National Institute for Health and Care Excellence

FINAL

Prostate cancer: diagnosis and management

[C] Evidence review for radical radiotherapy

NICE guideline NG131

Evidence reviews

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These evidence reviews were developed by the NICE Guideline Updates Team

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Radical radiotherapy

Review question

RQ4: What is the optimal dose and fractionation schedule for people with localised prostate cancer (T1b–T3a N0 M0) who are treated with radical radiotherapy?

Introduction

The aim of the review was to determine the optimal dose of radiotherapy for people with localised prostate cancer. This question was identified for update during the 2016 exceptional surveillance review. The update will determine the optimal dose and fractionation schedule for people with localised prostate cancer (T1b–T3a N0 M0) who are treated with radical radiotherapy.

The protocol defined the comparator of interest as 'conventional external beam fractionation'. For the purposes of this review, the committee defined conventional fractionation as 70 – 80 Gy in 2 Gy fractions or similar. Therefore, studies were included providing there was a conventional fractionation arm giving between 70 and 80 Gy total dose of external beam radiotherapy in 1.8–2.0 Gy fractions.

This review aims to determine the effectiveness of:

1) Hypofractionated external beam radiotherapy versus conventional external beam radiotherapy.
2) Brachytherapy, as a monotherapy or as a boost in combination with external beam radiotherapy, versus conventional external beam radiotherapy.

Image-guided, intensity-modulated radiotherapy (IG-IMRT) is a form of external beam radiotherapy - guided by imaging techniques to ensure accuracy – that allows the safe and precise delivery of radiation to a target area(s) to kill cancer cells. Conventionally fractionated radiotherapy involves around 7.5 weeks of treatment. Hypofractionated radiotherapy is a recent advancement in the delivery of external beam radiotherapy, allowing the delivery of higher dose-per-fraction treatment, condensing the length of treatment into roughly 4 weeks.

Brachytherapy involves the placement of a sealed radiation source into the prostate gland, either in the form of radioactive seeds (low-dose-rate brachytherapy) or thin tubes (high-dose-rate brachytherapy), both of which supply the prostate with radioactive material. Brachytherapy requires just one or two days in hospital. 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 for radical radiotherapy

Population	People with localised prostate cancer (T1b–T3a N0 M0)
Interventions	• Hypofractionated radiotherapy to the prostate • Brachytherapy plus external beam radiotherapy • Brachytherapy alone[1]
Comparator	Conventional fractionation with external beam therapy
Outcomes	• Prostate cancer-specific mortality • Overall survival

[1] Brachytherapy alone was added to the list of interventions at the advice of the committee

Population	People with localised prostate cancer (T1b–T3a N0 M0)
	• Metastasis-free survival • 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 ○ Biochemical relapse-free survival (using the Phoenix definition: a rise of 2 ng/mL or more above the prostate-specific antigen (PSA) nadir after external beam radiotherapy (EBRT) with or without hormonal therapy, dated 'at call') (Roach 2006) ○ 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. We will use individual protocol-based definitions. • Health-related quality of life - for example: ○ European Organisation for Research and Treatment of Cancer quality of life, ○ EPIC instrument

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A and the methods section Appendix B.

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

Protocol deviation

In a deviation from the review protocol, the committee decided that studies looking at brachytherapy alone should also be added to the interventions looked at. Since they represent a deviation from the protocol, brachytherapy alone studies are downgraded by one for indirectness during GRADE assessment.

The following steps were taken in the present analysis to ensure consistency:

- There was variability between included studies in the reporting of gastrointestinal (GI) and genitourinary (GU) toxicity, therefore, the present analysis focused on the frequency of participants reporting maximum toxicity of grade 2 or greater, according to the Radiation Oncology/Toxicity Grading (RTOG), at any point during follow-up. For studies reporting multiple measures of toxicity, RTOG was prioritised.
- Acute toxicity was defined as toxicity following completion of radiotherapy up until 18 weeks. Originally, a 3-month limit was used; however a key trial (CHHiP) used an acute period of 18 weeks.

- Late toxicity was defined as toxicity occurring from a minimum of 90 days after radiotherapy up to a follow-up of typically 5-years (see forest plots for length of follow-up for each study).
- Several of the trials included in the review have multiple papers reporting outcomes. Where 2 or more papers reported on the same outcome for a single trial, the paper with the longer follow-up was used. This ensured that data were not double-reported and that longer follow-up times were prioritised.
- Biochemical failure was defined according to Phoenix consensus guideline (PSA concentration greater than nadir plus 2 ng/mL, with nadir PSA being the lowest recorded PSA any time following commencement of radiation therapy or androgen deprivation therapy).
- Biochemical–clinical failure was defined as biochemical relapse (Phoenix definition), beginning of androgen deprivation therapy or clinical evidence of local or distant failure. Any additional criteria used by studies are reported in the GRADE tables.
- Studies used populations of people with differing severity prostate cancer (see appendix E for more information).

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 from 2008 onwards yielded 2,688 references (Please see Appendix C for search strategies). After being screened on title and abstract, 163 full-text papers were ordered as potentially relevant systematic reviews or RCTs.

After full-text screening, 11 RCTs reported across 23 publications were included. Ten systematic reviews were identified; however, none were included because the RCTs they included were already identified at full-text screening and/or because they contained studies that did not meet the inclusion criteria for the present review.

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; therefore there were 11 unique studies.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. These searches, which included articles up to August 2018, returned 363 references for this review question. These were screened on title and abstract and 1 additional relevant references was found. This study was part of an already included publication, therefore there was a total of 24 included publications, but 11 unique studies.

For study selection process please see Appendix D.

For the full evidence tables, forest plots and GRADE profiles for included studies, please see appendices E, F and G.

Excluded studies

For the list of studies excluded at full text, with reason for exclusion, see appendix H and all references in Appendix I

Summary of clinical studies included in the evidence review

Eleven randomised controlled trials were included in this review. Most of these had multiple publications associated with them. In the reporting of these studies the trial is referred to by the trial name (or institution if there is no trial name) followed by the specific report.

The 11 studies included participants of different risk categories. For example, the PROFIT trial enrolled exclusively intermediate risk prostate cancer patients, whereas other studies comprised a mixture of severities.

The overall evidence was as follows:

- Conventional versus hypofractionated radiation therapy – 10 RCTs reported in 21 papers:
  - HYPRO (Netherlands): Aluwini (2015, 2016), Incrocci (2016) and Wortel (2016)
  - RENCI (Italy): Arcangeli (2010, 2011, 2012 and 2017)
  - CHHiP (United Kingdom): Dearnaley (2012, 2016, 2018) and Wilkins (2015)
  - PROFIT (Canada, Austrailia and France): Catton (2017)
  - RTOG 0415 (United States): Lee (2016)
  - FCCC (United States): Pollack (2006 and 2013) and Shaikh (2017)
  - Hoffman (2014 and 2016) (United States)
  - Marzi (2009) (Italy)
  - Norkus (2009) (Lithuania)
  - Norkus (2013) (Lithuania)
- External beam therapy alone versus external beam therapy plus low-dose-rate brachytherapy boost – 1 RCT reported in 2 papers:
  - ASCENDE-RT (Canada): Morris (2016) and Rodda (2017)
- Brachtherapy alone
  - No studies met the inclusion criteria

Outcomes and sample sizes

The reported outcomes where data were extractable were:-

- Freedom from biochemical failure (and time to biochemical failure)
- Freedom from biochemical–clinical failure (and time to biochemical–clinical failure)
- Overall survival (and time to death)
- Freedom from prostate cancer-related death
- Acute toxicity (gastrointestinal and genitourinary)
- Late toxicity (gastrointestinal and genitourinary)
- Quality of life (for urinary, bowel, sexual and hormonal domains)

The sample sizes ranged from 162 to 3,216 participants across studies.

See full evidence tables for the included studies in appendix E.

Quality assessment of clinical studies included in the evidence review

See evidence tables in appendix E for quality assessment of individual studies and appendix G for GRADE 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, 1,541 references were returned, of which 1,508 could be confidently excluded on screening of titles and abstracts. The remaining 33 studies were reviewed in full text, and 28 were found not to be relevant. One US study was identified subsequently by reference searching from one of the reviews obtained from our search. One additional study was identified after the search date. This left 7 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

Four studies adopting a US focus were included:

Hodges et al. (2012) compared 2 external beam radiation therapy techniques for low- to intermediate-risk prostate cancer: stereotactic body radiation therapy (SBRT), delivering 36.25 Gy in 5 fractions, and intensity-modulated radiation therapy (IMRT), delivering the conventional radiation dose of 78 Gy over 36–40 fractions. The authors developed a Markov decision model to simulate a cohort of patients with a Gleason score < 7 and/or PSA ≤ 15 followed for 10 years. The authors assumed identical efficacy and toxicity for SBRT and IMRT. As a result, all simulated patients experienced identical quality of life in the base case. Costs were based on 2010 prices adopting a payer perspective (Medicare). The authors found that, compared with IMRT, SBRT for low- to intermediate-risk prostate cancer had substantial potential cost savings, and hypothesised that it may also improve access to radiation, increase patient convenience, and boost quality of life for patients. Sensitivity analysis revealed that, if the SBRT cohort experienced a decrease in quality of life of at least 4% or a decrease in efficacy of at least 6%, then SBRT would no longer be cost effective, if QALYs are valued at $50,000 each. The study was judged to be partially applicable with very serious limitations.

