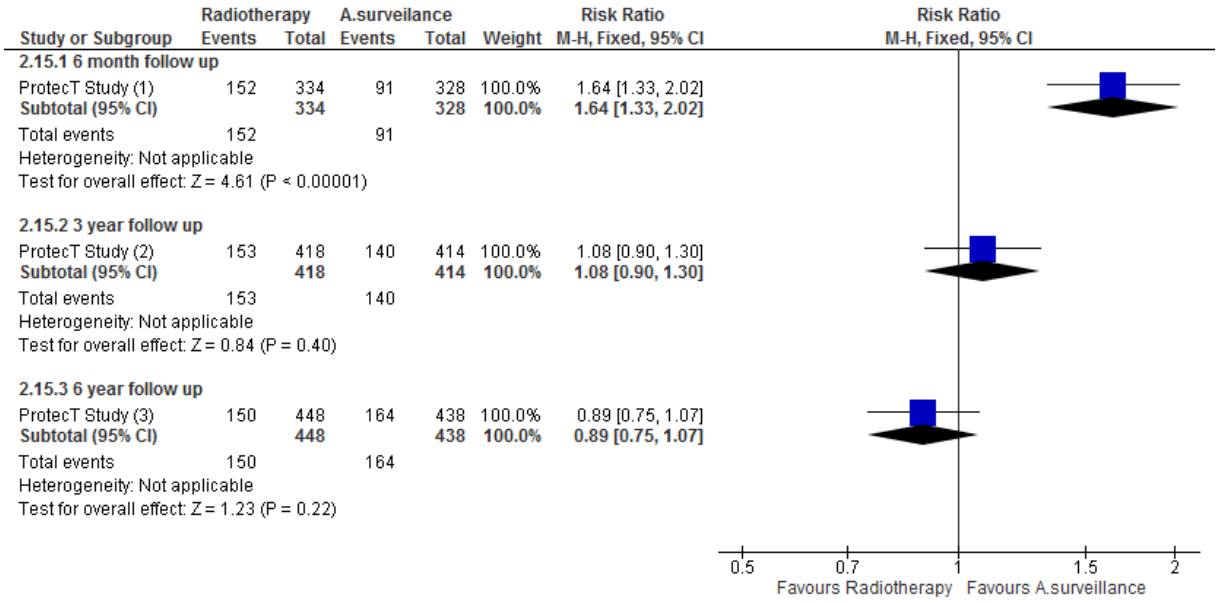
Footnotes
(1) 6 months follow-up
(2) 36 months follow-up
(3) 72 months follow-up

Moderate/severe impact of treatment on quality of life (incontinence)



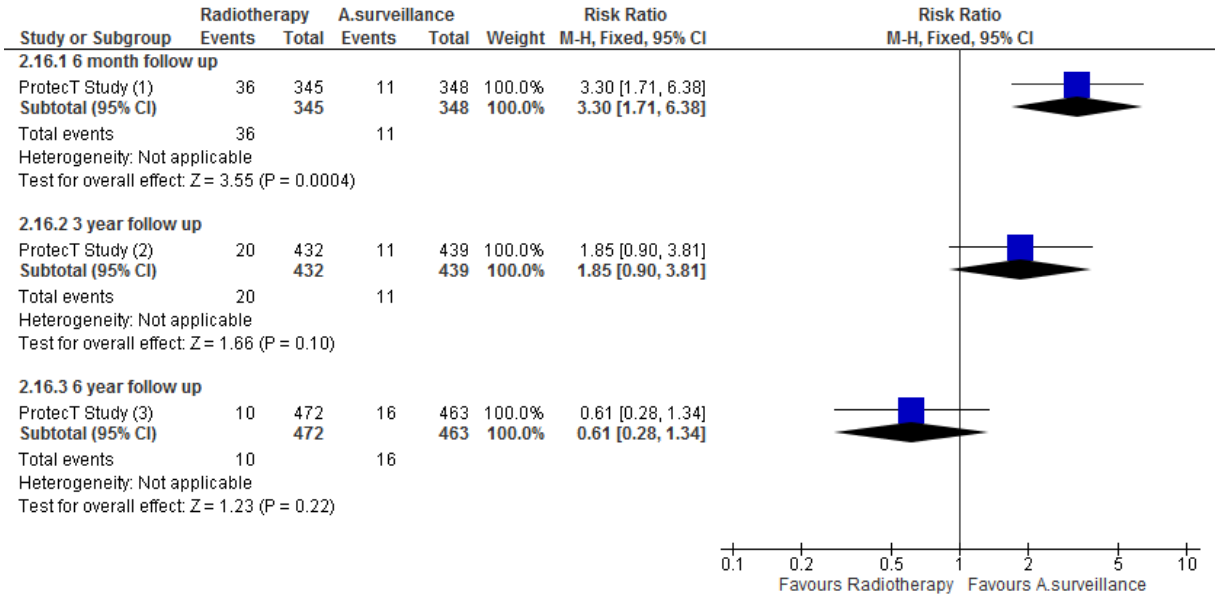
Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Moderate/severe impact of treatment on quality of life (sexual dysfunction)



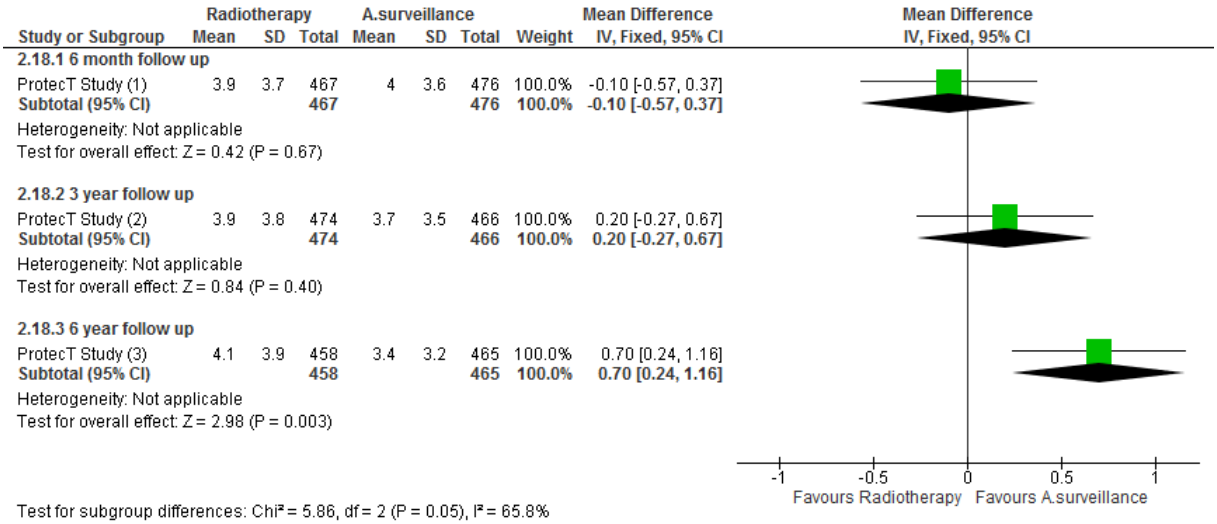
Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Moderate/severe impact of treatment on quality of life (bowel function)



Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Anxiety



Test for subgroup differences: Chi² = 5.86, df = 2 (P = 0.05), I² = 65.8%

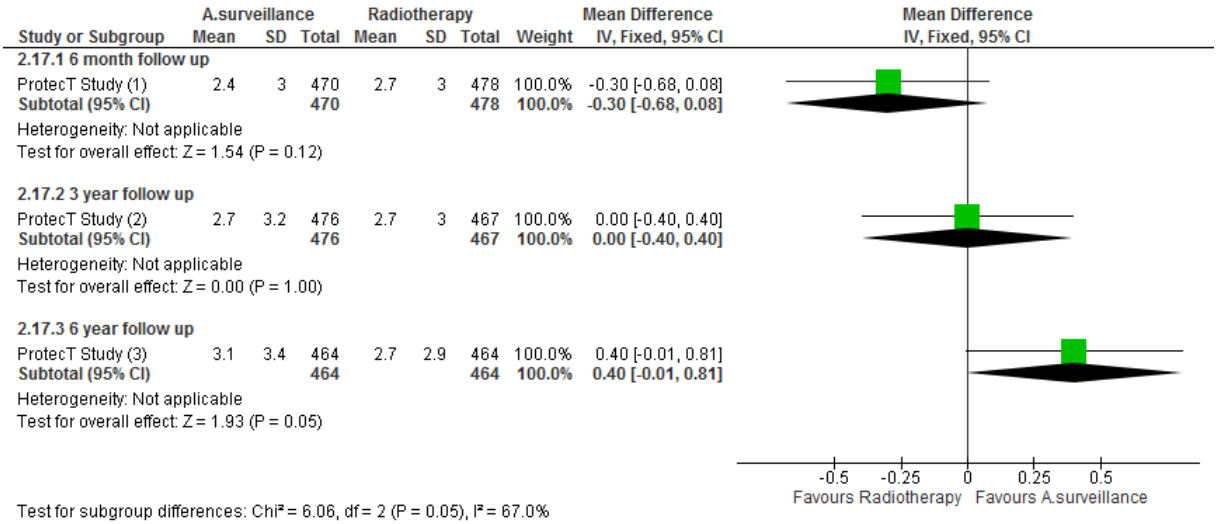
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Depression



Test for subgroup differences: Chi² = 6.06, df = 2 (P = 0.05), I² = 67.0%

Footnotes

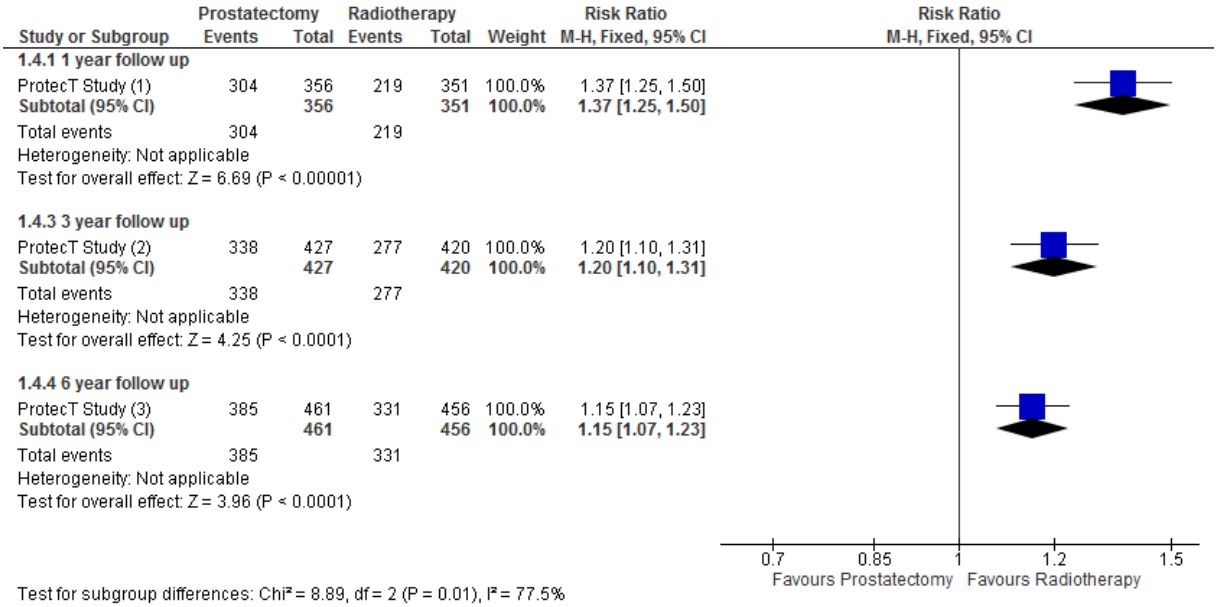
(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Radical prostatectomy versus radical radiotherapy

Number of severe adverse events (erectile dysfunction)



Test for subgroup differences: Chi² = 8.89, df = 2 (P = 0.01), I² = 77.5%

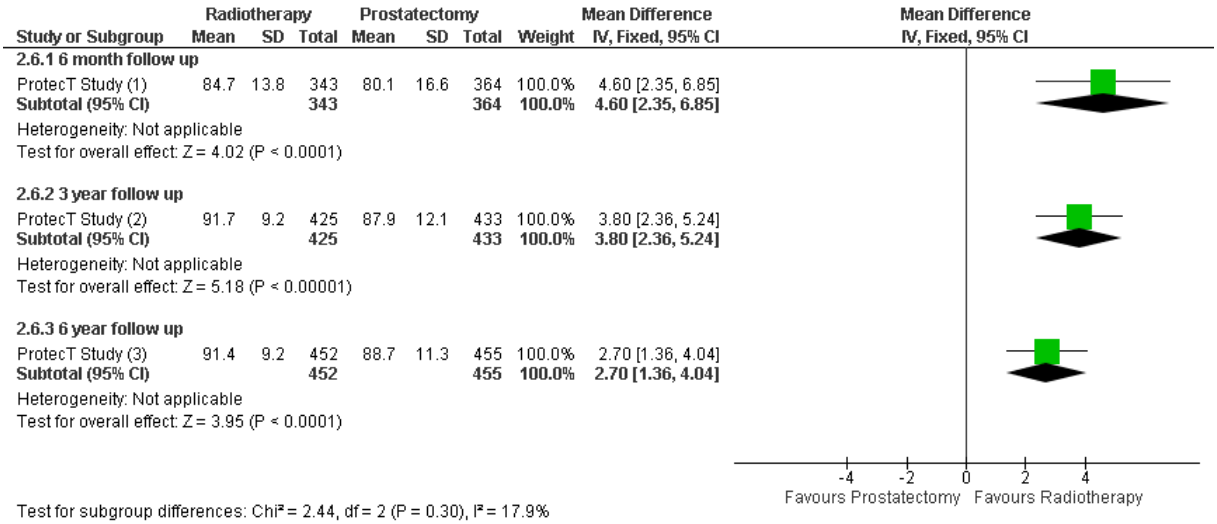
Footnotes

(1) 2016 (6 month follow up)

(2) 2016 (36 month follow up)

(3) 2016 (72 month follow up)

Treatment-related morbidity (EPIC summary scores): Urinary function



Test for subgroup differences: Chi² = 2.44, df = 2 (P = 0.30), I² = 17.9%

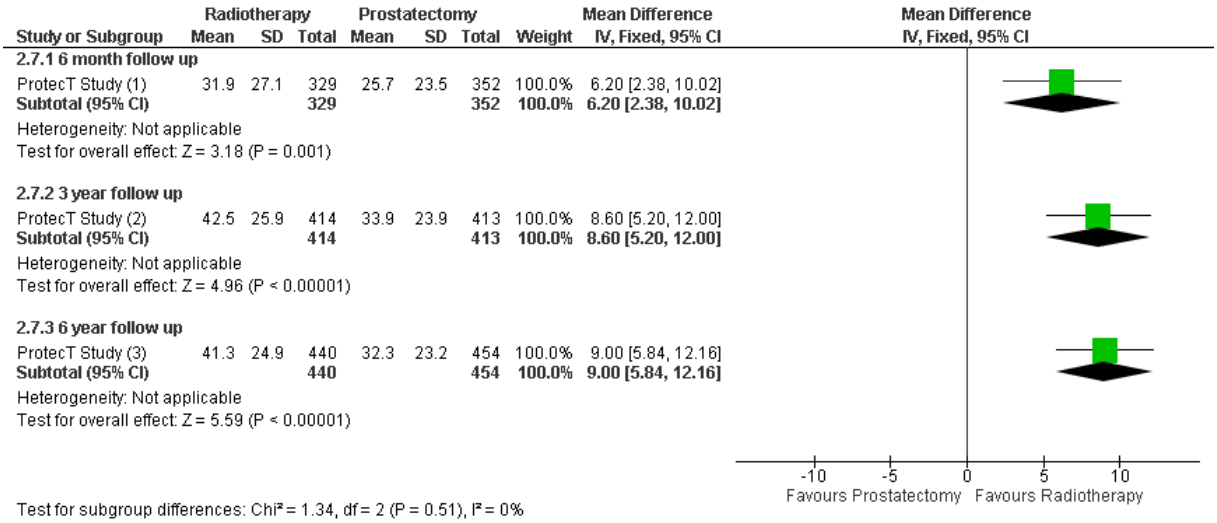
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Treatment-related morbidity (EPIC summary scores): Sexual dysfunction



Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%

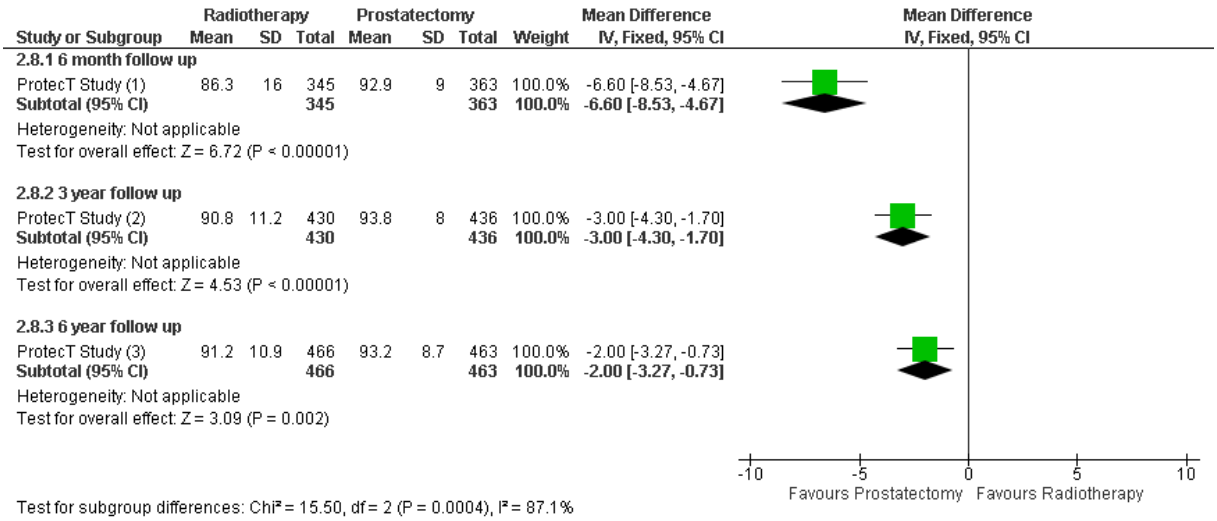
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Treatment-related morbidity (EPIC summary scores): Bowel function



Test for subgroup differences: Chi² = 15.50, df = 2 (P = 0.0004), I² = 87.1%

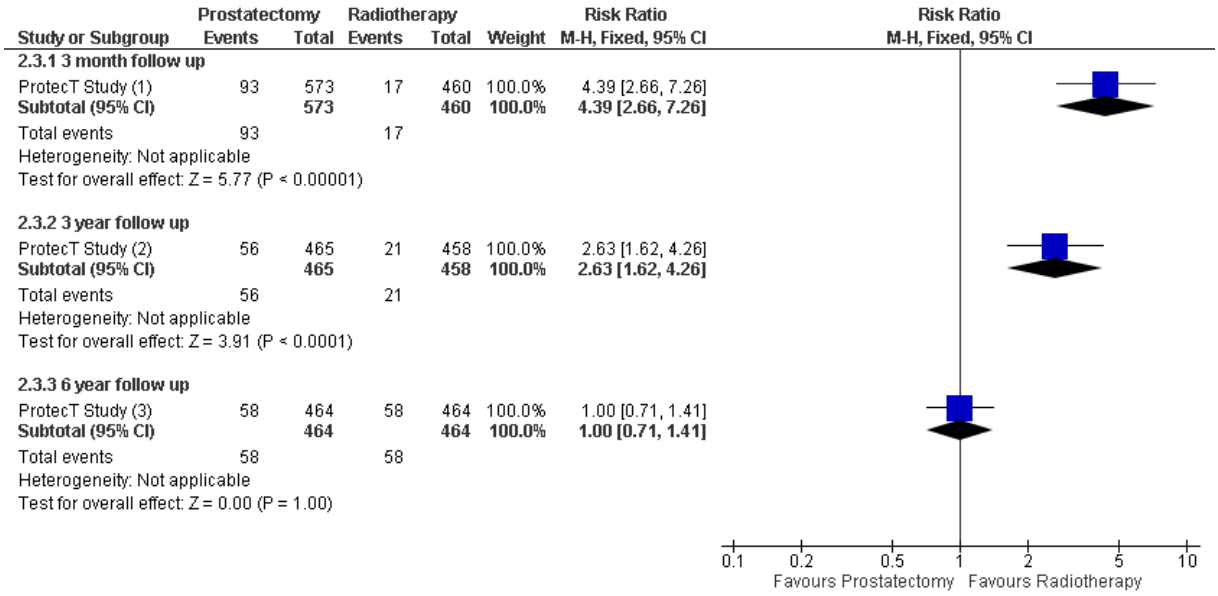
Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

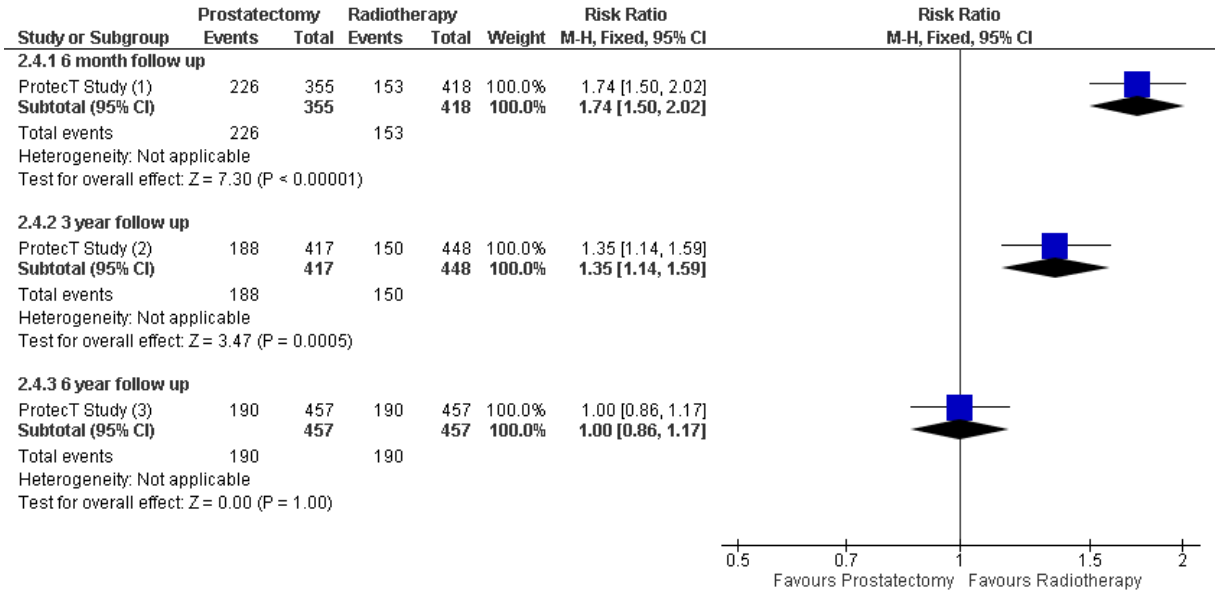
(3) 72 months follow-up

Moderate/severe impact on quality of life (incontinence)



Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

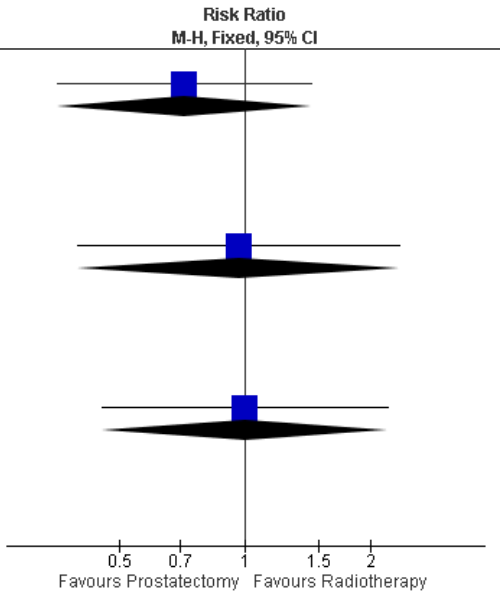
Moderate/severe impact on quality of life (sexual dysfunction)



Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Moderate/severe impact on quality of life (bowel function)

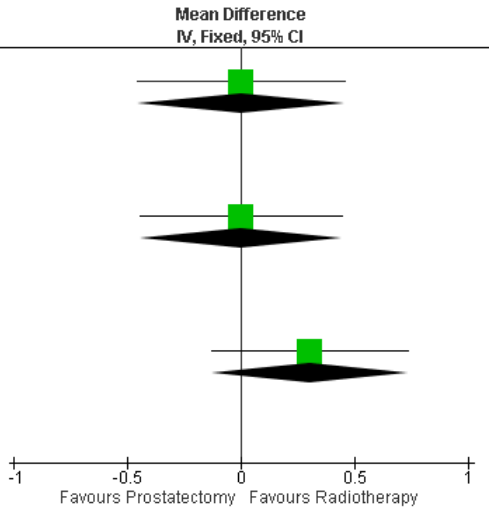
Study or Subgroup	Prostatectomy Events	Prostatectomy Total	Radiotherapy Events	Radiotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 6 month follow up						
ProtecT Study (1)	12	362	20	432	100.0%	0.72 [0.35, 1.44]
Subtotal (95% CI)		**362**		**432**	**100.0%**	**0.72 [0.35, 1.44]**
Total events	12		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.5.2 3 year follow up						
ProtecT Study (2)	9	439	10	472	100.0%	0.97 [0.40, 2.36]
Subtotal (95% CI)		**439**		**472**	**100.0%**	**0.97 [0.40, 2.36]**
Total events	9		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
2.5.3 6 year follow up						
ProtecT Study (3)	12	467	12	467	100.0%	1.00 [0.45, 2.20]
Subtotal (95% CI)		**467**		**467**	**100.0%**	**1.00 [0.45, 2.20]**
Total events	12		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



Footnotes
(1) 6 month follow up
(2) 36 month follow up
(3) 72 month follow up

Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Anxiety

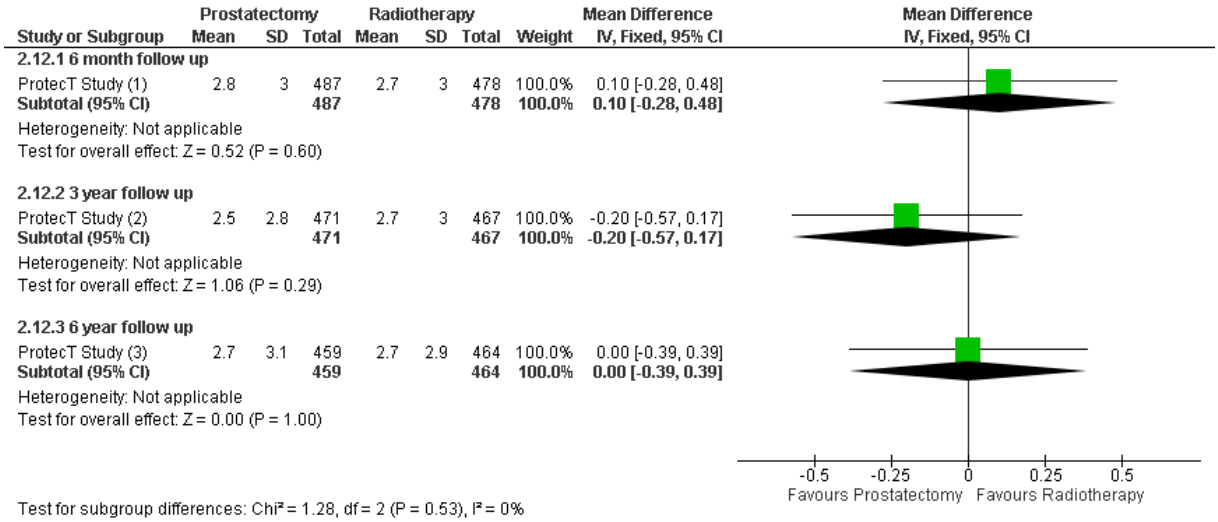
Study or Subgroup	Prostatectomy Mean	Prostatectomy SD	Prostatectomy Total	Radiotherapy Mean	Radiotherapy SD	Radiotherapy Total	Weight	Mean Difference IV, Fixed, 95% CI
2.11.1 6 month follow up								
ProtecT Study (1)	4	3.6	485	4	3.6	476	100.0%	0.00 [-0.46, 0.46]
Subtotal (95% CI)			**485**			**476**	**100.0%**	**0.00 [-0.46, 0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
2.11.2 3 year follow up								
ProtecT Study (2)	3.7	3.4	470	3.7	3.5	466	100.0%	0.00 [-0.44, 0.44]
Subtotal (95% CI)			**470**			**466**	**100.0%**	**0.00 [-0.44, 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
2.11.3 6 year follow up								
ProtecT Study (3)	3.7	3.5	465	3.4	3.2	465	100.0%	0.30 [-0.13, 0.73]
Subtotal (95% CI)			**465**			**465**	**100.0%**	**0.30 [-0.13, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								



Test for subgroup differences: Chi² = 1.21, df = 2 (P = 0.55), I² = 0%

Footnotes
(1) 6 months follow-up
(2) 36 months follow-up
(3) 72 months follow-up

Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Depression



Test for subgroup differences: Chi² = 1.28, df = 2 (P = 0.53), I² = 0%

Footnotes

(1) 6 months follow-up

(2) 36 months follow-up

(3) 72 months follow-up

Appendix G – GRADE tables

Radical prostatectomy versus active surveillance

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival – HR <1 favours radical prostatectomy group (10 year follow up)										
1 study ProtecT	RCT	1643	HR 0.93 (0.65, 1.33)	-	-	Not serious	Not serious	N/A	Serious[1]	Moderate
Prostate cancer-specific survival – HR <1 favours radical prostatectomy group (10 year follow up)										
1 study ProtecT	RCT	1643	HR 0.63 (0.21, 1.89)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis –RR <1 favours radical prostatectomy group (10 year follow up)										
1 study ProtecT	RCT	1643	RR 0.39 (0.21, 0.73)	6.1 per 100	2.4 per 100 (1.3, 4.4)	Not serious	N/A	Not serious	Not serious	High
Disease Progression –HR <1 favours radical prostatectomy group										
1 study ProtecT	RCTs	1643	HR 0.39 (0.27, 0.56)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of Severe Adverse Events: Incontinence –RR <1 favours radical prostatectomy group Subgroup analysis – 6 month follow up										
1 study ProtecT	RCT	935	RR 1.82 (1.60, 2.07)	38.9 per 100	71.0 per 100 (18.1, 46.8)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 2 year follow up										
1 study ProtecT	RCT	921	RR 1.49 (1.32, 1.67)	45.0 per 100	67.1 per 100 (59.4, 75.2)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 4 year follow up										
1 study ProtecT	RCT	925	RR 1.47 (1.31, 1.63)	49.0 per 100	72.1 per 100 (64.2, 79.9)	Serious[2]	N/A	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis - 6 year follow up)										
1 study ProtecT	RCT	914	RR 1.37 (1.23, 1.53)	50.1 per 100	68.7 per 100 (61.6, 76.7)	Serious[2]	N/A	Not serious	Serious[3]	Low
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical prostatectomy group **Subgroup analysis - 1 year follow up**										
1 study ProtecT	RCT	1643	RR 1.63 (1.48, 1.81)	53.9 per 100	87.8 per 100 (79.7, 97.4)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 2 year follow up										
1 study ProtecT	RCT	1643	RR 1.53 (1.38, 1.70)	52.9 per 100	81.0 per 100 (73.0, 89.9)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 4 year follow up										
1 study ProtecT	RCT	1643	RR 1.14 (1.06, 1.23)	69.9 per 100	79.7 per 100 (74.1, 86.0)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	1643	RR 1.19 (1.10, 1.28)	70.4 per 100	83.7 per 100 (77.4, 90.1)	Serious[2]	N/A	Not serious	Serious[3]	Low
Treatment-related morbidity (EPIC summary scores): Urinary function– MD <0 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	711	MD 10.50 (8.46, 12.54)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	866	MD 1.40 (-0.17, 2.97)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	909	MD 0.30 (-1.25, 1.85)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Treatment-related morbidity (EPIC summary scores): Erectile dysfunction– MD <0 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	679	MD 26.20 (22.30, 30.10)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	826	MD 12.00 (8.42, 15.58)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	891	MD 8.30 (5.01, 11.59)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
Treatment-related morbidity (EPIC summary scores): Bowel function– MD <0 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	711	MD 0.10 (-1.43, 1.23)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	869	MD -1.00 (-2.26, 0.26)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	920	MD -0.20 (-1.40, 1.00)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Moderate/severe impact of treatment on quality of life (incontinence)– RR >1 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	1037	RR 4.18 (2.56, 6.83)	3.8 per 100	16.2 per 100 (9.9, 26.5)	Serious[5]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study ProtecT	RCT	938	RR 1.78 (1.18, 2.70)	6.8 per 100	12.0 per 100 (7.9, 18.2)	Serious[2]	N/A	Not serious	Serious[3]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	919	RR 1.50 (1.02, 2.21)	12.5 per 100	18.8 per 100 (12.8, 27.6)	Serious[2]	N/A	Not serious	Serious[3]	Low
Moderate/severe impact of treatment on quality of life (erectile dysfunction)– RR >1 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	683	RR 2.29 (1.89, 2.78)	27.7 per 100	63.5 per 100 (52.4, 77.1)	Serious[2]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	831	RR 1.33 (1.12, 1.58)	33.8 per 100	44.9 per 100 (37.9, 53.4)	Serious[2]	N/A	Not serious	Serious[3]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	895	RR 1.11 (0.94, 1.31)	37.4 per 100	41.6 per 100 (35.1, 49.1)	Serious[2]	N/A	Not serious	Serious[3]	Low
Moderate/severe impact of treatment on quality of life (bowel habits)– RR >1 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	710	RR 1.05 (0.47, 2.35)	3.16 per 100	3.32 per 100 (1.49, 7.43)	Serious[2]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	878	RR 0.82 (0.34, 1.95)	2.51 per 100	2.05 per 100 (8.52, 4.89)	Serious[2]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	930	RR 0.74 (0.36, 1.55)	2.57 per 100	1.90 per 100 (0.92, 3.98)	Serious[2]	N/A	Not serious	Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Cancer-specific quality of life: Global health status – MD <0 favours radical prostatectomy group										
1 study ProtecT	RCT	1643	MD -1.60 (-4.08, 0.88)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
HADS Score: Anxiety – MD >0 favours radical prostatectomy group **Subgroup analysis – 1 year follow up**										
1 study ProtecT	RCT	952	MD -0.10 (-0.56, 0.36)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	944	MD 0.20 (-0.26, 0.66)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	923	MD -0.40 (-0.08, 0.88)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
HADS Score: Depression – MD >0 favours radical prostatectomy group **Subgroup analysis – 6 month follow up**										
1 study ProtecT	RCT	957	MD-0.40 (-0.78, -0.02)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	947	MD 0.20 (-0.18, 0.58)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	923	MD 0.40 (-0.02, 0.82)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low

1. 95% confidence intervals crosses the line of no effect, downgraded once
2. Moderate risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded once
3. 95% confidence interval for the effect size crossed one line of the MID, downgraded once

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
4. 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice										

Radical prostatectomy versus Watchful Waiting

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall mortality – HR <1 favours radical prostatectomy group **Subgroup analysis - 4 year follow up**										
1 study PIVOT	RCT	731	HR 0.68 (0.45, 1.03)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Overall mortality– HR <1 favours radical prostatectomy group **Subgroup analysis - 6 year follow up**										
1 study Scandinavian Prostatic Group-4	RCT	698	HR 0.83 (0.57, 1.21)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
Subgroup analysis - 8 year follow up										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	1429	HR 0.83 (0.69, 0.99)	-	-	Serious[3]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis - 12 year follow up										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	1429	HR 0.86 (0.75, 0.98)	-	-	Serious[3]	Serious[4]	Not serious	Not serious	Low
Subgroup analysis - 16 year follow up										
1 study PIVOT	RCT	731	HR 0.89 (0.79, 1.00)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Subgroup analysis - 18 year follow up										
1 study: Scandinavian Prostatic Group-4	RCT	698	HR 0.71 (0.59, 0.85)	-	-	Not serious	N/A	Not serious	Not serious	High
Prostate cancer-specific mortality– HR <1 favours radical prostatectomy group **Subgroup analysis - 4 year follow up**										
1 study: PIVOT	RCT	731	HR 1.01 (0.33, 3.09)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
Subgroup analysis - 6 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	698	HR 0.50 (0.27, 0.93)	-	-	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 8 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2 studies Scandinavian Prostatic Group-4 PIVOT	RCT	1429	HR 0.58 (0.39, 0.84)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
Subgroup analysis - 12 year follow up										
2 studies PIVOT Scandinavian Prostatic Group-4	RCT	1429	HR 0.61 (0.45, 0.83)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 16 year follow up										
1 study PIVOT	RCT	731	HR 0.60 (0.37, 0.97)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 18 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	698	HR 0.56 (0.41, 0.76)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of people who developed distant metastasis –RR <1 favours radical prostatectomy group **Subgroup analysis - 6 year follow up**										
1 study Scandinavian	RCT	698	RR 0.65 (0.44, 0.97)	15.5 per 100	10.0 per 100 (6.8, 15.1)	Not serious	N/A	Not serious	Serious[4]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostatic Group-4										
Subgroup analysis - 10 year follow up										
1 study PIVOT	RCT	731	RR 0.44 (0.25, 0.76)	10.6 per 100	4.7 per 100 (2.7, 8.1)	Serious[1]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 18 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	698	RR 0.65 (0.52, 0.81)	39.6 per 100	25.8 per 100 (20.6, 32.1)	Not serious	N/A	Not serious	Serious[4]	Moderate
Disease Progression - HR <1 favours radical prostatectomy group										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	1429	HR 0.37 (0.29, 0.47)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
Number of Severe Adverse Events: Incontinence –RR <1 favours radical prostatectomy group Subgroup analysis - 2-3 year follow up										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	696	RR 2.95 (1.91, 4.56)	7.1 per 100	21.0 per 100 (13.6, 32.4)	Serious[1]	Not serious	Not serious	Not serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis - 4-5 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	319	RR 2.29 (1.63, 3.22)	21.3 per 100	48.8 per 100 (34.7, 68.5)	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 6-8 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	698	RR 2.25 (1.31, 3.88)	25 per 100	56.2 per 100 (32.7, 97.0)	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 12 year follow up										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	103	RR 2.98 (1.85, 4.78)	9.8 per 100	29.1 per 100 (18.1, 46.8)	Serious[1]	Serious[3]	Not serious	Not serious	Low
Number of Severe Adverse Events: Erectile dysfunction - RR <1 favours radical prostatectomy group **Subgroup analysis - 2 year follow up**										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	668	RR 1.88 (1.64, 2.15)	48.3 per 100	83.6 per 100 (70.5, 99.5)	Serious$_1$	Not serious	Not serious	Not serious	Moderate
Subgroup analysis - 4-5 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study Scandinavian Prostatic Group-4	RCT	319	RR 1.78 (1.48, 2.15)	45.0 per 100	80.0 per 100 (66.5, 96.6)	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 6-8 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	108	RR 1.52 (1.16, 2.00)	68.7 per 100	89.3 per 100 (70.7, 100)	Not serious	N/A	Not serious	Serious[4]	Moderate
Subgroup analysis -18 year follow up										
2 studies Scandinavian Prostatic Group-4 PIVOT	RCTs	1097	1.69 (0.50, 5.78)	26.3 per 100	44.4 per 100 (13.1, 100)	Serious[1]	Very serious[7]	Not serious	Not serious	Very low
Number of people with moderate/high anxiety – RR <1 favours radical prostatectomy group **Subgroup analysis - 4 year follow up**										
1 study Scandinavian Prostatic Group-4	RCT	698	RR 0.74 (0.51, 1.07)	30.5 per 100	22.6 per 100 (15.6, 32.7)	Serious[5]	N/A	Not serious	Serious[4]	Very low
Subgroup analysis - 12 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study Scandinavian Prostatic Group-4	RCT	698	RR 1.01 (0.79, 1.10)	42.9 per 100	43.3 per 100 (33.9, 47.1)	Serious[5]	N/A	Not serious	Serious[4]	Very low
Number of people with moderate/high depression – RR <1 favours radical prostatectomy group **Subgroup analysis - 4 year follow up**										
1 study Scandinavian Prostatic Group-4	RCT	698	RR 0.91 (0.68, 1.21)	38.2 per 100	34.8 per 100 (25.9, 46.2)	Serious[5]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 12 year follow up										
1 study Scandinavian Prostatic Group-4	RCT	698	RR 0.92 (0.74, 1.14)	51.6 per 100	47.4 per 100 (38.2, 58.8)	Serious[5]	N/A	Not serious	Serious[4]	Very low

1. 95% confidence intervals crosses the line of no effect, downgraded once
2. Moderate risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded once
3. 95% confidence interval for the effect size crossed one line of the MID, downgraded once
4. 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Radical radiotherapy versus Active surveillance

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: radiotherapy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall mortality – HR <1 favours radical radiotherapy group										
1 study ProtecT	RCT	1643	HR 0.94 (0.65, 1.36)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Prostate cancer-specific mortality – HR <1 favours radical radiotherapy group										
1 study ProtecT	RCT	1643	HR 0.51 (0.15, 1.73)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis – RR <1 favours radical radiotherapy group										
1 study ProtecT	RCT	1643	RR 0.48 (0.27, 0.87)	6.1 per 100	2.9 per 100 (1.6, 5.3)	Not serious	N/A	Not serious	Serious[3]	Moderate
Disease Progression – HR <1 favours radical radiotherapy group										
1 study ProtecT	RCT	1643	RR 0.39 (0.27, 0.56)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical radiotherapy group Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	713	RR 1.44 (1.29, 1.61)	53.8 per 100	77.6 per 100 (69.5, 86.7)	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCTs	841	RR 1.12 (1.01, 1.24)	58.9 per 100	65.9 per 100 (59.5, 73.0)	Not serious	N/A	Not serious	Not serious	High
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCTs	908	RR 1.03 (0.95, 1.12)	70.3 per 100	72.5 per 100 (66.8, 78.8)	Not serious	N/A	Not serious	Not serious	High
Treatment-related morbidity (EPIC summary scores): Urinary function– MD <0 favours radical radiotherapy group Subgroup analysis - 6 month follow up										
1 study	RCT	690	MD 5.90	-	-	Serious[4]	N/A	Not serious	Serious[6]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: radiotherapy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ProtecT			(7.74, 4.06)							
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	858	MD -2.40 (-1.01, -3.79)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	906	MD -2.40 (-0.97, -3.83)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Treatment-related morbidity (EPIC summary scores): Sexual dysfunction– MD <0 favours radical radiotherapy group Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	656	MD 20.00 (24.21, 15.79)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	827	MD 3.40 (-0.30, 7.10)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	877	MD -0.70 (-4.12, 2.72)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Treatment-related morbidity (EPIC summary scores): Bowel function) – MD <0 favours radical radiotherapy group Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	693	MD 6.50 (4.56, 8.44)	-	-	Serious[4]	N/A	Not serious	Serious[7]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	863	MD 2.00 (0.53, 3.47)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 6 year follow up										
1 study	RCT	923	MD 1.80	-	-	Serious[4]	N/A	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: radiotherapy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ProtecT			(0.46, 3.14)							
Moderate/severe impact of treatment on quality of life (incontinence)– RR <1 favours radical radiotherapy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	938	RR 1.47 (0.82, 2.63)	3.9 per 100	5.7 per 100 (3.2, 10.2)	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	933	RR 0.55 (0.31, 0.97)	6.8 per 100	3.7 per 100 (2.1, 6.6)	Serious[4]	N/A	Not serious	Serious[3]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	913	RR 0.55 (0.33, 0.92)	8.4 per 100	4.6 per 100 (2.8, 7.7)	Serious[4]	N/A	Not serious	Serious[3]	Very low
Moderate/severe impact of treatment on quality of life (sexual dysfunction) – RR >1 favours radical radiotherapy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	662	RR 1.61 (1.33, 2.02)	27.7 per 100	45.5 per 100 (36.8, 56.0)	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	432	RR 1.08 (0.90, 1.30)	33.8 per 100	36.5 per 100 (30.4, 44.0)	Serious[4]	N/A	Not serious	Serious[3]	Very low
Subgroup analysis - 6 year follow up)										
1 study ProtecT	RCT	936	RR 0.89 (0.75, 1.07)	37.4 per 100	33.3 per 100 (28.0, 40.1)	Serious[4]	N/A	Not serious	Serious[3]	Very low
Moderate/severe impact of treatment on quality of life (bowel function) – RR <1 favours radical radiotherapy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	693	RR 3.30 (1.71, 6.38)	3.2 per 100	10.4 per 100 (5.4, 20.1)	Serious[4]	N/A	Not serious	Not serious	Low
Subgroup analysis - 3 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: radiotherapy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study ProtecT	RCT	871	RR 1.85 (0.90, 3.81)	2.5 per 100	4.6 per 100 (2.3, 9.6)	Serious[4]	N/A	Not serious	Serious[3]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	935	RR 0.61 (0.28, 1.34)	3.5 per 100	2.1 per 100 (0.97, 4.6)	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Cancer-specific quality of life: Global health status – MD >0 favours radical radiotherapy group										
1 study ProtecT	RCT	1643	MD 0.60 (-1.95, 3.15)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Anxiety– MD >0 favours radical radiotherapy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	943	MD -0.10 (-0.57, 0.37)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	940	MD 0.20 (-0.27, 0.67)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	923	MD 0.70 (-0.24, 1.16)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Depression– MD >0 favours radical radiotherapy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	948	MD -0.30 (-0.68,0.08)	-	-	Serious[4]	N/A	Not serious	Serious[3]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	943	MD 0.00 (-0.40, 0.40)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
6 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: observation	Absolute risk: radiotherapy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study ProtecT	RCT	928	MD 0.40 (0.01, 0.81)	-	-	Serious[4]	N/A	Not serious	Serious[3]	Very low

1. 95% confidence intervals crosses the line of no effect, downgraded once
2. Moderate risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded once
3. 95% confidence interval for the effect size crossed one line of the MID, downgraded once
4. 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Radical radiotherapy versus Radical prostatectomy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: radiotherapy	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prostate cancer-specific mortality – HR <1 favours radical prostatectomy group										
1 study ProtecT	RCT	1643	HR 0.80 (0.22, 2.91)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis – RR <1 favours radical prostatectomy group										
1 study ProtecT	RCT	1643	RR 1.25 (0.61, 2.57)	2.9 per 100	3.7 per 100 (1.4, 6.0)	Not serious	N/A	Not serious	Very serious[4]	Low
Disease progression – RR <1 favours radical prostatectomy group										
1 study ProtecT	RCT	1643	RR 0.99 (0.67, 1.46)	8.4 per 100	8.3 per 100 (5.7, 12.3)	Not serious	N/A	Not serious	Very serious[4]	Low
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	707	RR 1.37 (1.25, 1.50)	62.4.4 per 100	85.5 per 100 (77.9, 93.6)	Not serious	N/A	Not serious	Serious[2]	Moderate
Subgroup analysis - 3 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: radiotherapy	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study ProtecT	RCTs	847	RR 1.20 (1.10, 1.31)	65.9 per 100	79.1 per 100 (72.5, 86.4)	Not serious	N/A	Not serious	Serious[2]	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCTs	918	RR 1.15 (1.07, 1.23)	72.6 per 100	83.5 per 100 (77.7, 89.2)	Not serious	N/A	Not serious	Not serious	High
Treatment-related morbidity (EPIC summary scores): Urinary function– MD <0 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	709	MD 4.60 (2.35, 6.85)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	878	MD 3.80 (2.36, 5.24)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	907	MD 2.70 (1.36, 4.04)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Treatment-related morbidity (EPIC summary scores): Sexual dysfunction– MD <0 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	681	MD 6.20 (2.38, 10.02)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	827	MD 8.60 (5.20, 12.00)	-	-	Serious[3]	N/A	Not serious	Serious[5]	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	894	MD 9.00 (5.84, 12.16)	-	-	Serious[3]	N/A	Not serious	Serious[5]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: radiotherapy	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Treatment-related morbidity (EPIC summary scores): Bowel function– MD <0 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	698	MD -6.60 (-8.53, -4.67)	-	-	Serious[3]	N/A	Not serious	Serious[6]	Low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	866	MD -3.00 (-4.30, -1.70)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	929	MD -2.00 (-3.27, -0.73)	-	-	Serious[3]	N/A	Not serious	Not serious	Moderate
Moderate/severe impact on quality of life (incontinence)– RR <1 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	1033	RR 4.39 (2.66, 7.26)	3.7 per 100	16.2 per 100 (9.7, 26.8)	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	923	RR 2.63 (1.62, 4.26)	4.6 per 100	12.1 per 100 (7.43, 19.5)	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	1643	RR 1.00 (0.71, 1.41)	12.5 per 100	12.5 per 100 (8.8, 14.6)	Serious[3]	N/A	Not serious	Not serious	Moderate
Moderate/severe impact on quality of life (sexual dysfunction)– RR <1 favours radical prostatectomy group										
Subgroup analysis - 6 month follow up										
1 study ProtecT	RCT	928	RR 1.74 (1.50, 2.02)	36.6 per 100	63.7 per 100 (54.9, 80.5)	Serious[3]	N/A	Not serious	Not serious	Moderate
Subgroup analysis - 3 year follow up										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: radiotherapy	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study ProtecT	RCT	773	RR 1.35 (1.14, 1.59)	33.5 per 100	45.2 per 100 (38.2, 53.2)	Serious[3]	N/A	Not serious	Serious[2]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	914	RR 1.00 (0.86, 1.17)	41.6 per 100	41.6 per 100 (35.8, 48.6)	Serious[3]	N/A	Not serious	Not serious	Moderate
Moderate/severe impact on quality of life (bowel function)– RR <1 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	794	RR 0.72 (0.35, 1.44)	4.6 per 100	3.3 per 100 (1.6, 6.7)	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	911	RR 0.97 (0.40, 2.36)	2.1 per 100	2.0 per 100 (0.9, 0.5)	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	934	RR 1.00 (0.45, 2.20)	2.6 per 100	2.6 per 100 (1.2, 5.7)	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Cancer-specific quality of life: Global health status – MD <0 favours radical prostatectomy group										
1 study ProtecT	RCT	1643	MD -1.00 (-3.57, 1.57)	-	-	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Anxiety– MD <0 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	961	MD 0.00 (-0.46, 0.46)	-	-	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	936	MD 0.00 (-0.44, 0.44)	-	-	Serious[3]	N/A	Not serious	Very serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: radiotherapy	Absolute risk: prostatectomy (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	930	MD 0.30 (-0.13, -0.73)	-	-	Serious[3]	N/A	Not serious	Serious[3]	Low
Psychological aspects of quality of life (Hospital Anxiety & Depression Scores): Depression– MD <0 favours radical prostatectomy group **Subgroup analysis - 6 month follow up**										
1 study ProtecT	RCT	965	0.10 (-0.28, 0.48)	-	-	Serious[3]	N/A	Not serious	Very serious[4]	Very low
Subgroup analysis - 3 year follow up										
1 study ProtecT	RCT	938	-0.20 (-0.57, 0.17)	-	-	Serious[3]	N/A	Not serious	Serious[2]	Low
Subgroup analysis - 6 year follow up										
1 study ProtecT	RCT	923	0.00 (-0.39, 0.39)	-	-	Serious[3]	N/A	Not serious	Very serious[4]	Very low