Parthan et al. (2012) compared 3 types of external beam radiotherapy: SBRT (36.25 Gy in 5 fractions) and conventional fractionation (78 Gy over 36–40 fractions) delivered as either IMRT or proton beam therapy (PBT). The authors developed a lifetime Markov model incorporating gastrointestinal (GI) and genitourinary (GU) toxicity and sexual dysfunction (SD). A simulated cohort of 65-year-old patients with localised prostate cancer was followed up to death, adopting a US healthcare payer perspective (Medicare) at 2011 reimbursement rates. The model assumed that all comparators deliver the same time to biochemical recurrence, but are associated with different levels of toxicity. Transition probabilities to different toxicities were synthesised meta-analytic techniques of ten studies, clinical trials with no control

group or single cohort observational studies. The authors' base-case finding was that SBRT dominates both IMRT and PBT. If QALYs are valued at $50,000 each, SBRT was the optimal option in 75% and 94% of probabilistic simulations. The study was judged to be partially applicable with very serious limitations.

Sher et al (2014) compared SBRT (35 Gy in 5 fractions) with IMRT (75.6 Gy in 42 fractions). The authors developed a Markov decision model with a 4-month cycle length predicting lifetime costs and QALYs of 65-year-old man with low-risk prostate cancer. Probabilities of recurrence and toxicity (sexual, rectal and urinary) were obtained by reviewing published observational studies. The SBRT cohort had a higher probability of rectal and urinary dysfunction than IMRT, whereas sexual dysfunction probabilities were similar. Costs were taken from 2012 prices adopting the US payer perspective (Medicare). The study showed that QALYs were slightly higher with IMRT than SBRT (9.96 vs 9.93), reflecting the higher toxicity rate in the SBRT group. However, SBRT was deemed cost effective, as it was shown to be considerably cost saving compared with IMRT ($10,109 vs $27,564), suggesting over $500,000 could be saved for every QALY forgone. Treatment efficacy estimates, rectal toxicity and sexual dysfunction, and the uncertain potential for late effects from SBRT were significant drivers of the cost effectiveness. Applying the extreme values of these favouring IMRT did not change the base-case conclusion. The study was judged to be partially applicable with potentially serious limitations.

Ollendorf et al. (2008) developed an economic model to assess the cost effectiveness of brachytherapy, delivered as 100 iodine-125 at dose of 145 Gy compared with proton beam therapy (PBT) and IMRT (each 74–78 Gy in 39 fractions), to treat people with low-risk localised prostate cancer. Assuming that the 3 modalities have the same efficacy, the study's focus was on different toxicities. Acute and late GI and/or GU toxicities and sexual dysfunction were modelled. GI toxicity was higher with IMRT than brachytherapy in the short term. Costs were included adopting public payer perspective for the base case including capital expenditures in its reimbursement framework and patient time in therapy cost. Scenario analysis excluding patients' time costs was performed. The three techniques have comparable toxicity in the long run. The authors found that brachytherapy was dominant compared with IMRT and PBT, delivering higher QALYs and saving costs. The study was judged to be partially applicable with potentially serious limitations.

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) or IMRT (74 - 78 Gy in 37 fractions). Additional comparators – cryotherapy, high-intensity focused ultrasound and radical prostatectomy – 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. 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.

Sanyal et al. (2016), a Canadian study, developed a Markov model to predict lifetime direct costs and QALYs of 65-year-old men with local prostate cancer, stratified into low-, intermediate- and high-risk groups. Transition probabilities, AEs associated with treatment options, health state utility values and costs were derived from informal searches of the literature. The relevant comparators for low- and for the intermediate-risk groups were conventional IMRT (38 fractions), brachytherapy (using palladium-103 seeds) and IMRT plus brachytherapy (delivered over 19 fractions overall). Interventions used for the high-risk groups were out of the scope, as they did not include conventional IMRT. Annual probabilities of moving to the recurrence state were assumed identical between the comparators. Short- and long-term toxicities were modelled. The authors found that, for the low-risk group, IMRT and brachytherapy delivered equal effectiveness, but brachytherapy was associated with lower costs. For intermediate-risk group, conventional IMRT was slightly more effective than a combination of IMRT and brachytherapy and was associated with lower costs; this reflects the high toxicity assigned to the combination of IMRT plus brachytherapy. One-way sensitivity analysis was performed but not PSA; the results seemed to be consistent with the base-case ones. The study was judged to be partially applicable with very serious limitations.

Zemplényi et al. (2018), a Hungarian study, developed a 10-year Markov decision model evaluating the cost effectiveness of hypo-fractionated IMRT (HF-IMRT; 25 fractions) compared with conventional fractionation IMRT or three dimensional conformal radio-therapy (3DCRT), each 38 fractions, for 70-year-old men with localised prostate cancer. Based on data from a large cohort study, 3DCRT was assigned inferior recurrence-free survival to IMRT; HF-IMRT was assumed to have identical recurrence-free survival to IMRT. Health state utility values were obtained from an existing literature using the standard gamble technique. Treatment-related acute and late toxicities were obtained from existing literature; values assigned to the HF-IMRT acute toxicity were lower than the IMRT; however, HF-IMRT was associated with higher late GU toxicity than the IMRT and 3DCRT. Sexual dysfunction was ignored in the model, since no studies could be identified presenting relevant comparative data. The authors found that HF-IMRT was slightly more effective and less expensive compared with both IMRT and 3DCRT. Probabilistic sensitivity analysis showed that HF-IMRT was dominant and cost effective in 99% of the 1000 iterations, considering the threshold of €20,000 per QALY gain. Results from different scenarios using progression rates from different publications did not alter the base-case conclusion. 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

The format of the evidence statements is explained in the methods in appendix B.

Conventional versus hypofractionated radiation therapy

Low- to high-quality evidence from up to 10 RCTs reporting data on up to 7,050 people with localised prostate cancer shows there is no difference in overall freedom from biochemical or biochemical–clinical failure, overall freedom from prostate

cancer-related death, overall survival, late genitourinary and gastrointestinal toxicity, and acute genitourinary toxicity between people receiving hypofractionated radiation therapy and those receiving conventional radiation therapy.

Low- to moderate-quality evidence from up to 6 RCTs reporting data on up to 6,621 people with localised prostate cancer could not differentiate time to biochemical or biochemical–clinical failure, time to death from any causes or time to prostate cancer-related death between people receiving hypofractionated radiation therapy and those receiving conventional radiation therapy.

Moderate-quality evidence from 9 RCTs reporting data on 5,709 people with localised prostate cancer found higher rates of people reporting grade 2 or worse acute gastrointestinal toxicity in people receiving hypofractionated radiation therapy than those receiving conventional radiation therapy.

Very low-quality evidence from up to 5 RCTs reporting data on up to 303 people with localised prostate cancer could not differentiate time to worsening of quality of life (on any sub-domain), or rates of worsening quality of life (on any sub-domain) between hypofractionated and conventional radiation therapy.

Economic evidence

One partially applicable model-based cost–utility analysis with potentially serious limitations found that hypofractionated radiotherapy dominates conventional fractionation (IMRT or 3DCRT), as it is slightly more effective and saves costs for a cohort of people with localised prostate cancer.

Extremely hypofractionated radiotherapy (stereotactic body radiotherapy; SBRT) versus conventional fractionation

Economic evidence

Three partially applicable model-based cost–utility analyses with potentially serious or very serious limitations found that hypofractionated SBRT is cost saving compared with conventional IMRT. The studies found that SBRT may be slightly more or slightly less effective than IMRT; however, all 3 found that SBRT provides best value for money, unless QALYs are valued at over $500,000 each.

External beam radiation therapy (EBRT) alone versus external radiation beam therapy plus low-dose-rate brachytherapy

High-quality evidence from 1 RCT reporting data on 398 people with localised prostate cancer found a greater length of time to biochemical failure in people given EBRT with a low dose rate brachytherapy boost than those given EBRT alone.

Moderate-quality evidence from 1 RCT reporting data on 398 people with localised prostate cancer found a greater length of time to grade 2 late genitourinary toxicity and lower rates of acute genitourinary toxicity, 5-year catheterization and 5-year usage of pads for urinary incontinence in people given EBRT alone than in those people given EBRT with a brachytherapy boost.

Moderate- to high- quality evidence from 1 RCT reporting data on 398 people with localised prostate cancer found no difference in acute gastrointestinal toxicity or freedom-from prostate cancer-related death between those given EBRT alone and those given EBRT with a brachytherapy boost.

Low- to moderate- quality evidence from 1 RCT reporting data on 398 people with localised prostate cancer could not differentiate time to grade 2 late gastrointestinal toxicity or death from any cause between those given EBRT alone and those given EBRT with a brachytherapy boost.

Economic evidence

One partially applicable model-based cost–utility analysis with potentially serious limitations found that a combination of brachytherapy and IMRT is dominated by conventional IMRT alone, producing fewer QALYs and incurring higher costs for people with intermediate localised prostate cancer.

Brachytherapy versus conventional fractionated external beam RT

Economic evidence

One directly applicable model-based cost–utility analysis with potentially serious limitations found that brachytherapy produces slightly more QALYs than IMRT but at a higher cost, with an ICER of around £85,000 per QALY gained.