1. 95% confidence intervals crosses the line of no effect, downgraded once
2. 95% confidence interval for the effect size crossed one line of the MID, downgraded once
3. High risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded twice
4. 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Appendix H – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Aizer (2009)	Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma	Study does not contain any relevant interventions
Akakura (2006)	A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: Results at median follow-up of 102 months	Does not contain a population of people with localised Prostate cancer
Albertsen (2014)	Randomised controlled trial: radical prostatectomy reduces prostate cancer-specific mortality among men with intermediate-grade disease, but provides minimal benefit for men with low-grade and high-grade disease	Discussion of SPCG-4 study
Block (2012)	Watchful waiting and radical prostatectomy offer equivalent survival in localized prostate cancer	Discussion of PIVOT study
Catton (2017)	Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer	Study does not contain any relevant interventions
Chen (2017)	Comparison on efficacy of radical prostatectomy versus external beam radiotherapy for the treatment of localized prostate cancer	Comparator in study does not match that specified in protocol No active surveillance
Chen (2017)	Comparisons of health-related quality of life among surgery and radiotherapy for localized prostate cancer: a systematic review and meta-analysis	Comparator in study does not match that specified in protocol No active surveillance
Chin (2017)	Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update	Comparator in study does not match that specified in protocol
Concato (2012)	Randomised trial of radical prostatectomy versus watchful waiting finds reduced risk for death but uncertainty still reigns	Discussion of SPCG-4 study
Datta (2017)	Conventional Versus Hypofractionated Radiation Therapy for Localized or Locally Advanced Prostate Cancer: A Systematic Review and Meta-analysis along with Therapeutic Implications	Study does not contain any relevant interventions
Dayes (2017)	Long-Term Results of a Randomized Trial Comparing Iridium Implant Plus External Beam Radiation Therapy With External Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate	Study does not contain any relevant interventions
De Carlo (2014)	Retropubic, laparoscopic, and robot-assisted radical prostatectomy: surgical, oncological, and functional outcomes: a systematic review	Comparator in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
		Prostatectomy only
Dearnaley (2007)	Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial	Comparator in study does not match that specified in protocol Radiotherapy doses
Dearnaley (2011)	Escalated-dose conformal radiotherapy for localised prostate cancer: long-term overall survival results from the MRC RT01 randomised controlled trial	Conference abstract
Dearnaley (2014)	Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial	Comparator in study does not match that specified in protocol Radiotherapy doses
Dearnaley (2015)	5 year outcomes of a phase III randomised trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CRUK/06/016): report from the CHHiP Trial Investigators Group	Conference abstract
Dearnaley (2016)	Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial	Comparator in study does not match that specified in protocol Radiotherapy doses
Di Franco (2017)	Rectal/urinary toxicity after hypofractionated vs. conventional radiotherapy in high risk prostate cancer: systematic review and meta analysis	Study does not contain any relevant interventions
Di Franco (2017)	Rectal/urinary toxicity after hypofractionated vs conventional radiotherapy in low/intermediate risk localized prostate cancer: systematic review and meta analysis	Comparator in study does not match that specified in protocol Radiotherapy only
Felix (2012)	Morbidity results in a prospective randomized trial of hypofractionation versus standard fractionation for prostate cancer using conformal radiation therapy	Conference abstract
Fiori (2016)	Four-year outcome of a prospective randomised trial comparing laparoscopic versus robotassisted radical prostatectomy	Study does not contain any relevant interventions Journal Supplement
Fiori (2016)	Laparoscopic versus robot-assisted radical prostatectomy: four-year results of a prospective randomised trial	Conference abstract
Fiori (2017)	Long term complications and quality of life after pure versus robotassisted laparoscopic prostatectomy: results of a prospective randomised controlled trial	Study does not contain any relevant interventions Journal Supplement
Fonteyne (2018)	4 Weeks Versus 5 Weeks of Hypofractionated High-dose Radiation Therapy as Primary Therapy for Prostate Cancer: Interim Safety Analysis of a Randomized Phase 3 Trial	Study does not contain any relevant interventions
Fransson (2001)	Quality of Life and Symptoms in a Randomized Trial of Radiotherapy versus Deferred Treatment of Localized Prostate Carcinoma	Data not reported in an extractable format

Short Title	Title	Reason for exclusion
Fransson (2009)	Health-related quality of life 10 years after external beam radiotherapy or watchful waiting in patients with localized prostate cancer	Data not reported in an extractable format
Giberti (2009)	Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study	Comparator in study does not match that specified in protocol Prostatectomy v brachytherapy. No active surveillance
Giberti (2017)	Robotic prostatectomy versus brachytherapy for the treatment of low risk prostate cancer	Data not reported in an extractable format
Greco (2017)	Acute toxicity following single-dose radiation therapy in the management of intermediate risk prostate cancer: results from a phase 2 randomized trial	Conference abstract
Griffin (2013)	Radical prostatectomy does not improve survival compared to observation for localised prostate cancer in a prospective randomised trial	Discussion of PIVOT study
Guix (2016)	Dose escalation with high-dose-3D-conformal/ IMRT (HD-3D-CRT/IMRT) compared with low-dose 3D-conformal/IMRT plus HDR brachytherapy (LD-3D-CRT/IMRTDHDR-B) for intermediate- or high-risk prostate cancer: higher disease control and survival with lower toxicity	Conference abstract
Hajdenberg (2014)	Radical prostatectomy reduced long-term mortality more than watchful waiting in early prostate cancer	Discussion of SPCG-4 study
Hamdy (2016)	The protect study	Conference abstract
Hegarty (2007)	Watchful waiting versus prostatectomy for prostate cancer	Protocol for systematic review
Hennequin (2015)	Randomized phase 3 trial of dose escalation (80 vs 70 gy) in high-risk prostate cancers combined with long-term androgen deprivation: getug-AFU 18 trial, acute and 1-year toxicities	Conference abstract
Hoffman (2016)	Patient-reported Urinary, Bowel, and Sexual Function After Hypofractionated Intensity-modulated Radiation Therapy for Prostate Cancer: results From a Randomized Trial	Study does not contain any relevant interventions
Hoffman (2016)	Randomized trial of hypofractionated dose-escalated intensity modulated radiation therapy versus conventionally fractionated intensity modulated radiation therapy for localized prostate cancer	Conference abstract
Holmberg (2012)	Results from the Scandinavian Prostate Cancer Group Trial Number 4: a randomized controlled trial of radical prostatectomy versus watchful waiting	Discussion of SPCG-4 study
Horrill (2016)	Active surveillance in prostate cancer: a concept analysis	Study does not contain any relevant interventions
Hoskin (2007)	High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment	Study does not contain any relevant interventions

Short Title	Title	Reason for exclusion
	of prostate cancer: initial results of a randomised phase three trial	
Hoskin (2012)	Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer	Comparator in study does not match that specified in protocol Radiotherapy doses
Ilic (2017)	Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer	Duplicate reference
Ilic (2017)	Laparoscopic and robot-assisted vs open radical prostatectomy for the treatment of localized prostate cancer: A Cochrane systematic review	Comparator in study does not match that specified in protocol Prostatectomy only
Incrocci (2016)	Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial	Comparator in study does not match that specified in protocol Radiotherapy doses
Jereczek-Fossa (2009)	Systemic therapies for non-metastatic prostate cancer: review of the literature	Review article but not a systematic review
Kari (2017)	In localized prostate cancer, radical prostatectomy and observation did not differ for mortality at 13 years	Article commentary
Kim (2013)	A phase II study of hypofractionated proton therapy for prostate cancer	Study does not contain any relevant interventions Hypofractionated proton therapy
Kozuka (2017)	Acute and late complications after hypofractionated intensity modulated radiotherapy in prostate cancer	Not a relevant study design (not RCT)
Kuban (2008)	Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer	Study does not contain any relevant interventions
Lane (2010)	Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies	Study does not contain any relevant interventions
Lane (2014)	Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial	Protocol for ProtecT trial
Lee (2016)	Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer	Comparator in study does not match that specified in protocol Radiotherapy doses
Lennernäs (2015)	Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: a Swedish multicenter randomized trial with patient-reported outcomes	Does not contain a population of people with localised PCa Localised and locally advanced PCa

Short Title	Title	Reason for exclusion
Liu (2014)	Functional outcomes of transvesical single-site versus extraperitoneal laparoscopic radical prostatectomy for low-risk prostate cancer	Study does not contain any relevant interventions Study not reported in English
Manikandan (2015)	Combined HDR brachytherapy and external beam radiotherapy vs external beam radiotherapy alone by IMRT in localized prostate cancer; interim analysis of acute genitourinary and gastrointestinal toxicity and biological dose volume parameters from a prospective randomized control trial	Conference abstract
Martin (2016)	A randomised trial of a shorter radiation fractionation schedule for the treatment of localised prostate cancer (PC): profit-an OCOG/TROG intergroup study	Conference abstract
Martis (2007)	Retropubic versus perineal radical prostatectomy in early prostate cancer: eight-year experience	Study does not contain any relevant interventions
Marzi (2009)	Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer	Study does not contain any of the outcomes of interest
McDermott (2009)	Health-related quality-of-life effects of watchful waiting re-evaluated in SPCG-4	Article commentary
Merrick (2012)	20 Gy versus 44 Gy of supplemental external beam radiotherapy with palladium-103 for patients with greater risk disease: results of a prospective randomized trial	Study does not contain any relevant interventions Radiotherapy comparisons only
Michalski (2014)	Initial results of a phase 3 randomized study of high dose 3DCRT/IMRT versus standard dose 3D-CRT/IMRT in patients treated for localized prostate cancer (RTOG 0126)	Conference abstract
Michalski (2015)	A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer	Conference abstract
Monninkhof (2018)	Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial	Comparator in study does not match that specified in protocol Radiotherapy doses
Morgan (2016)	Hypofractionated versus conventionally fractionated radiotherapy for localized prostate cancer: systematic review and meta-analysis of the randomized trials in the dose-escalation era	Conference abstract
Morris (2015)	ASCENDERT*: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRTB) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer	Conference abstract
Morris (2015)	LDR brachytherapy is superior to 78 Gy of EBRT for unfavourable risk prostate cancer: the results of a randomized trial	Conference abstract
Morris (2015)	Low-dose-rate brachytherapy is superior to dose-escalated EBRT for unfavourable risk prostate	Conference abstract

Short Title	Title	Reason for exclusion
	cancer: the results of the ascende-Rt* randomized control trial	
Morris (2016)	Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer	Study does not contain any relevant interventions
Morton (2017)	Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy	Study does not contain any relevant interventions
Morton (2017)	Acute toxicity and early patient reported outcomes in a randomized phase II trial of high dose-rate brachytherapy as monotherapy in low and intermediate risk prostate cancer	Conference abstract
Murthy (2017)	Patient-reported outcome measures with prostate only or whole pelvic radiation therapy in high risk prostate cancer: a randomized controlled trial data	Conference abstract
Niazi (2017)	Phase 3 study of hypofractionated, dose escalation radiation therapy for high-risk adenocarcinoma of the prostate	Conference abstract
Norkus (2009)	A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response	Study does not contain any relevant interventions Types of radiotherapy only
Norkus (2013)	A randomized hypofractionation dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients	Comparator in study does not match that specified in protocol Radiotherapy doses
Peeters (2006)	Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy	Study does not contain any relevant interventions
Peinemann (2011)	Low-dose rate brachytherapy for men with localized prostate cancer	Study does not contain any relevant interventions
Peinemann (2012)	Permanent interstitial low-dose rate brachytherapy for patients with localized prostate cancer-a systematic review of randomized and non-randomized controlled clinical trials	Journal Supplement
Pollack (2013)	Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer	Study does not contain any of the outcomes of interest
Porpiglia (2012)	Pure or robotic-assisted laparoscopic prostatectomy? Results of a prospective randomized study	Conference abstract
Porpiglia (2013)	Randomised controlled trial comparing laparoscopic and robot-assisted radical prostatectomy	Study does not contain any relevant interventions

Short Title	Title	Reason for exclusion
Porpiglia (2016)	Five-year Outcomes for a Prospective Randomised Controlled Trial Comparing Laparoscopic and Robot-assisted Radical Prostatectomy	Study does not contain any relevant interventions Prostatectomy comparisons only
Porpiglia (2017)	Oncological and functional outcomes of laparoscopic versus robotassisted radical prostatectomy: five years results of a prospective randomised controlled trial	Conference abstract
Porpiglia (2017)	5 years follow-up of a prospective randomised controlled trial comparing laparoscopic versus robot-assisted radical prostatectomy: oncological and functional outcomes	Conference abstract
Prestidge (2016)	Initial report of NRG oncology/RTOG 0232: a phase 3 study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate-risk prostatic carcinoma	Conference abstract
Rodda (2015)	GU and GI toxicity in ASCENDE-RT*: a multicentre randomized trial of dose-escalated radiation for prostate cancer	Conference abstract
Rodda (2015)	Low-dose-rate prostate brachytherapy is superior to dose-escalated EBRT for unfavorable risk prostate cancer: the results of the ascende-RT randomized control trial	Conference abstract
Rodda (2015)	Toxicity outcomes in ascende-RT: a multicenter randomized trial of dose-escalation trial for prostate cancer	Conference abstract
Rodda (2015)	Quality of life outcomes: ascende-RT a multicenter randomized trial of radiation therapy for prostate cancer	Conference abstract
Rodda (2017)	ASCENDE-RT: an Analysis of Health-Related Quality of Life for a Randomized Trial Comparing Low-Dose-Rate Brachytherapy Boost With Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer	Study does not contain any relevant interventions
Saracino (2014)	Hypo versus conventionally fractionated 3dcrt for high risk prostate cancer: updated results of a randomized trial	Conference abstract
Schulz (2009)	Re: Prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian Prostate Cancer Group-4 randomized trial	Article commentary
Shaikh (2016)	Dosimetric and clinical predictors of long-term toxicity in patients undergoing hypofractionated prostate radiation therapy: results from a randomized phase 3 trial	Conference abstract
Shaikh (2017)	Long-Term Patient-Reported Outcomes From a Phase 3 Randomized Prospective Trial of Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer	Comparator in study does not match that specified in protocol Radiotherapy doses