Two partially applicable modelling-based cost-utility analyses with potentially serious limitations found that brachytherapy dominates conventional IMRT, as it is cost saving and at least as effective for people with low-risk localised prostate cancer.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that there are several critical outcomes related to the use of radiotherapy in prostate cancer. Biochemical failure has major impact on survival in prostate cancer and is typically the primary measure of efficacy in studies assessing radiotherapy in prostate cancer. Toxicity (gastrointestinal and genitourinary) are important, particularly in those with comorbid conditions, such as inflammatory bowel disease, which affect the decision to use radiotherapy.

Quality of life is an important factor related to radiotherapy. In particular, convenience of treatment is of critical importance. Conventional radiotherapy takes an average of 7.5 weeks to deliver whereas hypofractionated radiotherapy is given over a shorter time. The committee noted that this needed to be balanced against the greater short-term toxicity of hypofractionated radiotherapy when discussing treatment options with patients.

The quality of the evidence

All 11 included studies were at moderate or high risk of bias owing to a lack of blinding of participants and/or investigators and variability in allocation concealment. The lack of blinding procedures in these studies was of greater concern for those studies using subjective outcome measures such as physician-rated toxicity and patient-reported quality of life, the latter of which also suffered from low response rates.

The committee was concerned that the long-term end points reported in the majority of studies were at the 5–6 year period whereas a 10-year end point is preferred to capture survival effects.

The decision to consider low dose rate brachytherapy was based on evidence provided by the ASCENDRE-RT trial demonstrating greater efficacy associated with dose-escalated external beam radiotherapy with a brachytherapy boost than dose-escalated external beam radiotherapy alone.

There was no new evidence reviewed on high-dose brachytherapy, therefore the committee agreed that high-dose rate brachytherapy continued to be useful. The committee added the evidence from the ASCENDE trial was not strong enough to influence a change in practice from considering high-dose rate brachytherapy.

It decided to recommend 'brachtherapy' rather than specifying high or low dose rate because both are effective. Since most centres do not offer both types, this recommendation allows this population to get treatment regardless of what is available at centres.

Benefits and harms

The committee was concerned about the increased gastrointestinal toxicity associated with hypofractionated radiotherapy, but noted that this does not translate into higher rates of toxicity in the long term, with long-term rates of toxicity being similar between hypofractionated and conventional radiotherapy.

The committee agreed that the short scheduling period of hypofractionated radiotherapy greatly improves the convenience for people undergoing radiotherapy for prostate cancer as it reduces the average length of treatment from 7.5 weeks to around 4 weeks.

The committee was similarly concerned with the high rates of genitourinary toxicity associated with low-dose rate brachytherapy in both the short and long term. However, it decided that this was justified by the significant reduction in biochemical failure associated with low-dose rate brachytherapy compared with conventional external beam radiotherapy.

The committee agree that on balance, hypofractionated radiotherapy was the preferred choice because it was more convenient for patients, was as effective as conventional radiotherapy, and was cheaper because it was less resource intensive. It was also agreed that hypofractionated treatment is not suitable for all patients and therefore recommended a conventional radiotherapy schedule for those in whom hypofractionated treatment is not appropriate, for example those people with previous inflammatory bowel disease, significant bladder instability, urinary incontinence or those having received previous colorectal surgery.

The committee also reviewed evidence that showed subgroup analysis by age. The committee decided the evidence was not useful because the initial study design did not randomise by age. The subgroup analysis was not decided *apriori* as result the committee was not confident to base any recommendations on this evidence.

Cost effectiveness and resource use

The committee reviewed the included economic evidence. It agreed that the cost–utility analysis performed by Zemplenyi et al. (2018) provided partially applicable evidence. The committee noted that, given the clinical evidence provided in the clinical review showing no inferiority for hypofractionated external beam radiotherapy compared with conventional fractionation in terms of efficacy and toxicity, the reduction in the number of radiotherapy sessions would lead to cost saving. Thus, the economic evidence provided by Zemplenyi et al. was agreed to be sufficient to underpin strong recommendations in favour of offering external beam radiotherapy at

a dose of 60 Gy in 20 fractions to people receiving radiotherapy for localised prostate cancer.

The committee reviewed the included economic evidence on the comparison between the extremely hypofractionated radiotherapy using stereotactic body radiotherapy (36.5 Gy over 5 fractions) and the conventional fractionation delivering total dose at 76–80 Gy over 38–40 fractions. It agreed that the 3 US studies included in this context provided partially applicable evidence. As 2 of these were judged as having very serious limitations and given that the clinical review did not report clinical evidence on stereotactic body radiotherapy, the committee did not make recommendations on the use of this radiotherapy technique.

The committee reviewed the included economic evidence provided by a Canadian study (Sanyal et al. 2016), judged as partially applicable with very serious limitations, on the comparison between a combination of external beam radiotherapy plus brachytherapy and external beam radiotherapy only for the treatment of intermediate-risk localised prostate cancer. It noted that this study made the assumption of equal efficacy measured by time to recurrence, which was not realistic based on evidence provided by a UK RCT (ASCENDE-RT) included in the clinical review. This trial showed that patients on a combination of brachytherapy and EBRT experience half the rate of recurrence of people receiving EBRT alone. The committee noted that the improved efficacy associated with the combination of brachytherapy and EBRT would result in overall improved QALYs that were not captured in the economic evidence. The committee agreed that the clinical evidence provided by ASCENDE-RT was sufficient to consider this combination for this population, as this would not change the current practice, affecting a small population, and hence not having a significant resource impact.

The committee reviewed the included economic evidence on the comparison of brachytherapy monotherapy versus external beam radiotherapy using conventional fractionation. It noted that the clinical review did not provide evidence on this comparison. The committee agreed that the economic evidence on this comparison, provided by the 3 studies included in the economic review, was not sufficient to make recommendations regarding the use of brachytherapy only for the treatment of localised prostate cancer.

Other considerations

The committee agreed that the new recommendations are consistent with the recommendations made by NHS England, who encourage the use of hypofractionated image-guided IMRT for the treatment of localised prostate cancer.

Appendices

Appendix A– Review protocols

Review protocol for radical therapy

ID	Field (based on PRISMA-P	Content
I	Review question	What is the optimal dose and fractionation schedule for people with localised prostate cancer (T1b–T3a N0 M0) who are treated with radical radiotherapy?
II	Type of review question	Intervention
III	Objective of the review	This question was identified as requiring updating during the 2016 exceptional surveillance review.
IV	Eligibility criteria – population/disease/condition/issue/domain	People with localised prostate cancer (T1b–T3a N0 M0)
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Hypofractionated radiotherapy to the prostate • Brachytherapy plus external beam radiotherapy
VI	Eligibility criteria – comparator(s)/control or	Conventional fractionation with external beam therapy

	reference (gold) standard	
VII	Outcomes and prioritisation	• Prostate cancer-specific mortality • Overall survival • Metastasis-free survival • 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 ○ Biochemical relapse-free survival (using the Phoenix definition: a rise of 2 ng/mL or more above the prostate-specific antigen (PSA) nadir after EBRT with or without hormonal therapy, dated 'at call') (Roach 2006) ○ 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. We will use individual protocol-based definitions. • Health-related quality of life - for example: ○ European Organisation for Research and Treatment of Cancer quality of life, ○ EPIC instrument *If reported – <u>psychological aspects</u> of quality of life to be reported separately*

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	• Total dose • Different hypo-fractionation schedules.
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were 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 from 2008, this question is an update from a previous guideline, committee agreed to limit searches to 2008

XIV	Identify if an update	This is an update. Original question: from 2008, no question located. **Recommendations affected:** 1.3.17 Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. **[2008]** 1.3.18 For men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage**. [2008]** Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. **[new 2014]**
XV	Author contacts	Guideline updates team
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter
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 developed the evidence review. 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 undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted 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

Appendix B – Methods

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. 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 Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, 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.

Since no other MID was available, an MID of 0.2 was used for Standardised Mean Differences, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For relative risks a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

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 based on the criteria given in Table 2

Table 2: 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. 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.

GRADE criteria	Reasons for downgrading quality
	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.

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 show 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 showed that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- We state the evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology ‘up to’ in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement

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 3.

Table 3 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 4.

Table 4 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 *(pages 11&16).*

A date limit from 2008 has been applied. The consensus from committee members was there would be no relevant studies from more than 10 years ago - this is due to newer technologies and that the terminology for localised prostate cancer will now be different.

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 December 2017

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 exp radiotherapy/
7 radiotherap*.tw.
8 (radiat* adj4 (therap* or treatment*)).tw.
9 ((external* or conformal*) adj4 (irradiat* or therap* or treat*)).tw.
10 ((interstitial* or intracavit* or implant* or surface* or internal*) adj4 (irradiat* or radiation*)).tw.
11 curietherap*.tw.
12 (radioisotope* adj4 (irradiat* or therap* or treat*)).tw.
13 ((seed* or permanent*) adj2 implant*).tw.
14 or/6-13
15 Brachytherapy/
16 brachytherap*.tw.
17 exp radiotherapy dosage/
18 exp dose-response relationship, radiation/
19 (Hyperfraction* or Hyper-fraction* or Hyper fraction* or Hypofraction* or Hypo-fraction* or Hypo fraction*).tw.

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
20 ((optim* or fraction* or respons* or relation* or dependence* or effect* or scheme* or curve*) adj4 (dose* or dosage or schedule*)).tw. 21 ((high* or full* or maximum* or larg* or escalat* or supplement* or low* or minimum* or small*) adj4 (dose* or dosage* or schedule*)).tw. 22 (HDR or LDR).tw. 23 or/15-22 24 5 and 14 and 23

Study design filters and limit

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

The MEDLINE SR and RCT filters are presented below.
Systematic Review 1 Meta-Analysis.pt. 2 Network Meta-Analysis/ 3 Meta-Analysis as Topic/ 4 Review.pt. 5 exp Review Literature as Topic/ 6 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. 7 (review$ or overview$).ti. 8 (systematic$ adj5 (review$ or overview$)).tw. 9 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. 10 ((studies or trial$) adj2 (review$ or overview$)).tw. 11 (integrat$ adj3 (research or review$ or literature)).tw. 12 (pool$ adj2 (analy$ or data)).tw. 13 (handsearch$ or (hand adj3 search$)).tw. 14 (manual$ adj3 search$).tw. 15 or/1-14
RCT 1 Randomized Controlled Trial.pt. 2 Controlled Clinical Trial.pt. 3 Clinical Trial.pt. 4 exp Clinical Trials as Topic/ 5 Placebos/ 6 Random Allocation/ 7 Double-Blind Method/ 8 Single-Blind Method/ 9 Cross-Over Studies/ 10 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 11 (random$ adj3 allocat$).tw. 12 placebo$.tw. 13 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 14 (crossover$ or (cross adj over$)).tw. 15 or/1-14

A date limit from 2008 to 2017 and English language limit has been applied. Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been 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)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

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

The economic searches were conducted in December 2017.

Health Economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

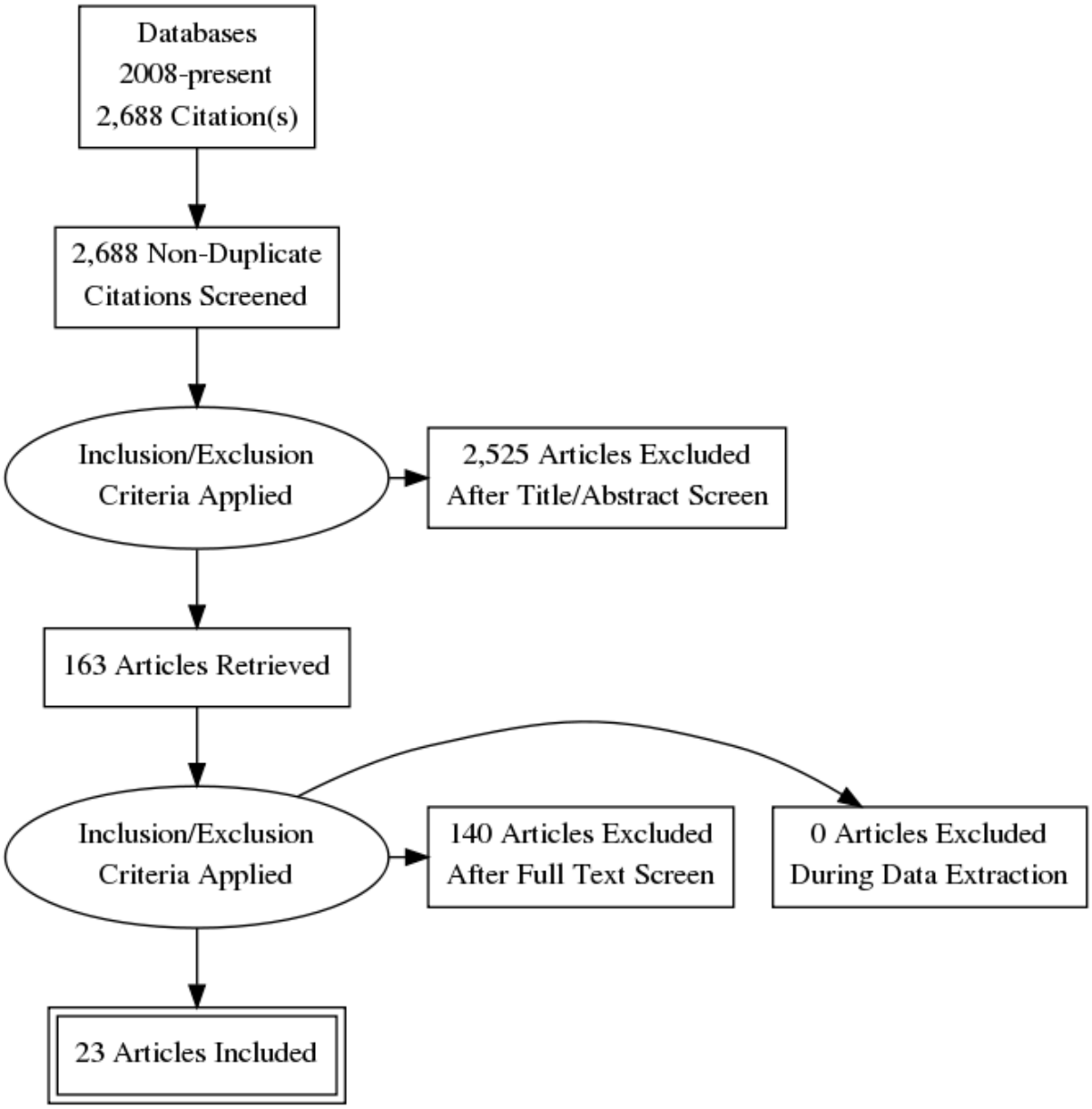
Economic evaluations

1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/
9	exp Models, Economic/
10	Markov Chains/
11	Monte Carlo Method/
12	Decision Trees/
13	econom$.tw.
14	cba.tw.
15	cea.tw.
16	cua.tw.
17	markov$.tw.
18	(monte adj carlo).tw.
19	(decision adj3 (tree$ or analys$)).tw.
20	(cost or costs or costing$ or costly or costed).tw.
21	(price$ or pricing$).tw.
22	budget$.tw.

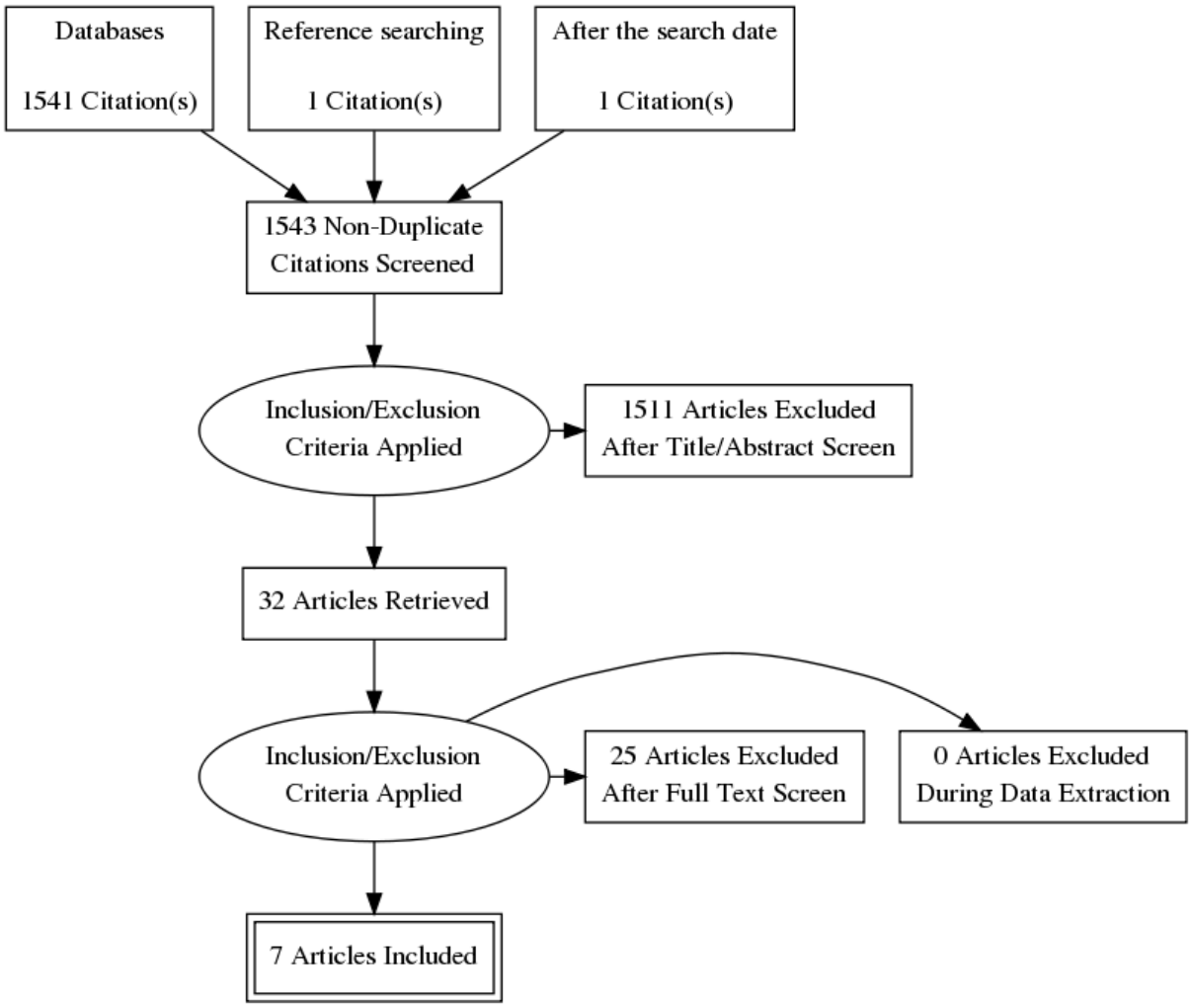
The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ 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.
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