Short Title	Title	Reason for exclusion
Smith (2017)	In localised prostate cancer, radical prostatectomy was associated with more sexual dysfunction and urinary incontinence than radiation or active surveillance	Article commentary
Stolzenburg (2010)	A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy	Study does not contain any relevant interventions
Syed (2017)	Current Management Strategy for Active Surveillance in Prostate Cancer	Review article but not a systematic review
Syndikus (2010)	Late gastrointestinal toxicity after dose-escalated conformal radiotherapy for early prostate cancer: results from the UK Medical Research Council RT01 trial (ISRCTN47772397)	Comparator in study does not match that specified in protocol Radiotherapy doses
Tang (2017)	Robotic vs. Retropubic radical prostatectomy in prostate cancer: A systematic review and an meta-analysis update	Comparator in study does not match that specified in protocol Prostatectomy only
Thompson (2009)	Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial	Study does not contain any relevant interventions Adjuvant radiotherapy after radical prostatectomy
Vargas (2018)	Hypofractionated Versus Standard Fractionated Proton-beam Therapy for Low-risk Prostate Cancer: Interim Results of a Randomized Trial PCG GU 002	Study does not contain any relevant interventions
Vogelius (2018)	Dose Response and Fractionation Sensitivity of Prostate Cancer After External Beam Radiation Therapy: A Meta-analysis of Randomized Trials	Study does not contain any relevant interventions
Wallis (2016)	Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis	Comparator in study does not match that specified in protocol No active surveillance
Watkins (2015)	Bowel and bladder function of men on a phase 3 randomized study of high versus standard dose of 3D-CRT/IMRT in patients treated for localized prostate cancer	Conference abstract
Watkins (2016)	NRG oncology/RTOG 0415, phase 3 noninferiority study comparing 2 fractionation schedules in patients with low-risk prostate cancer: prostate-specific quality of life results	Conference abstract
Widmark (2016)	Extreme hypofractionation versus conventionally fractionated radiotherapy for intermediate risk prostate cancer: early toxicity results from the scandinavian randomized phase III trial "HYPO-RT-PC"	Conference abstract
Wilkins (2015)	Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial	Comparator in study does not match that specified in protocol Radiotherapy doses

Short Title	Title	Reason for exclusion
Wilt (2012)	Implications of the prostate intervention versus observation trial (PIVOT)	Article commentary
Wilt (2017)	Radical prostatectomy versus observation for early prostate cancer: follow-up results of the prostate cancer intervention versus observation trial (PIVOT)	Conference abstract
Yaxley (2016)	Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study	Study does not contain any relevant interventions
Yeoh (2009)	Anorectal function after three- versus two-dimensional radiation therapy for carcinoma of the prostate	Study does not contain any relevant interventions
Yeoh (2011)	Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial	Study does not contain any relevant interventions
Yu (2016)	The Effectiveness of Intensity Modulated Radiation Therapy versus Three-Dimensional Radiation Therapy in Prostate Cancer: A Meta-Analysis of the Literatures	Comparator in study does not match that specified in protocol Prostatectomy only
Zhu (2014)	Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis	Comparator in study does not match that specified in protocol Radiotherapy only
Zhu (2015)	Laparoendoscopic single-site radical prostatectomy vs conventional laparoscopic radical prostatectomy: a prospective randomized clinical trial	Conference abstract

Economic studies

Short Title	Title	Reason for exclusion
Cooperberg et al 2013	Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis	Non-European study
Hayes et al 2013	Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis	Non-European study
Lao et al 2017	The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer	Non-European study
Sanyal et al 2016	Management of localized and advanced prostate cancer in Canada: A lifetime cost and quality-adjusted life-year analysis	Non-European study
Becerra et al 2016	Economic evaluation of treatments for patients with localized prostate cancer in Europe: a systematic review	Sys. Rev. reporting studies already identified
Dahm et al 2017	Similar prostate cancer and all-cause mortality in men with localised prostate cancer undergoing surgery or radiation therapy versus active monitoring at 10 years of follow-up	Commentary on ProtecT results

Short Title	Title	Reason for exclusion
Dorth et al 2018	Cost-Effectiveness of Primary Radiation Therapy Versus Radical Prostatectomy for Intermediate- to High-Risk Prostate Cancer	Non-European study
Gordon et al 2017	Cost-effectiveness analysis of multiparametric MRI with increased active surveillance for low-risk prostate cancer in Australia	Comparing different AS scenarios
Hayes et al 2010	Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis	Not a full economic evaluation
Hussein et al 2015	Point: Surgery is the most cost-effective option for prostate cancer needing treatment	Not a full economic evaluation
Perlroth et al 2012	An economic analysis of conservative management versus active treatment for men with localized prostate cancer	Not a full economic evaluation
Philippou et al 2014	Localised prostate cancer: clinical and cost-effectiveness of new and emerging technologies	Review reporting studies comparing robotic surgery vs laparoscopic
Winn et al 2016	Cost-Utility Analysis of Cancer Prevention, Treatment, and Control: A Systematic Review	Review addressing cancer studies in general not specific to PCa
Keegan et al 2013	Active Surveillance for Prostate Cancer Compared with Immediate Treatment: An Economic Analysis	Not a full economic evaluation

Appendix I – References

Clinical studies – Included

Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Swen-Olofersson A, Bratell S, Spångberg A, Busch C, Nordling S, Garmo H, Palmgren J, Adami H, Norlén BJ, and Johansson Je (2005) Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. The New England Journal of Medicine ,

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Bill-Axelson A, Garmo H, Holmberg L, Johansson Je, Adami Ho, Steineck G, Johansson E, and Rider Jr (2013) Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the Scandinavian Prostate Cancer Group-4 randomized clinical trial. European urology 64(6), 920-928

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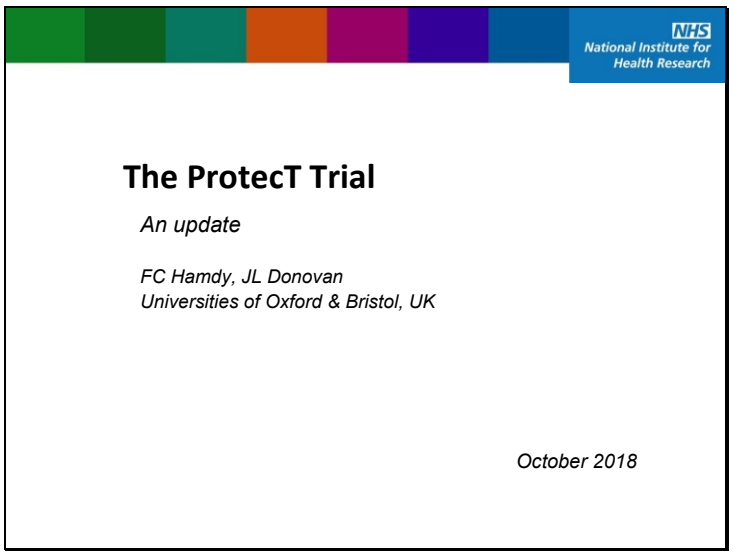
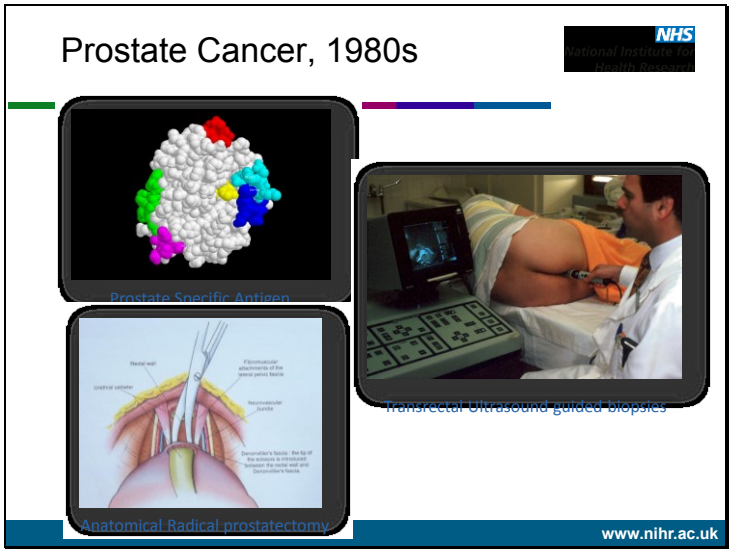
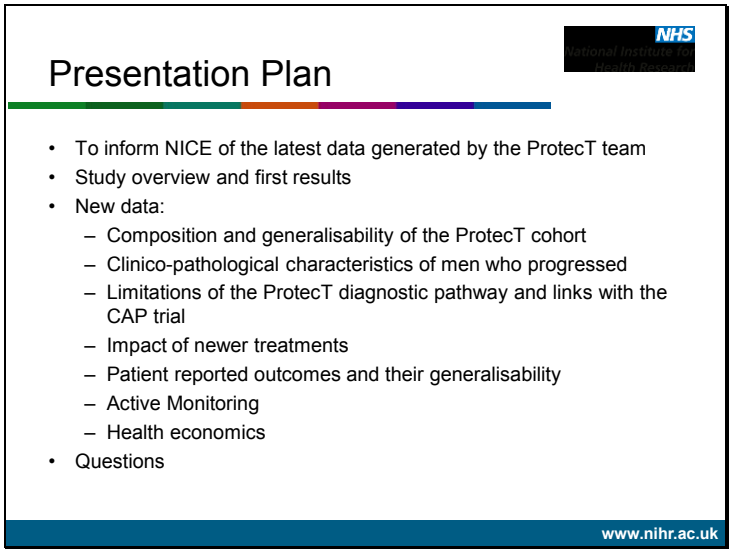
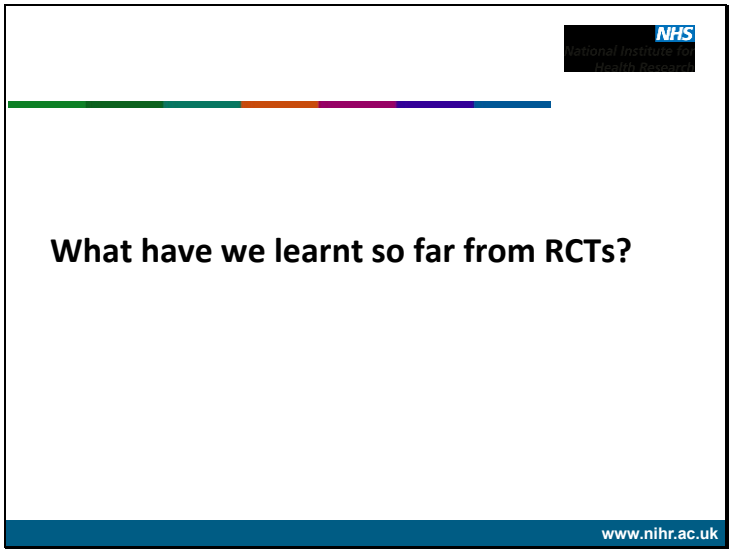
Appendix J – Clinical and economic evidence from ProtecT presentation



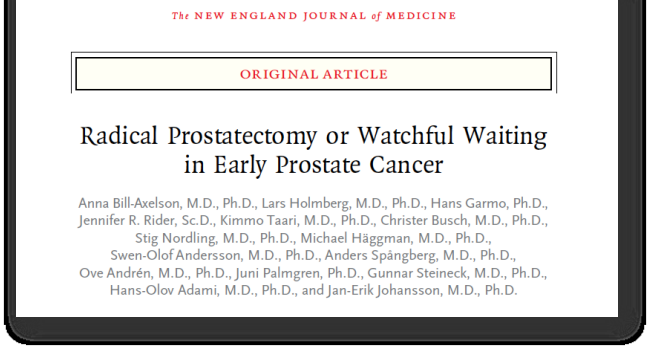

Prostate Cancer, 1980s
NHS
National Institute for Health Research
Prostate Specific Antigen
Transrectal Ultrasound guided biopsies
Anatomical Radical prostatectomy
www.nihr.ac.uk


Over-detection
Over-treatment
Under-treatment
(31 men die of prostate cancer
in the UK every day)


Presentation Plan
To inform NICE of the latest data generated by the ProtecT team
Study overview and first results
New data:
Composition and generalisability of the ProtecT cohort
Clinico-pathological characteristics of men who progressed
Limitations of the ProtecT diagnostic pathway and links with the CAP trial
Impact of newer treatments
Patient reported outcomes and their generalisability
Active Monitoring
Health economics
Questions
www.nihr.ac.uk


What have we learnt so far from RCTs?
www.nihr.ac.uk

Scandinavian RCT SPCG-4



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

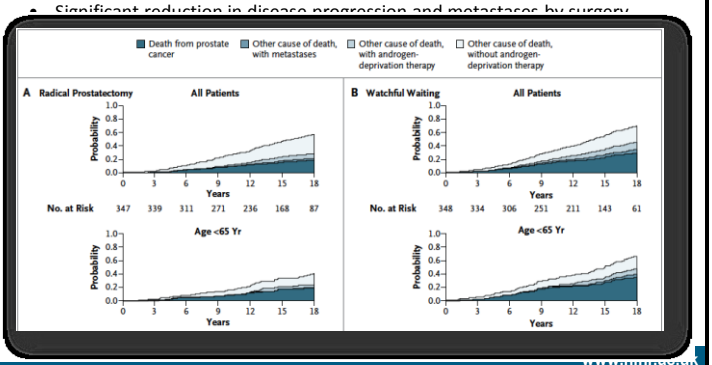
Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Rider, Sc.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Ove Andrén, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

N Engl J Med 2014;370:932-42.

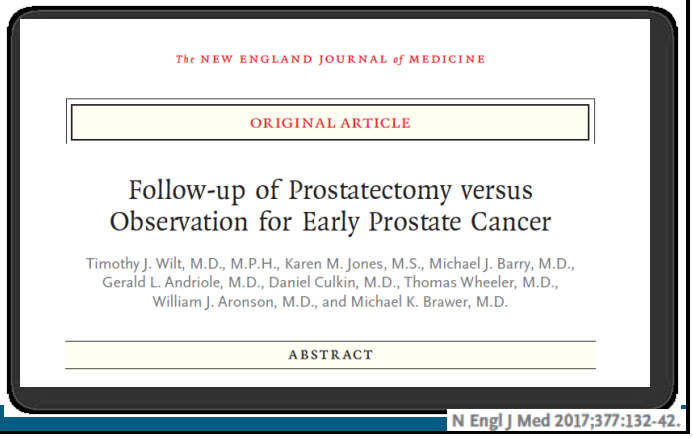
www.nihr.ac.uk

SPCG-4 Bill-Axelson et al, NEJM 2014

- Radical prostatectomy versus watchful waiting
- Significant reduction in disease-specific and all cause mortality by surgery
- Significant reduction in disease progression and metastases by surgery



US PIVOT RCT


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

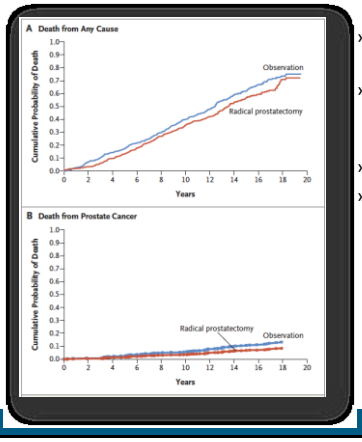
Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Karen M. Jones, M.S., Michael J. Barry, M.D., Gerald L. Andriole, M.D., Daniel Culkin, M.D., Thomas Wheeler, M.D., William J. Aronson, M.D., and Michael K. Brawer, M.D.

ABSTRACT

N Engl J Med 2017;377:132-42.