Appendix D – Study selection

Clinical evidence


Databases
2008-present
2,688 Citation(s)
2,688 Non-Duplicate
Citations Screened
Inclusion/Exclusion
Criteria Applied
2,525 Articles Excluded
After Title/Abstract Screen
163 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
140 Articles Excluded
After Full Text Screen
0 Articles Excluded
During Data Extraction
23 Articles Included

Economic evidence



Appendix E– Evidence tables

Clinical evidence

Short Title	Title	Study characteristics	Quality Assessment
Aluwini (2016)	Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial	Study type Randomised control trials Associated studies HYPRO -: Aluwini S, Pos F, Schimmel E et al. (2015) Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. The lancet. Oncology 16(3), 274-283 Aluwini S, Pos F, Schimmel E et al. (2016) Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. The lancet. Oncology 17(4), 464-474 Incrocci L, Wortel Rc, Alemayehu Wg et al. (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. The lancet. Oncology 17(8), 1061-1069 Wortel Rc, Heemsbergen Wd, Smeenk Rj et al. (2017) Local Protocol Variations for Image Guided Radiation Therapy in the Multicenter Dutch Hypofractionation (HYPRO) Trial: impact of Rectal Balloon and MRI Delineation on Anorectal Dose and Gastrointestinal Toxicity Levels. International journal of radiation oncology biology physics (no pagination) Randomised controlled trial Study details Study location The Netherlands	Random sequence generation Low risk of bias Patients were randomly assigned (1:1) to open-label treatment groups with standard fractionation or hypofractionation, applying a minimisation procedure. There was a random element in the randomisation and it ensured overall balance and within each stratum of the stratifi cation factors (ie, treatment centre and risk group). Allocation concealment Unclear risk of bias Unclear if outcome assessor was blinded Blinding of participants and personnel High risk of bias "The local investigators were treating physicians, so they were not masked to treatment." Blinding of outcome assessment Unclear risk of bias Unclear if outcome assessor was blinded Incomplete outcome data Low risk of bias 38/820 lost to follow up (less than 10%)

Short Title	Title	Study characteristics	Quality Assessment
		Study setting 7 radiotherapy centre Study dates Between March 19, 2007, and Dec 3, 2010 Duration of follow-up "We assessed late toxicity from 90 days after treatment (at 6, 12, 24, 36, 48, and 60 months)." After radiation treatment, participants seen every 3 months for first 2years, every 6 months for years 2-5 and once a year up to 10 years Sources of funding Study was funded by the Dutch Cancer Society (grant CKTO 2006-08). Inclusion criteria Prostate cancer Intermediate to high risk prostate cancer (T1b–T4 NX–0 MX–0, SPSA 60 ng/mL or less, WHO performance status of 0–2) Age 44-85 years Exclusion criteria Prior surgery Prior radical prostatectomy Prior radiology Prior pelvis irradiation Low risk PCa Patients low-risk patients (stage T1b–T2a, Gleason score ≤6, prostate-specific antigen ≤10 ng/mL). Comorbidities Evidence of pelvic nodal disease or distant metastases Sample characteristics Sample size	Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias Moderate Unclear whether outcome assessors were blind and unclear allocation concealment and participant blinding. Investigators not blinded. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		820 participants, 795 included in ITT Split between study groups 410 in each arm Loss to follow-up 38/820 lost to follow-up %female Not reported Median age (IQR) Intervention arm: 70 (66–74) years Conventional arm: 71 (67–75) years Interventions hypofractionated radiotherapy 63.6gy/ 19 x 3.4 fr Conventional radiotherapy 78gy / 39 x 2gy fr Outcome measure(s) Toxicity Long term toxicity survival 5-year relapse-free survival	
Catton (2017)	Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer	Study type Randomised controlled trial Study details Study location Centres in Canada (14), Austrailia (12) and France (one) Study setting 27 centres Study dates 2006-2016 Duration of follow-up Toxicity assessments done weekly during RT followed by	Random sequence generation Low risk of bias Stratified using use of androgen deprivation therapy, risk of seminal vescicle involvement and treatment centre. Used a computer generated randomisation schedule Allocation concealment Unclear risk of bias Unclear if outcome assessor was blinded

Short Title	Title	Study characteristics	Quality Assessment
		telephone assessments to week 14 and again every 6m follow-up visit for 5 years. HRQoL assessed at baseline, 24m and 48m. Sources of funding Several contributors received funding and/or are affiliated to pharmaceutical companies Inclusion criteria Prostate cancer Intermediate risk (T1-T2a, Gleason score of 6 or less and PSA 10.1 to 20; T2b-T2c, Gleason score of 6 or less and PSA 20ng/mL or less; or T1-2, Gleason score of 7 and PSA 20 ng/mL or less) without evidence of spreading to lymph nodes or bones. Exclusion criteria Prior radiology Prior PCa therapy other than biopsy or transurethral resection Comorbidities malignancy diagnosed within 5 years of entry other than non-melanoma skin cancer, or inflammatory bowel disease Other PCa diagnosis 6 months or more before study entry Sample characteristics Sample size 1206 randomly assigned, 1192 completed treatment, 1116 analysed. Split between study groups 598 conventional; 608 hypofractionated Loss to follow-up 76 lost to follow-up Median age (IQR)	Blinding of participants and personnel Unclear risk of bias Unclear whether any blinding was attempted Blinding of outcome assessment Unclear risk of bias Unclear if assessor was blind Incomplete outcome data Low risk of bias Similar attrition between groups Selective reporting Low risk of bias Other sources of bias Low risk of bias Balanced baseline characteristics Overall risk of bias Moderate Likely no blinding procedures. This will have a relatively small impact on bias risk for biochemical outcomes and moderate risk for physician assessed toxicity. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		Median. conventional arm: 72 (IQR 68-75) years Hypofractionated arm: 71 (IQR 67-75) years Interventions hypofractionated radiotherapy 60 gy in 20 x 3gy fractions over 4 weeks Conventional radiotherapy 78gy in 39 x 2gy fractions over 8 weeks Type of radiotherapy used IMRT encouraged however 3D-CRT was permitted if all pre-mandated dose constraints were met Outcome measure(s) Toxicity Acute (14-week) and late (5 year) toxicity survival Overall survival and freedom from prostate cancer-related death. Biochemical failure Biochemical failure, biochemical-clinical failure	
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	Study type Randomised controlled trial Study details Study location UK Study setting 71 centres Study dates Oct 18, 2002 - June 17, 2016 Duration of follow-up 5 years Sources of funding We acknowledge support of Cancer Research UK	Random sequence generation Low risk of bias Randomly assigned (1:1:1) Allocation concealment High risk of bias Non blinded Blinding of participants and personnel High risk of bias Non-blinded Blinding of outcome assessment Unclear risk of bias

Short Title	Title	Study characteristics	Quality Assessment
		(C8262/A7253, C1491/A9895, C1491/A15955, SP2312/021), the Department of Health, the National Institute for Health Research (NIHR) Cancer Research Network, and NHS funding to the NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. Associated studies Dearnaley 2012: Preliminary data Wilkins 2015: QoL Inclusion criteria Prostate cancer T1b–T3aN0M0 and WHO performance status 0-1. Until Aug 1, 2006 participants must have had a PSA concentration < 40 ng/mL and < 30% risk of lymph node involvement. After Aug 1, 2006 this was revised to PSA concentration < 30 ng/mL and < 30% risk of senubak vesicle involvement. Age Older than 16 Exclusion criteria prior surgery Radical prostatectomy Prior radiology Prior pelvis radiotherapy Comorbidities another active malignancy in the past 5 years (other than cutaneous basal-cell carcinoma), comorbid conditions precluding radical radiotherapy, hip prosthesis (criterion amended to bilateral hip prosthesis Jan 30, 2009), and full anticoagulation treatment (criterion removed July 1, 2009). Other T3 tumors and Gleason score of 8+. Life expectancy <10 years Androgen suppression	Likely non-blinded Incomplete outcome data Low risk of bias Less than 10% lost to follow-up Selective reporting Low risk of bias All reported Other sources of bias Low risk of bias Overall risk of bias Moderate Likely no blinding procedures. This will have a relatively small impact on bias risk for biochemical outcomes, moderate risk for physician assessed toxicity, and high risk of bias for patient reported quality of life outcomes in Wilkins (2015) associated study. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		Prior androgen suppression Sample characteristics Sample size 3216 randomly assigned. 3133 received at least one dose of allocated treatment. Split between study groups 1065 conventional; 1074 hypofractionated arm-1 (60 gy); 1077 hypofractionated arm-2 (57 gy). Loss to follow-up 35 lost to follow-up An additional 64 did not receive treatment following random assignment (primarily due to ineligibility and technical unsuitability) Median age (IQR) conventional: 68 (range 48-85) years hypofractionated arm-1 (60 gy): 69 (range 48-84) years hypofractionated arm-2 (57 gy): 69 (44-83) years Androgen deprivation therapy "Short-course androgen deprivation treatment was given for 3–6 months before and during radiotherapy; this was optional for patients with low-risk disease." Interventions hypofractionated radiotherapy 60 gy in 20 x 3 gy fractions or; 57 gy in 19 x 3 gy fractions Conventional radiotherapy 74 gy in 37 x 2 gy fractions Type of radiotherapy used Forward or inverse 3D methods Outcome measure(s) Toxicity Acute (18-week) and late toxicity survival Disease-free and overall survival	

Short Title	Title	Study characteristics	Quality Assessment
		Biochemical failure Biochemical-clinical failure	
Lee (2016)	Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer	Study type Randomised controlled trial Study details Study dates 2006 - 2014 Duration of follow-up Minimum 5 years; median 5.8 years Sources of funding Supported by National cancer institute grants Inclusion criteria Prostate cancer Low-risk: T1b - T2c, Gleason score 2-6, PSA <10, Zubrod performance status <2. Age Over 18 years Male Exclusion criteria prior surgery Prior bilateral orchiectomy, cryosurgery or definitive surgery for PC Prior radiology Prior chemotherapy, RT Comorbidities Other invasive cancer (other than localized basal or squamous cell skin carcinoma) unless continually cancer-free for minimum of 5-years. Sample characteristics Sample size	Random sequence generation Low risk of bias Allocation concealment Unclear risk of bias Blinding of participants and personnel Unclear risk of bias Blinding of outcome assessment Unclear risk of bias Incomplete outcome data Low risk of bias Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias Moderate Likely no blinding procedures. This will have a relatively small impact on bias risk for biochemical outcomes and moderate risk for physician assessed toxicity. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		1,115 participants; 1,092 analysed Split between study groups 558 assigned to conventional (542 received treatment) 557 assigned to hypofractionated (550 received treatment) Loss to follow-up 33 lost to follow-up Median age (IQR) not reported Interventions hypofractionated radiotherapy 70 gy in 28 x 2.5gy fractions (over 5.6 weeks) Conventional radiotherapy 73.8gy in 41 x 1.8gy fractions (over 8.2 weeks) Type of radiotherapy used randomized to 3D-CRT or IMRT Outcome measure(s) Toxicity Acute and late GI and GU toxicity survival disease-free and overall survival Biochemical failure PSA PSA measured every 3 months for first 2 years, every 6 months for following 3 years and annually thereafter.	
Marzi (2009)	Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated	Study type Randomised controlled trial Study details Study location Italy Study setting	Random sequence generation Low risk of bias Participants were randomized Allocation concealment Unclear risk of bias

Short Title	Title	Study characteristics	Quality Assessment
	scheme for localized prostate cancer	Single institution Study dates March 2003 - June 2008 Duration of follow-up Median follow-up: 30 months Sources of funding none reported Inclusion criteria Prostate cancer High risk, with two of following factors: T2c-T4, PSA > 10 ng/ml, Gleason score 7-10. Age under 85 years Exclusion criteria prior surgery prior prostatectomy Prior radiology Comorbidities no node involvement or other malignant disease (except for Basal cell carcinoma) or other tumours in past 5 years Sample characteristics Sample size 162 participants; 114 used in analysis (only those with a follow-up of over 6 months) Split between study groups 57 each arm Loss to follow-up 48 lost to follow-up Median age (IQR) Not reported	Unlikely to have been concealed Blinding of participants and personnel Unclear risk of bias Likely non-blinded Blinding of outcome assessment Unclear risk of bias Likely to be non-blinded Incomplete outcome data Low risk of bias Selective reporting Low risk of bias Other sources of bias High risk of bias 48 patients excluded from analysis due to < 6month follow-up. Overall risk of bias High Potential for all outcomes of interest to this paper (physician reported toxicity) to be impacted by lack of blinding procedures Directness Partially directly applicable Study took place between 2003 and 2008

Short Title	Title	Study characteristics	Quality Assessment
		Interventions hypofractionated radiotherapy 62gy in 20 x 3.1gy fractions (over 5 weeks) Conventional radiotherapy 80gy in 40 x 2gy fractions (over 8 weeks) Type of radiotherapy used 3DCRT Outcome measure(s) Toxicity Late rectal toxicity using RTOG scale	
Morris (2017)	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 type Randomised controlled trial Associated studies Rodda S, Tyldesley S, Morris WJ et al. (2017) ASCENDE-RT: an Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. International journal of radiation oncology, biology, and physics 98(2), 286-295 Study details Study location Study dates 2002-2014 Duration of follow-up median 6.5 years Sources of funding Received unrestricted educational grants from Oncura corporation and Sanofi-Aventis Canada.	Random sequence generation Low risk of bias Participants were randomized Allocation concealment Unclear risk of bias Unlikely to have been concealed Blinding of participants and personnel Unclear risk of bias Unlikely to be blinded however at data lockdown trial investigators only had knowledge of median follow-up length and total number of biochemical events Blinding of outcome assessment Unclear risk of bias Unlikely blinded Incomplete outcome data Low risk of bias

Short Title	Title	Study characteristics	Quality Assessment
		Inclusion criteria Prostate cancer Intermediate to high risk Exclusion criteria None reported Sample characteristics Sample size 398 participants Split between study groups 200 allocated to EBRT (187 received intervention) 198 allocated to LDR-BT (182 received intervention) Loss to follow-up 1 lost to follow-up 29 did not receive allocated intervention All included in ITT 15 not included in toxicity assessment follow-up Median age (IQR) 68 (range 45-86) years Androgen deprivation therapy All patients received 8 months ADT prior to RT Interventions Type of radiotherapy used 3D-CRT External beam therapy (Mono) Dose-escalated 46Gy in 23 fractions plus 32 Gy boost in 16 fractions External beam + brachytherapy 46Gy in 20 fractions plus LDR-BT boost of I125 brachytherapy implant of 116Gy Outcome measure(s) Toxicity Rodda 2017: Acute (within 6 months) and late (after 6	Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias Moderate Likely no blinding procedures. This will have a relatively small impact on bias risk for biochemical and survival outcomes, and moderate risk for physician assessed toxicity. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		months) toxicity survival Overall survival and freedom from prostate cancer-related death Biochemical failure Biochemical failure	
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 type Randomised controlled trial Study details Duration of follow-up All patients underwent weekly follow-up for 12 weeks and a underwent 12 months minimum follow-up Sample characteristics Loss to follow-up 7 lost to follow-up Outcome measure(s) Toxicity evaluated weekly for 12-weeks and them every 3 months during first year after irradiation and every 6months subsequently	Random sequence generation Low risk of bias Allocation concealment Unclear risk of bias Blinding of participants and personnel Unclear risk of bias Blinding of outcome assessment Unclear risk of bias Incomplete outcome data Low risk of bias Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias Moderate Unclear blinding and allocation concealment procedures

Short Title	Title	Study characteristics	Quality Assessment
			Directness Directly applicable
Norkus (2009)	A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional external-beam radiotherapy for localized prostate adenocarcinoma: AAAAA report on acute toxicity	Study type Randomised controlled trial Study details Study location Lithuania Study setting Vilnius University Study dates 2004 Duration of follow-up Minimum 3 months Inclusion criteria Prostate cancer Low-Intermediate risk with less than 15% risk of seminal vesicle and/or lymph node involvement Exclusion criteria prior surgery No surgical castration before RT Androgen suppression No hormonal therapy prior to RT Sample characteristics Sample size 91 Split between study groups 44 conventional; 47 hypofractionated Loss to follow-up none Median age (IQR)	Random sequence generation Low risk of bias Patients were randomised Allocation concealment Unclear risk of bias Unlikely to have been concealed Blinding of participants and personnel Unclear risk of bias Unlikely to have been blinded Blinding of outcome assessment High risk of bias Non-blinded Incomplete outcome data Low risk of bias Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias High High risk due to potential for all outcomes of interest to this paper (physician reported toxicity) to be affected by lack of blinding procedures

Short Title	Title	Study characteristics	Quality Assessment
		Conventional arm median: 65 years (range 50-78) Hypofractionared arm median: 63 years (range 53-75) Interventions hypofractionated radiotherapy 57gy in 13 x 3gy fractions (over 3.5 weeks) plus 4 x 4.5gy fractions Conventional radiotherapy 74gy in 37 x 2 gy fractions (over 7.5 weeks) Type of radiotherapy used 3DCRT Outcome measure(s) Toxicity GI+GU measured using RTOG/EORTC toxicity scale	Directness Partially directly applicable Study took place in 2004
Pollack (2013)	Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer	Study type Main study Associated studies FCCC: Pollack A, Hanlon AL, Horwitz EM et al. (2006) Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial.. International journal of radiation oncology, biology, and physics 64(2), 518-26 Shaikh T, Li T, Handorf EA et al. (2017) Long-Term Patient-Reported Outcomes From a Phase 3 Randomized Prospective Trial of Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer. International journal of radiation oncology, biology, and physics 97(4), 722-731 Randomised controlled trial Study details Study location USA	Random sequence generation Low risk of bias Patients were randomised Allocation concealment Unclear risk of bias Unlikely to have been concealed Blinding of participants and personnel Unclear risk of bias Likely non-blinded Blinding of outcome assessment Unclear risk of bias Likely non-blinded Incomplete outcome data High risk of bias