US PIVOT – Wilt et al, NEJM 2017



- RCT Radical prostatectomy versus observation
- No statistically significant benefit from surgery at 12 y median follow-up
- Low randomisation rate
- High level of co-morbidity in randomised cohort

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So what was missing from other RCTs

- PSA-detected cases (SPCG-4 & PIVOT)
- Cohorts are no longer contemporary (SPCG-4 & PIVOT)
- Active Surveillance ('watchful waiting'/observation used)
- Radiotherapy was not evaluated
- Competing morbidity high and randomisation low (PIVOT)
- Genomic diversity unknown, poor risk stratification
- 'Trade-off' insufficiently considered between oncological outcomes and patient-reported outcomes
- Effective but unacceptable over-detection and over-treatment by PSA testing/biopsy (ERSPC)

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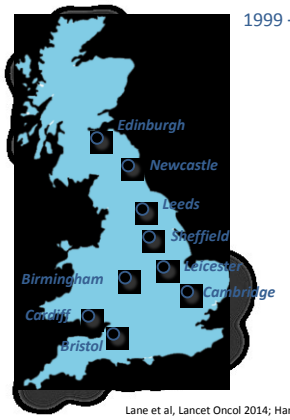
The ProtecT trial

(*Pro*state *te*sting for *c*ancer and *T*reatment)

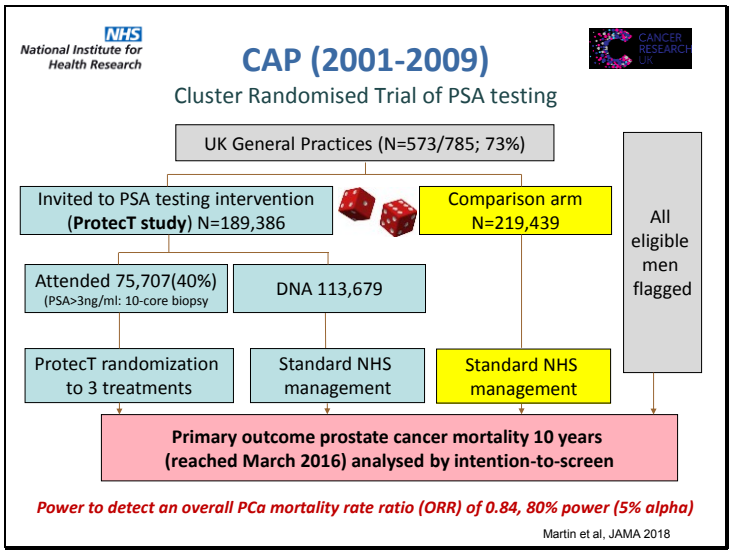
1999 – 2008

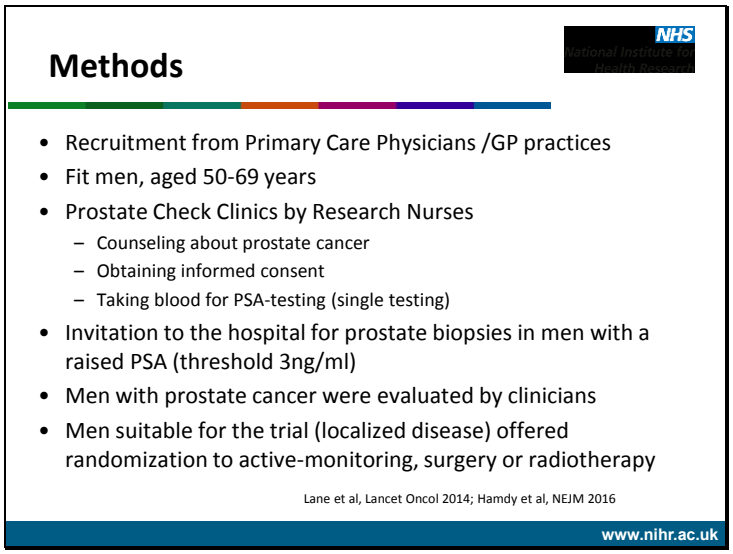


82,429 men PSA-tested
2,965 prostate cancers

To date, largest RCT comparing active monitoring, surgery and radiotherapy for PSA-detected localised prostate cancer
1ry endpoint: 10-y disease-specific mortality
2ry endpoints: all-cause mortality, progression, PROMs

Lane et al, Lancet Oncol 2014; Hamdy et al, NEJM 2016; Donovan et al, NEJM 2016; Johnston et al, Eur Urol 2016


NHS
National Institute for Health Research
CAP (2001-2009)
Cluster Randomised Trial of PSA testing
CANCER RESEARCH UK
UK General Practices (N=573/785; 73%)
Invited to PSA testing intervention (ProtecT study) N=189,386
Comparison arm N=219,439
All eligible men flagged
Attended 75,707(40%)
(PSA>3ng/ml: 10-core biopsy
DNA 113,679
ProtecT randomization to 3 treatments
Standard NHS management
Standard NHS management
Primary outcome prostate cancer mortality 10 years (reached March 2016) analysed by intention-to-screen
Power to detect an overall PCa mortality rate ratio (ORR) of 0.84, 80% power (5% alpha)
Martin et al, JAMA 2018


Methods
NHS
National Institute for Health Research
• Recruitment from Primary Care Physicians /GP practices
• Fit men, aged 50-69 years
• Prostate Check Clinics by Research Nurses
– Counseling about prostate cancer
– Obtaining informed consent
– Taking blood for PSA-testing (single testing)
• Invitation to the hospital for prostate biopsies in men with a raised PSA (threshold 3ng/ml)
• Men with prostate cancer were evaluated by clinicians
• Men suitable for the trial (localized disease) offered randomization to active-monitoring, surgery or radiotherapy
Lane et al, Lancet Oncol 2014; Hamdy et al, NEJM 2016
www.nihr.ac.uk

ProtecT study options

- **Active Monitoring** is a surveillance programme. Men were followed up with PSA-testing and re-evaluation of their disease. They were offered radical treatments if the disease appeared to progress. The purpose was to **avoid unnecessary treatment**, but to keep them in a '**window-of-curabillity**' if treatment became necessary.
  - Triggers (PSA rise >50%/12m; symptoms; changes in DRE; patient anxiety)
  - Investigations (imaging, repeat biopsies)
  - Change of management (suggestion of disease progression, patient/physician anxiety)
- **Surgery** was performed as radical prostatectomy with routine follow-up and additional treatments as necessary
- **Radiotherapy** with neoadjuvant androgen deprivation therapy and 74 gray 3-D conformal external beam, regular follow-up, and additional interventions as necessary

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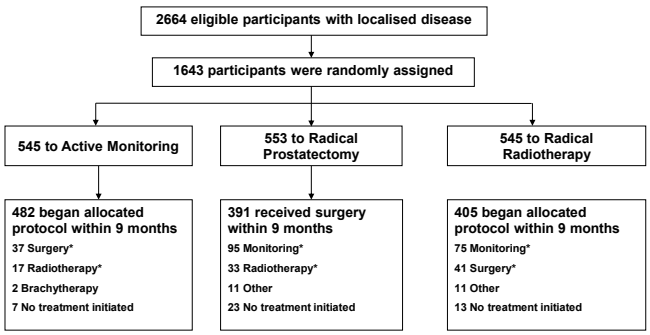
Study accrual (Consort Diagram)



Hamdy et al, NEJM 2016

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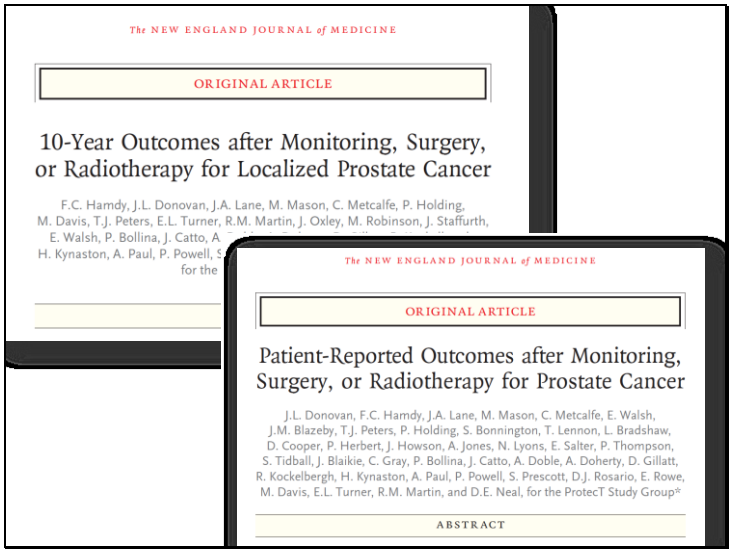
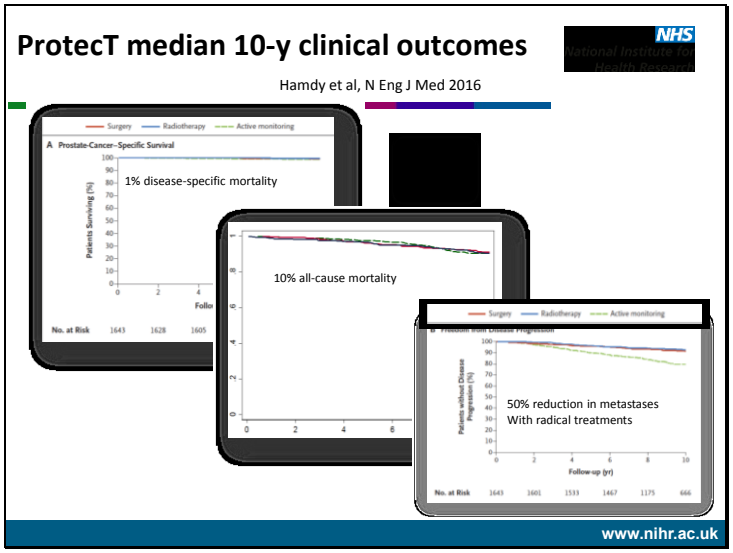
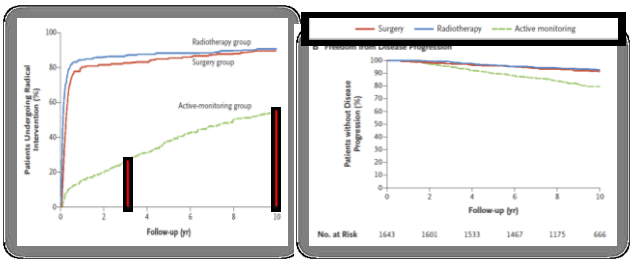

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer
F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A
H. Kynaston, A. Paul, P. Powell,
for the
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer
J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh, J.M. Blazeby, T.J. Peters, P. Holding, S. Bonnington, T. Lennon, L. Bradshaw, D. Cooper, P. Herbert, J. Howson, A. Jones, N. Lyons, E. Salter, P. Thompson, S. Tidball, J. Blaikie, C. Gray, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, M. Davis, E.L. Turner, R.M. Martin, and D.E. Neal, for the ProtecT Study Group*
ABSTRACT


ProtecT median 10-y clinical outcomes
NHS
National Institute for Health Research
Hamdy et al, N Eng J Med 2016
1% disease-specific mortality
10% all-cause mortality
50% reduction in metastases
With radical treatments
www.nihr.ac.uk

ProtecT patients receiving treatments

Hamdy et al, N Eng J Med 2016



- More than half had received treatment by 10 years
- Approximately 80% of men on active monitoring had no sign of progression
- 44% of men on active monitoring avoided treatment

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ProtecT numbers needed to treat

- To prevent one man from developing metastases:
  - 27 RPs
  - 33 radiation
- To prevent one man from developing clinical progression
  - 9 RPs or radiation

Hamdy et al, NEJM 2016

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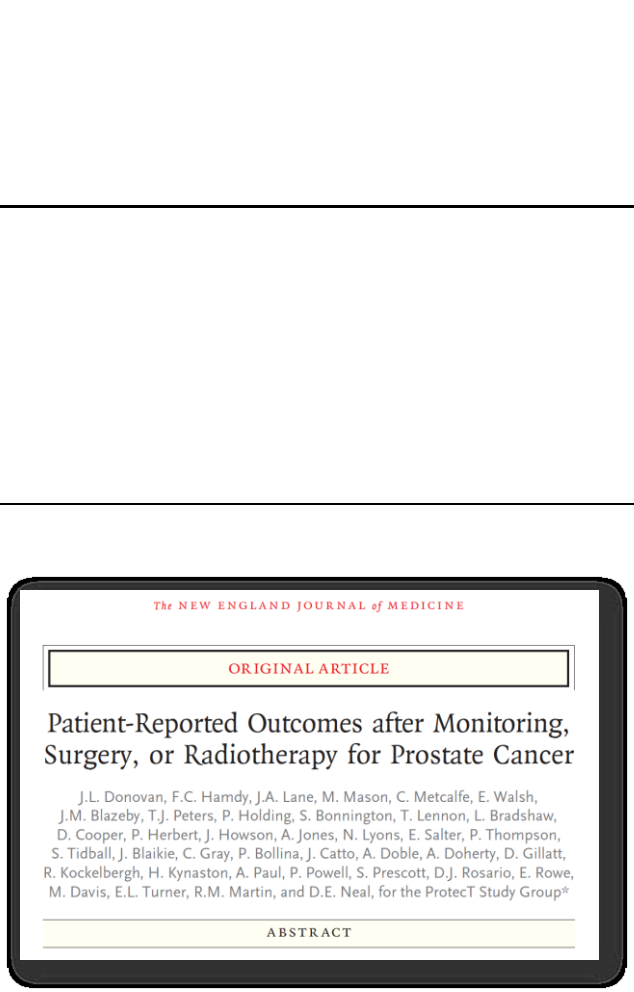
ProtecT Patient reported outcomes (PROMs)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

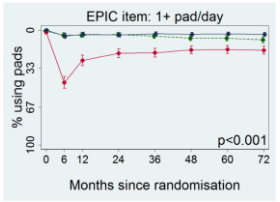
Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

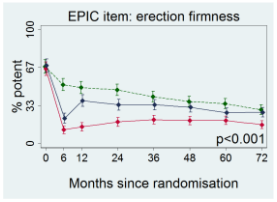
J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh, J.M. Blazeby, T.J. Peters, P. Holding, S. Bonnington, T. Lennon, L. Bradshaw, D. Cooper, P. Herbert, J. Howson, A. Jones, N. Lyons, E. Salter, P. Thompson, S. Tidball, J. Blaikie, C. Gray, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, M. Davis, E.L. Turner, R.M. Martin, and D.E. Neal, for the ProtecT Study Group*

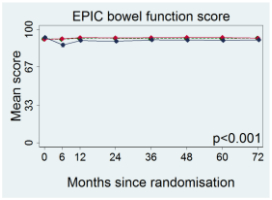
ABSTRACT

Functional profiles

Donovan et al, NEJM 2016







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What have we learnt from the ProtecT results at 10-y median follow-up?

- The risk of death from prostate cancer over an average of 10 years is very low – 1% - most PSA-detected clinically localised prostate cancers grow slowly
- Surgery and radiotherapy reduce the risk of cancer progression and spread, but cause bothersome urinary, sexual and bowel symptoms
- Staying on active monitoring avoids treatment side-effects, but there is an increased risk of cancer progression and spread, and some symptoms increase gradually over time
- Longer follow up (5-10 years) is essential to provide data about the 'trade-off' between the shorter-term effects of radical treatments, the risks of disease progression and if any, longer-term benefits in cancer cure and survival

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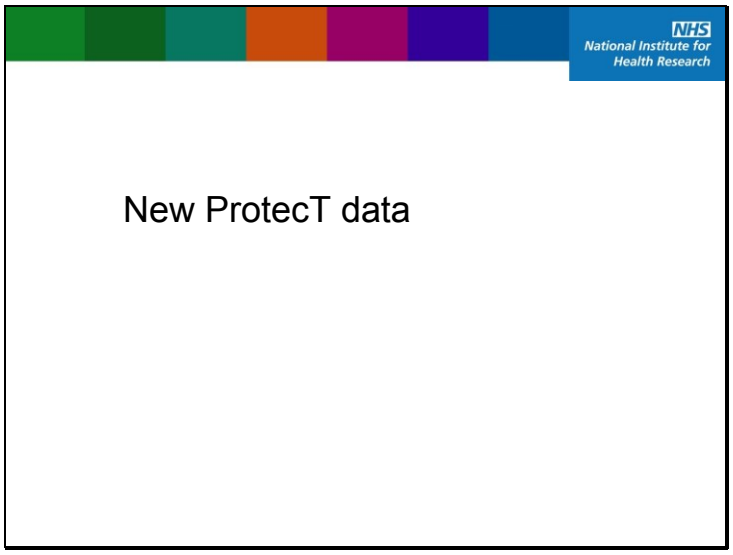
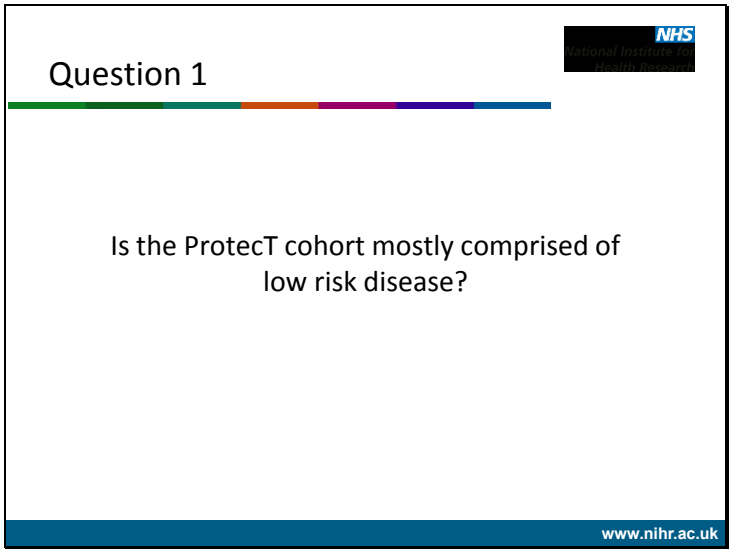

NHS
National Institute for Health Research
New ProtecT data


NHS
Question 1
Is the ProtecT cohort mostly comprised of low risk disease?
www.nihr.ac.uk

Baseline data suggest ProtecT cohort mostly low risk men

Lane et al, Lancet Oncol, 2014

	Active monitoring (n=545)	Radiotherapy (n=545)	Radical prostatectomy (n=553)
Age at invitation (years)			
49–54	58 (11%)	62 (11%)	69 (12%)
55–59	140 (26%)	141 (26%)	137 (25%)
60–64	184 (34%)	176 (32%)	172 (31%)
65–69	163 (30%)	166 (30%)	175 (32%)
Median age (range)	62 (50–69)	62 (49–69)*	62 (50–69)
PSA (µg/L)			
3·0–5·9	373 (68%)	373 (68%)	371 (67%)
6·0–9·9	116 (21%)	121 (22%)	123 (22%)
≥10·0	56 (10%)	51 (9%)	59 (11%)
Median PSA (range; µg/L)	4·6 (3·0–20·9)†	4·6 (3·0–18·8)	4·7 (3·0–18·4)
Gleason score			
[redacted]			
7	111 (20%)	108 (20%)	120 (22%)
8–10	13 (2%)	14 (3%)	10 (2%)
Missing	0	0	1 (<1%)
Clinical stage			
[redacted]			
T2	135 (25%)	116 (21%)	143 (26%)

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ProtecT randomised cohort risk categories according to D'Amico's classification (new)

- 133 (8.1%) of 1,643 randomised men could not be evaluated
- Among 1,510 evaluated:
  - 1,021 (67.6%) were low risk
  - 489 (32.4%) were intermediate or high risk
- Around two-thirds rather than three-quarters were low risk according to the D'Amico classification

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Question 2

Are the treatments in ProtecT outdated?