Short Title	Title	Study characteristics	Quality Assessment
		Study setting Fox Chase Cancer Center and Department of Radiation Oncology, University of Miami Study dates 2002-2013 Duration of follow-up Median 69 months (range, 7-136 months) Sources of funding Supported by National Cancer Institute Grants and a Florida Department of Health Biomed Bankhead Coley Grant Associated studies Shaikh 2017 Inclusion criteria Prostate cancer T1-T3, Gleason score 5 or more if they had intermediate/high risk features. Exclusion criteria Androgen suppression Up to 4 months ADT permitted. High risk patients were planned to receive 24 months ADT, less than high risk planned to receive up to 4-months beginning 4 or fewer months before random assignment. Sample characteristics Sample size 307 randomly assigned;303 analysed Split between study groups 152 conventional; 151 hypo Loss to follow-up None Median age (IQR) Conventional: 67 (range, 45-86) years Hypo: 67 (49-86)	Incomplete data for QoL outcomes Selective reporting Low risk of bias Other sources of bias Low risk of bias Overall risk of bias High Potential for both outcomes (QoL and physician reported toxicity) to be affect by lack of blinding, and high number of QoL questionnaires not completed. Directness Directly applicable

Short Title	Title	Study characteristics	Quality Assessment
		years Interventions hypofractionated radiotherapy 70.2gy in 26 x 2.7gy fractions Conventional radiotherapy 76gy in 38 x 2gy fractions Type of radiotherapy used IMRT Outcome measure(s) Toxicity Protocol toxicity was measured using modified LENT (Late Effects of Normal Tissues)/RTOG (Radiation Therapy Oncology Group) criteria. Quality of life Shaikh 2017: QoL measured using EPIC, IPSS and EQ5D	

Economic Evidence

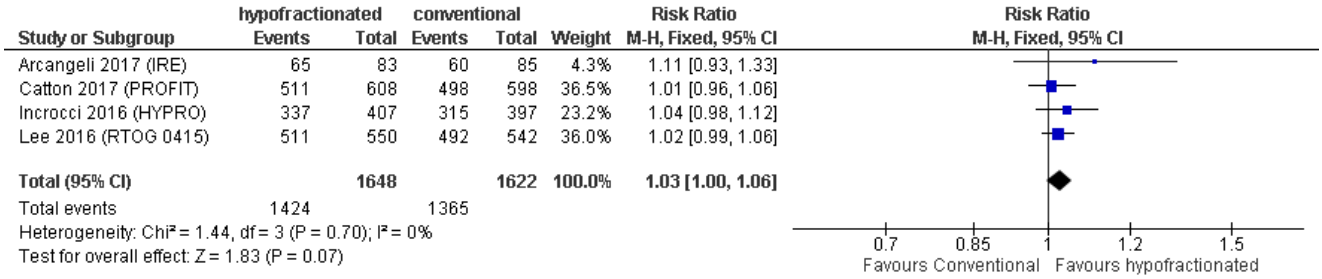
Study, population, country and quality	Data sources	Other comments	Incremental Cost ($)	Incremental Effect (QALY)	ICER	Conclusions	Uncertainty
Hodges et al 2012			Base-case				

Study, population, country and quality	Data sources	Other comments	Incremental Cost ($)	Incremental Effect (QALY)	ICER	Conclusions	Uncertainty
Patients with low- to intermediate-risk prostate cancer US study **Partly applicable** [a, b, c] **very serious limitations** [d, e, f, j]	Effects: Time to biological recurrence based on Phoenix definition Costs: Based on 2010 ambulatory payment classification for technical component of treatments. The analysis took the perspective of the payer (Medicare). Utilities: Derived from an existing literature, SG techniques to assess utility weights for health states experienced after PCa diagnosis and radio treatment in 162 men aged 60+, half of whom had been diagnosed with PCa	SBRT, delivering 36.25 Gy in five fractions Vs IMRT with the conventional fraction (78 Gy in 36 to 40 fractions) 10 year Markov decision model with a yearly cycle and 4 health states: disease-free; hormone therapy; CT and death Sexual dysfunction not addressed	-13,279	0	Dominant	The base-case analysis shows that SBRT is dominant compared to IMRT.	One-way sensitivity analysis, two-way sensitivity analysis and PSA were performed Results are sensitive to the assumption of equal efficacy and safety; when assumed that SBRT associated with 4% decrease in QoL or 6% decrease in efficacy, conclusion changed ICERs were within the CE threshold pre-defined in 66% of the PSA iterations

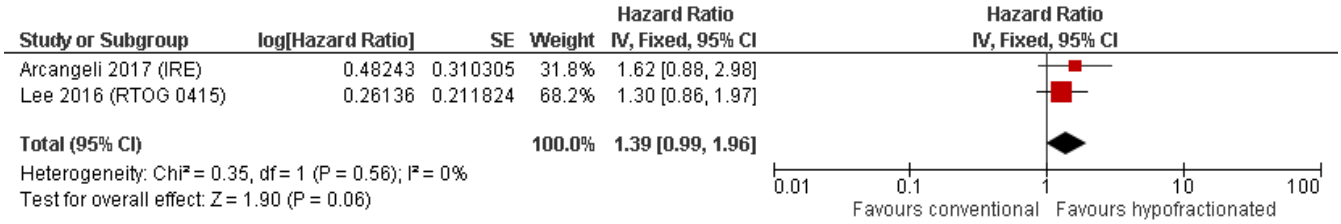
Appendix F - Forest plots

Conventional versus hypofractionated radiation therapy

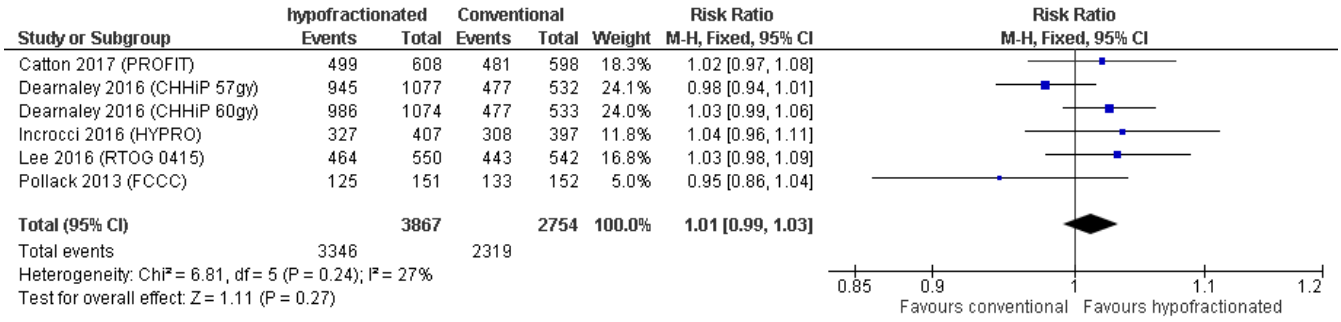
Freedom from biochemical failure



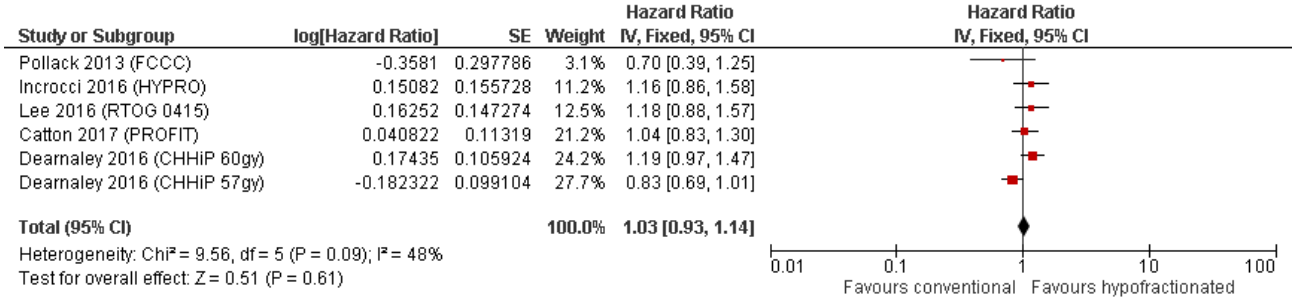
Time to biochemical failure



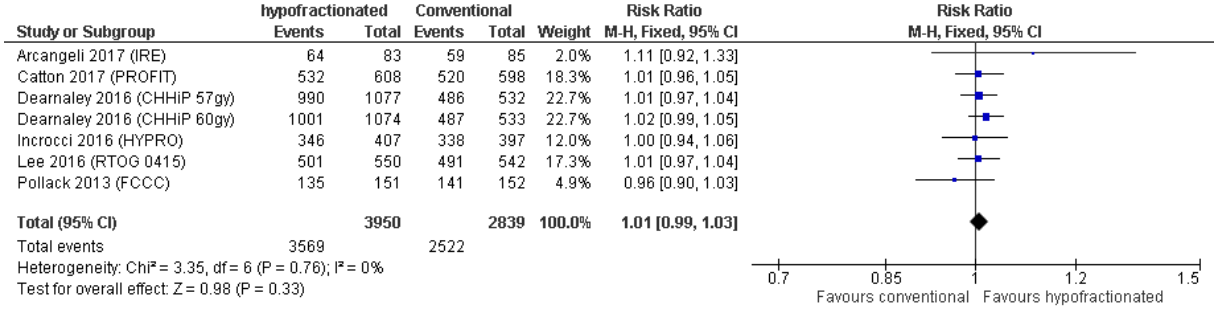
Freedom from biochemical-clinical failure