Do more modern therapies have better outcomes?

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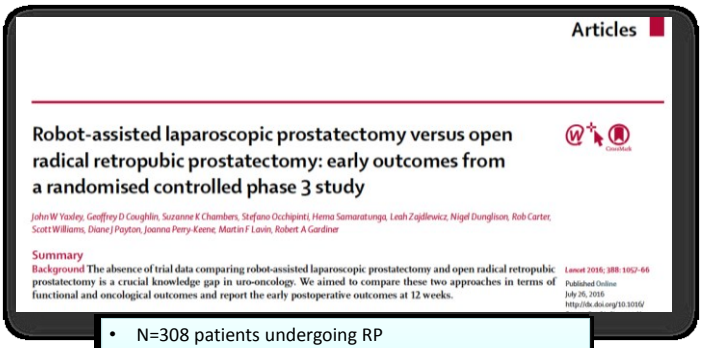
Is 'new' surgery better than old?



Articles

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study

John W Yaxley, Geoffrey D Coughlin, Suzanne K Chambers, Stefano Occhipinti, Hema Samaratunga, Leah Zajdlewicz, Nigel Dunglison, Rob Carter, Scott Williams, Diane J Payton, Joanna Perry-Keene, Martin F Lavin, Robert A Gardiner

Summary

Background The absence of trial data comparing robot-assisted laparoscopic prostatectomy and open radical retropubic prostatectomy is a crucial knowledge gap in uro-oncology. We aimed to compare these two approaches in terms of functional and oncological outcomes and report the early postoperative outcomes at 12 weeks.

Lancet 2016; 388: 1057–66

Published Online July 26, 2016

- N=308 patients undergoing RP
- Randomised to open or robot-assisted prostatectomy
- 12-week oncological and patient-reported outcomes:
  - No significant differences between both techniques

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Question 3

How generalizable are ProtecT PROMs to new treatments?

Robotic surgery, IMRT, brachytherapy, active surveillance?

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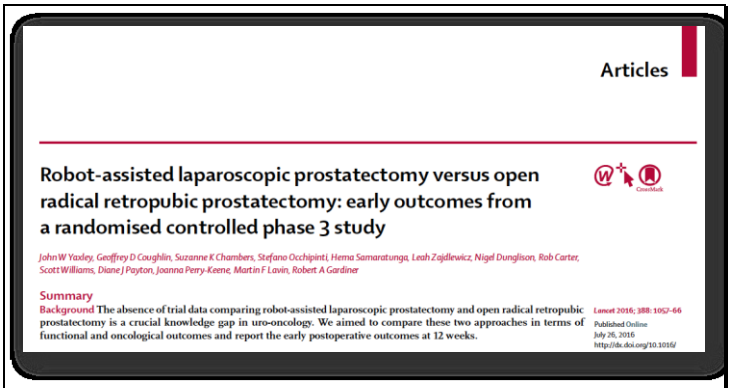

Articles

Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study

John W Yaxley, Geoffrey D Coughlin, Suzanne K Chambers, Stefano Occhipinti, Hema Samaratunga, Leah Zajdlewicz, Nigel Dunglison, Rob Carter, Scott Williams, Diane J Payton, Joanna Perry-Keene, Martin F Lavin, Robert A Gardiner

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Lancet 2016; 388: 1057–66
Published Online
July 26, 2016
http://dx.doi.org/10.1016/

Robot-assisted and open surgery have:

- Very similar functional outcomes (erectile function and urinary incontinence)

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Two studies on PROMs after contemporary treatments

JAMA | Original Investigation

Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years

Daniel A. Barocas, MD, MPH; JoAnn Alvarez, MA; Matthew J. Resnick, MD, MPH; Tatsuki Koyama, PhD; Karen E. Hoffman, MD, MHSc, MPH; Mark D. Tyson, MD; Ralph Conwill, BS; Dan McCollum, BS; Matthew R. Cooperberg, MD, MPH; Michael Goodman, MD, MPH; Sheldon Greenfield, MD; Ann S. Hamilton, PhD, MA; Mia Hashibe, PhD, MPH; Sherrie H. Kaplan, PhD, MS, MPH; Lisa E. Paddock, PhD, MPH; Antoinette M. Stroup, PhD; Xiao-Cheng Wu, MD, MPH; David F. Penson, MD, MPH

IMPORTANCE Understanding the adverse effects of contemporary approaches to localized prostate cancer treatment could inform shared decision making.

OBJECTIVE To compare functional outcomes and adverse effects associated with radical prostatectomy, external beam radiation therapy (EBRT), and active surveillance.

DESIGN, SETTING, AND PARTICIPANTS Prospective, population-based, cohort study involving 2550 men (≤80 years) diagnosed in 2011-2012 with clinical stage cT1-2, localized prostate cancer, with prostate-specific antigen levels less than 50 ng/mL, and enrolled within 6 months of diagnosis.

Editorial page 1121
Related article page 1141
Supplemental content

Barocas et al, JAMA 2017

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Two studies on PROMS after contemporary treatments

JAMA | Original Investigation

Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer

Ronald C. Chen, MD, MPH; Ramsankar Basak, PhD; Anne-Marie Meyer, PhD; Tzy-Mey Kuo, PhD; William R. Carpenter, PhD; Robert P. Agans, PhD; James R. Broughman, BS; Bryce B. Reeve, PhD; Matthew E. Nielsen, MD, MS; Deborah S. Usinger, BA; Kayni C. Spearman, BS; Sarah Walden, BA; Dianne Kaleel, BA; Mary Anderson, MPH; Til Stürmer, MD, PhD; Paul A. Godley, MD, PhD

IMPORTANCE Patients diagnosed with localized prostate cancer have to decide among treatment strategies that may differ in their likelihood of adverse effects.

OBJECTIVE To compare quality of life (QOL) after radical prostatectomy, external beam radiotherapy, and brachytherapy vs active surveillance.

DESIGN, SETTING, AND PARTICIPANTS Population-based prospective cohort of 1141 men (57% participation among eligible men) with newly diagnosed prostate cancer were enrolled from January 2011 through June 2013 in collaboration with the North Carolina Central Cancer Registry. Median time from diagnosis to enrollment was 5 weeks, and all men were enrolled with written informed consent prior to treatment. Final follow-up date for current analysis was September 9, 2015.

Editorial page 1121
Related article page 1126
Supplemental content
CME Quiz at jamanetworkcme.com

Chen et al, JAMA 2017

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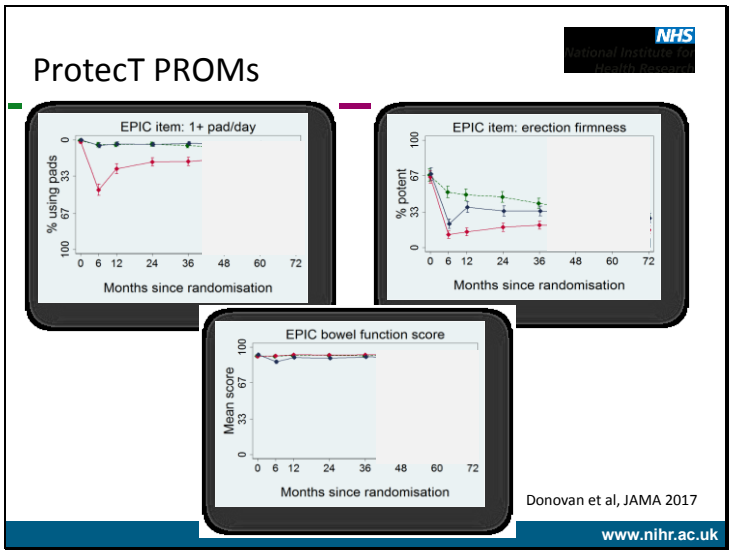
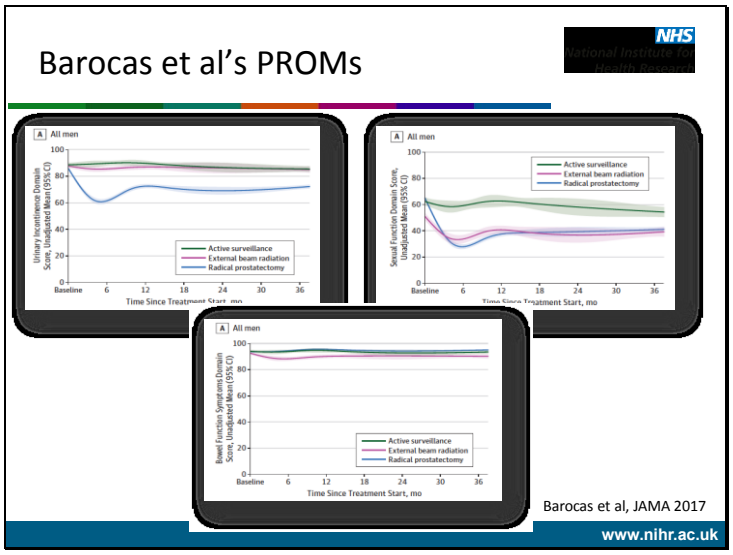
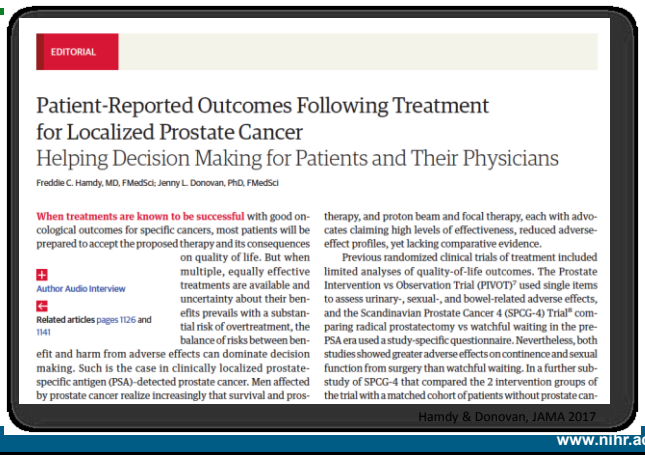

ProtecT PROMs
EPIC item: 1+ pad/day
% using pads
Months since randomisation
EPIC item: erection firmness
% potent
Months since randomisation
EPIC bowel function score
Mean score
Months since randomisation
Donovan et al, JAMA 2017
www.nihr.ac.uk


Barocas et al's PROMs
All men
Active surveillance
External beam radiation
Radical prostatectomy
Time Since Treatment Start, mo
Barocas et al, JAMA 2017
www.nihr.ac.uk

Editorial



EDITORIAL

Patient-Reported Outcomes Following Treatment for Localized Prostate Cancer

Helping Decision Making for Patients and Their Physicians

Freddie C. Hamdy, MD, FMedSci; Jenny L. Donovan, PhD, FMedSci

When treatments are known to be successful with good oncological outcomes for specific cancers, most patients will be prepared to accept the proposed therapy and its consequences on quality of life. But when multiple, equally effective treatments are available and uncertainty about their benefits prevails with a substantial risk of overtreatment, the balance of risks between benefit and harm from adverse effects can dominate decision making. Such is the case in clinically localized prostate-specific antigen (PSA)-detected prostate cancer. Men affected by prostate cancer realize increasingly that survival and prostherapy, and proton beam and focal therapy, each with advocates claiming high levels of effectiveness, reduced adverse-effect profiles, yet lacking comparative evidence.

Previous randomized clinical trials of treatment included limited analyses of quality-of-life outcomes. The Prostate Intervention vs Observation Trial (PIVOT)[2] used single items to assess urinary-, sexual-, and bowel-related adverse effects, and the Scandinavian Prostate Cancer 4 (SPCG-4) Trial[3] comparing radical prostatectomy vs watchful waiting in the pre-PSA era used a study-specific questionnaire. Nevertheless, both studies showed greater adverse effects on continence and sexual function from surgery than watchful waiting. In a further substudy of SPCG-4 that compared the 2 intervention groups of the trial with a matched cohort of patients without prostate can-

Author Audio Interview

Related articles pages 1126 and 1141

Hamdy & Donovan, JAMA 2017

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Question 2

What about men with PSA-detected advanced and high risk disease?

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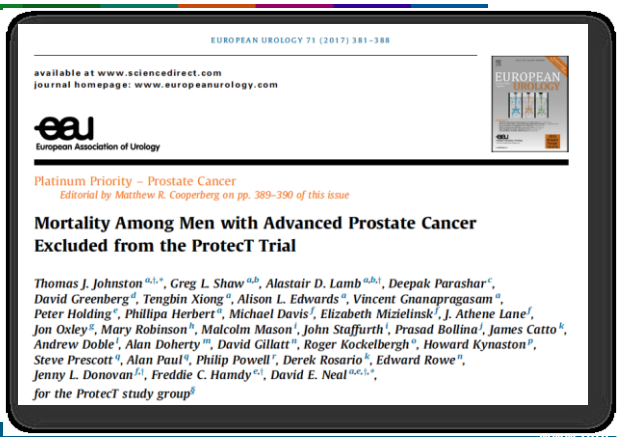
High-risk/advanced Prostate Cancer



EUROPEAN UROLOGY 71 (2017) 381–388

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

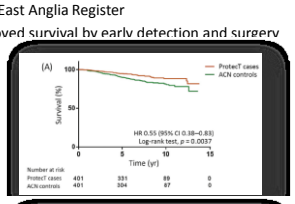
Platinum Priority – Prostate Cancer
Editorial by Matthew R. Cooperberg on pp. 389–390 of this issue

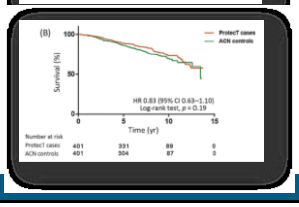
Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial

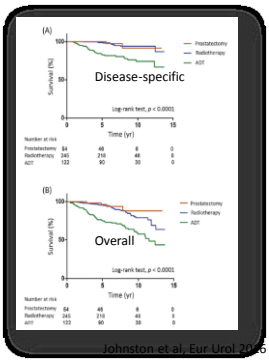
Thomas J. Johnston [a,†,], Greg L. Shaw [a,b], Alastair D. Lamb [a,b,†], Deepak Parashar [c], David Greenberg [d], Tengbin Xiong [a], Alison L. Edwards [a], Vincent Gnanapragasam [a], Peter Holding [e], Phillipa Herbert [a], Michael Davis [f], Elizabeth Mizielinsk [f], J. Athene Lane [f], Jon Oxley [g], Mary Robinson [h], Malcolm Mason [i], John Staffurth [i], Prasad Bollina [j], James Catto [k], Andrew Doble [l], Alan Doherty [m], David Gillatt [n], Roger Kockelbergh [o], Howard Kynaston [p], Steve Prescott [q], Alan Paul [q], Philip Powell [r], Derek Rosario [k], Edward Rowe [n], Jenny L. Donovan [f,†], Freddie C. Hamdy [e,†], David E. Neal [a,e,†,*], for the ProtecT study group [§]*

Advanced cases excluded from ProtecT

- Non-randomised comparison with age-matched patients from East Anglia Register
- Improved survival by early detection and surgery







Johnston et al, Eur Urol 2015

ProtecT 'new' messages

- ProtecT randomised cohort represents low and intermediate risk clinically localised disease
- Risk stratification at diagnosis is inaccurate, and may be improved by pre-biopsy imaging, targeting and genomics
- Results from ProtecT are generalisable, and there is a place for each of the three treatment options in disease management
- Longer follow up (15-20 years) is essential in ProtecT to provide data about the 'trade-off' between the shorter-term effects of radical treatments, the risks of disease progression and if any, the long-term benefits in cancer cure and survival

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Economic evaluation of ProtecT trial management strategies

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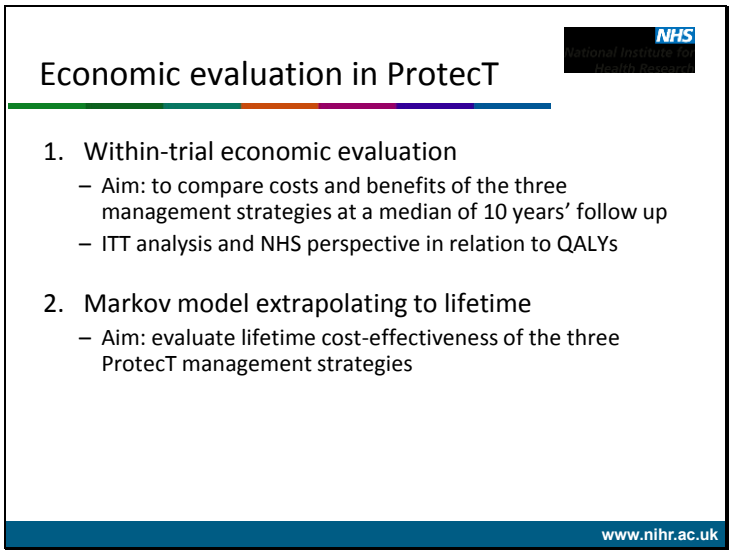
Economic evaluation in ProtecT
1. Within-trial economic evaluation
– Aim: to compare costs and benefits of the three management strategies at a median of 10 years' follow up
– ITT analysis and NHS perspective in relation to QALYs
2. Markov model extrapolating to lifetime
– Aim: evaluate lifetime cost-effectiveness of the three ProtecT management strategies
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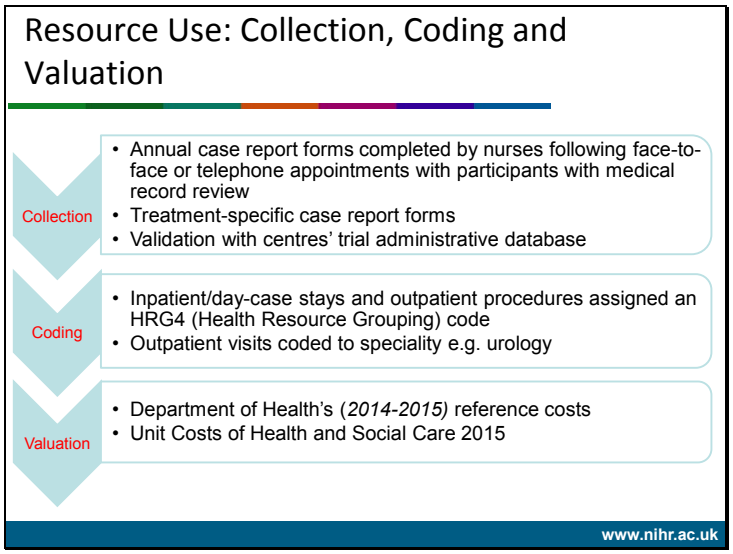
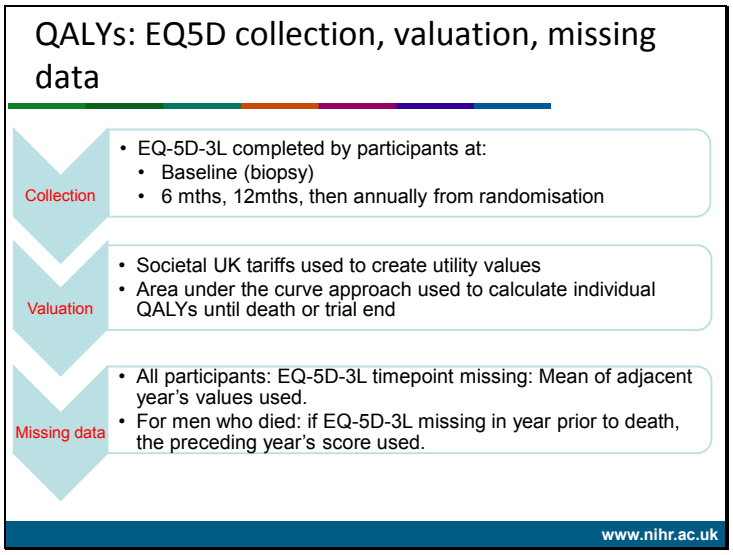

Resource Use: Collection, Coding and Valuation
Collection
• Annual case report forms completed by nurses following face-to-face or telephone appointments with participants with medical record review
• Treatment-specific case report forms
• Validation with centres' trial administrative database
Coding
• Inpatient/day-case stays and outpatient procedures assigned an HRG4 (Health Resource Grouping) code
• Outpatient visits coded to speciality e.g. urology
Valuation
• Department of Health's (*2014-2015)* reference costs
• Unit Costs of Health and Social Care 2015
www.nihr.ac.uk


QALYs: EQ5D collection, valuation, missing data
Collection
• EQ-5D-3L completed by participants at:
• Baseline (biopsy)
• 6 mths, 12mths, then annually from randomisation
Valuation
• Societal UK tariffs used to create utility values
• Area under the curve approach used to calculate individual QALYs until death or trial end
Missing data
• All participants: EQ-5D-3L timepoint missing: Mean of adjacent year's values used.
• For men who died: if EQ-5D-3L missing in year prior to death, the preceding year's score used.
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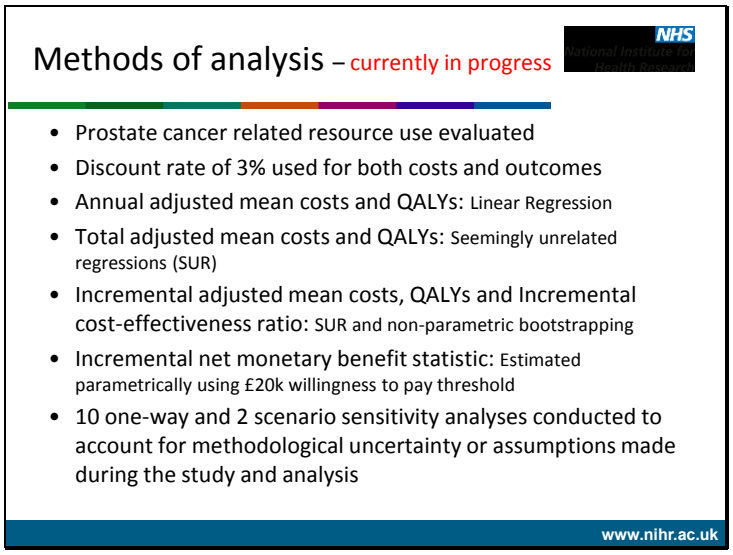
Methods of analysis – currently in progress
NHS
• Prostate cancer related resource use evaluated
• Discount rate of 3% used for both costs and outcomes
• Annual adjusted mean costs and QALYs: Linear Regression
• Total adjusted mean costs and QALYs: Seemingly unrelated regressions (SUR)
• Incremental adjusted mean costs, QALYs and Incremental cost-effectiveness ratio: SUR and non-parametric bootstrapping
• Incremental net monetary benefit statistic: Estimated parametrically using £20k willingness to pay threshold
• 10 one-way and 2 scenario sensitivity analyses conducted to account for methodological uncertainty or assumptions made during the study and analysis
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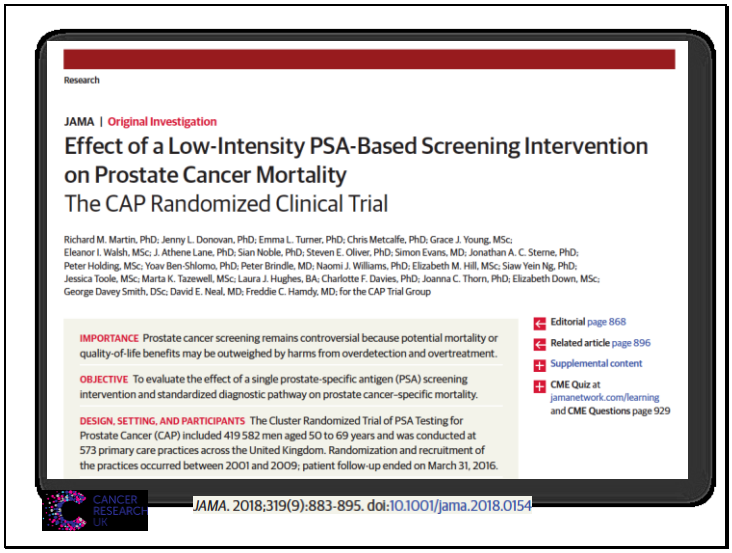
NHS National Institute for Health Research

CAP Trial first results



Research

JAMA | Original Investigation

Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality

The CAP Randomized Clinical Trial

Richard M. Martin, PhD; Jenny L. Donovan, PhD; Emma L. Turner, PhD; Chris Metcalfe, PhD; Grace J. Young, MSc; Eleanor I. Walsh, MSc; J. Athene Lane, PhD; Sian Noble, PhD; Steven E. Oliver, PhD; Simon Evans, MD; Jonathan A. C. Sterne, PhD; Peter Holding, MSc; Yoav Ben-Shlomo, PhD; Peter Brindle, MD; Naomi J. Williams, PhD; Elizabeth M. Hill, MSc; Siaw Yein Ng, PhD; Jessica Toole, MSc; Marta K. Tazewell, MSc; Laura J. Hughes, BA; Charlotte F. Davies, PhD; Joanna C. Thorn, PhD; Elizabeth Down, MSc; George Davey Smith, DSc; David E. Neal, MD; Freddie C. Hamdy, MD; for the CAP Trial Group

IMPORTANCE Prostate cancer screening remains controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment.

OBJECTIVE To evaluate the effect of a single prostate-specific antigen (PSA) screening intervention and standardized diagnostic pathway on prostate cancer–specific mortality.

DESIGN, SETTING, AND PARTICIPANTS The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419 582 men aged 50 to 69 years and was conducted at 573 primary care practices across the United Kingdom. Randomization and recruitment of the practices occurred between 2001 and 2009; patient follow-up ended on March 31, 2016.

Editorial page 868

Related article page 896

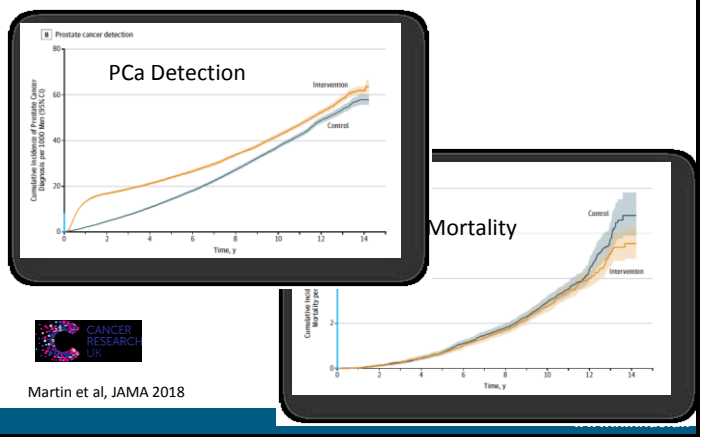
Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 929

CANCER RESEARCH UK

JAMA. 2018;319(9):883-895. doi:10.1001/jama.2018.0154

Outcomes at 10-y median follow-up



Martin et al, JAMA 2018

Missed lethal cancers in the CAP trial intervention group (ProtecT)

- Of 549 men who died in the intervention-group
  - Attended a screening appointment: 188 (34%)
- Of the 188 attendees who died, 129 (69%) had not been identified by a PSA test
  - Not received a PSA test: n = 42
  - Eligible men not receiving a biopsy: n = 15
  - PSA level < 3ng/ml: n = 68
  - Benign prostate biopsy result: n = 4

Martin et al, JAMA 2018

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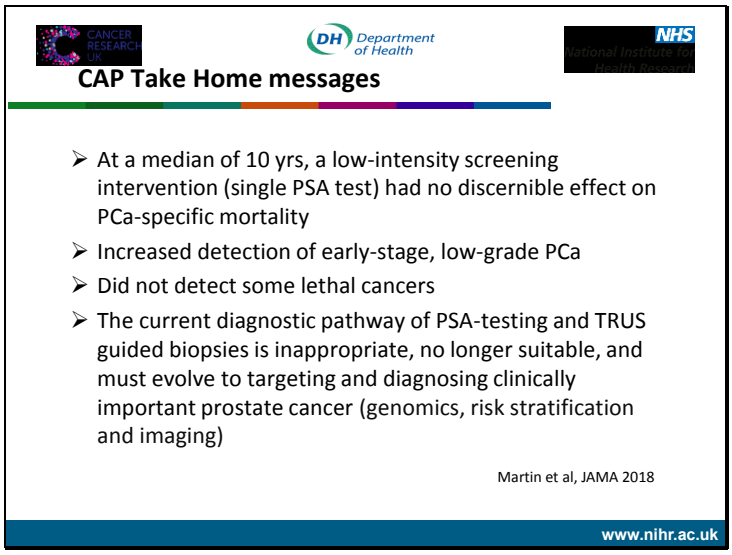
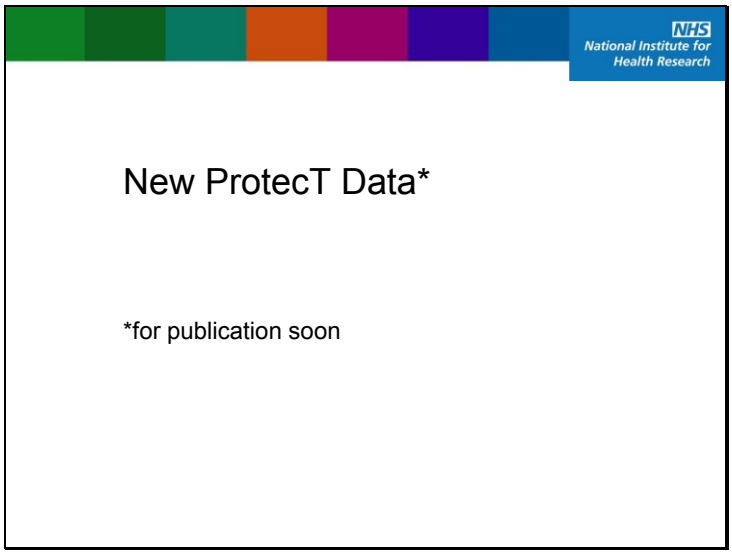
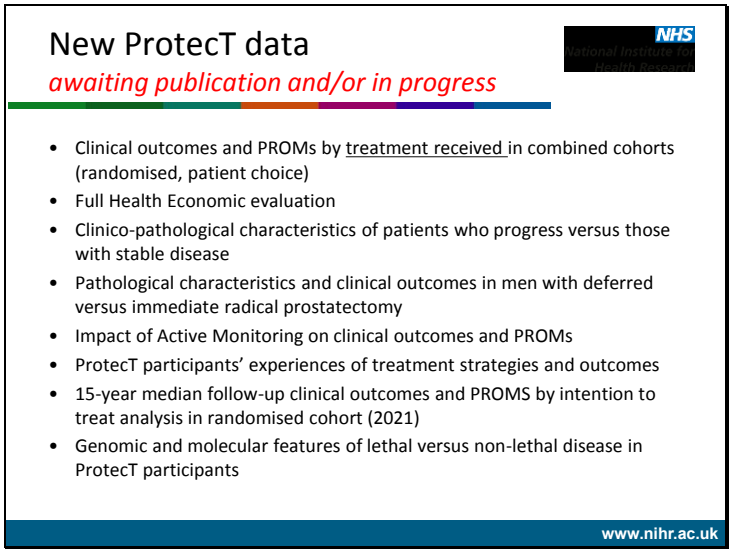

CANCER RESEARCH UK
DH Department of Health
NHS National Institute for Health Research
CAP Take Home messages
At a median of 10 yrs, a low-intensity screening intervention (single PSA test) had no discernible effect on PCa-specific mortality
Increased detection of early-stage, low-grade PCa
Did not detect some lethal cancers
The current diagnostic pathway of PSA-testing and TRUS guided biopsies is inappropriate, no longer suitable, and must evolve to targeting and diagnosing clinically important prostate cancer (genomics, risk stratification and imaging)
Martin et al, JAMA 2018
www.nihr.ac.uk


NHS National Institute for Health Research
New ProtecT Data*
*for publication soon


New ProtecT data
awaiting publication and/or in progress
NHS
National Institute for Health Research
• Clinical outcomes and PROMs by treatment received in combined cohorts (randomised, patient choice)
• Full Health Economic evaluation
• Clinico-pathological characteristics of patients who progress versus those with stable disease
• Pathological characteristics and clinical outcomes in men with deferred versus immediate radical prostatectomy
• Impact of Active Monitoring on clinical outcomes and PROMs
• ProtecT participants' experiences of treatment strategies and outcomes
• 15-year median follow-up clinical outcomes and PROMS by intention to treat analysis in randomised cohort (2021)
• Genomic and molecular features of lethal versus non-lethal disease in ProtecT participants
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