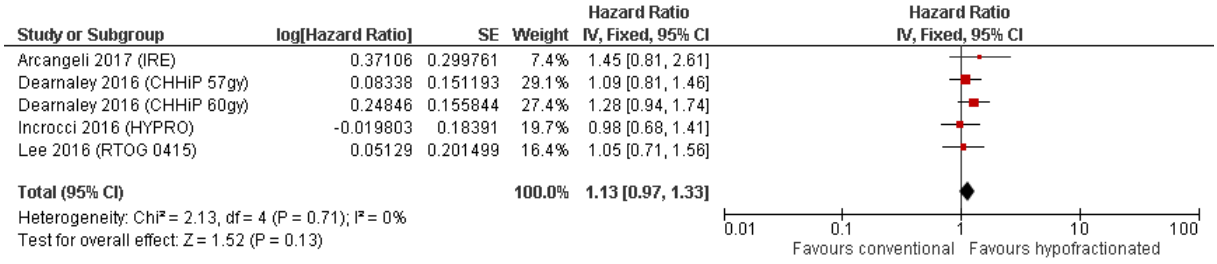
Time to biochemical-clinical failure



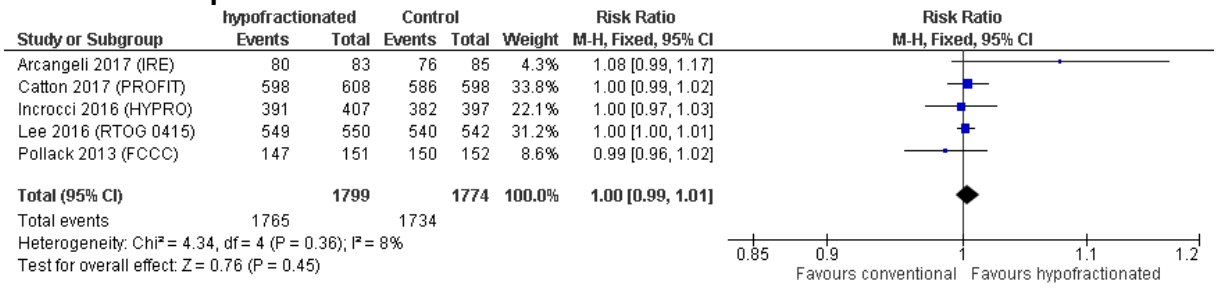
Overall survival



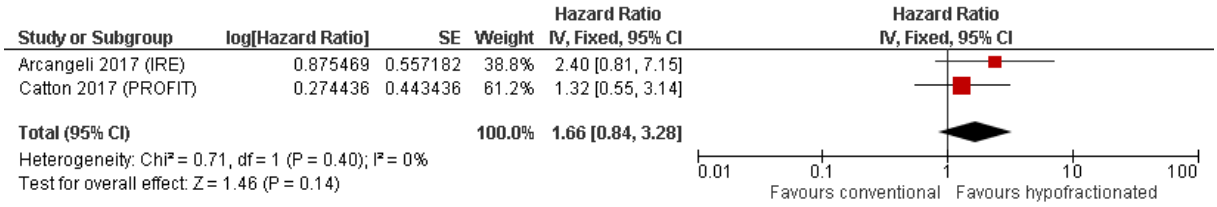
Time to death from any cause



Freedom from prostate cancer-related death

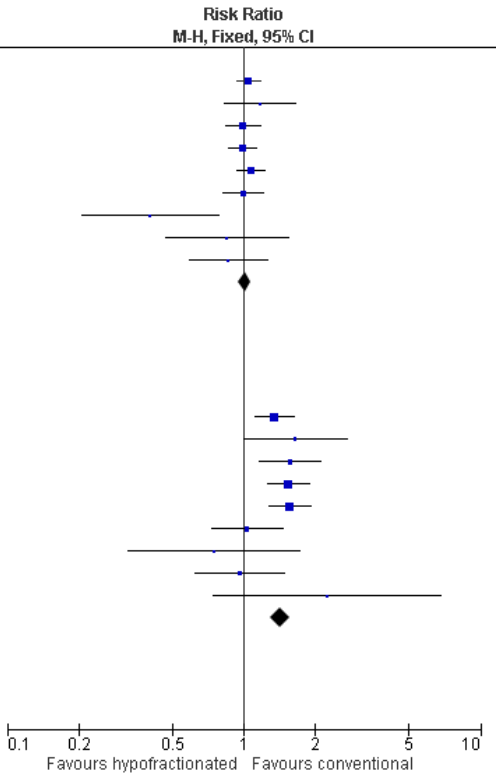


Time to prostate cancer-related death



Acute toxicity

Study or Subgroup	hypofractionated Events	Total	Conventional Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Genitourinary						
Aluwini 2015 (HYPRO) (1)	244	403	226	391	20.8%	1.05 [0.93, 1.18]
Arcangeli 2011 (IRE) (2)	39	83	34	85	3.0%	1.17 [0.83, 1.66]
Catton 2017 (PROFIT) (3)	185	608	183	598	16.7%	0.99 [0.84, 1.18]
Dearnaley 2016 (CHHiP 57gy)	327	713	166	358	20.0%	0.99 [0.86, 1.13]
Dearnaley 2016 (CHHiP 60gy) (4)	356	720	165	357	20.0%	1.07 [0.94, 1.22]
Lee 2016 (RTOG 0415) (5)	147	545	145	534	13.3%	0.99 [0.82, 1.21]
Norkus 2009	9	47	21	44	2.0%	0.40 [0.21, 0.78]
Norkus 2013	16	67	16	57	1.6%	0.85 [0.47, 1.54]
Pollack 2006 (FCCC) (6)	24	50	28	50	2.5%	0.86 [0.59, 1.25]
Subtotal (95% CI)		**3236**		**2474**	**100.0%**	**1.01 [0.95, 1.07]**
Total events	1347		984			
Heterogeneity: Chi² = 10.47, df = 8 (P = 0.23); I² = 24%						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.1.2 Gastrointestinal						
Aluwini 2015 (HYPRO)	169	402	122	391	23.2%	1.35 [1.12, 1.62]
Arcangeli 2011 (IRE)	29	83	18	85	3.3%	1.65 [1.00, 2.73]
Catton 2017 (PROFIT)	99	608	62	598	11.7%	1.57 [1.17, 2.11]
Dearnaley 2016 (CHHiP 57gy)	270	713	88	358	22.0%	1.54 [1.26, 1.89]
Dearnaley 2016 (CHHiP 60gy)	277	720	88	357	22.1%	1.56 [1.27, 1.91]
Lee 2016 (RTOG 0415)	58	545	55	534	10.4%	1.03 [0.73, 1.46]
Norkus 2009	8	47	10	44	1.9%	0.75 [0.33, 1.72]
Norkus 2013	26	67	23	57	4.7%	0.96 [0.62, 1.49]
Pollack 2006 (FCCC)	9	50	4	50	0.7%	2.25 [0.74, 6.83]
Subtotal (95% CI)		**3235**		**2474**	**100.0%**	**1.42 [1.29, 1.56]**
Total events	945		470			
Heterogeneity: Chi² = 11.70, df = 8 (P = 0.17); I² = 32%						
Test for overall effect: Z = 7.08 (P < 0.00001)						



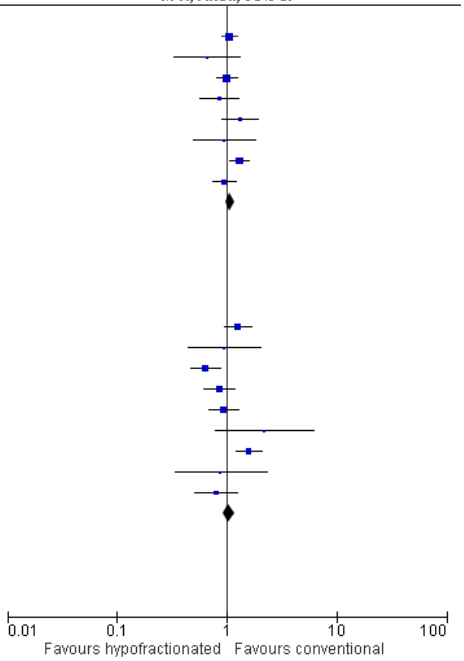
Test for subgroup differences: Chi² = 33.77, df = 1 (P < 0.00001), I² = 97.0%

Footnotes

(1) 3-months (defined as between 60 - 120 days after RT completion)
(2) 3-months
(3) Defined acute toxicity as worst grade in first 14 weeks
(4) 18 week acute period; conventional sample size split to account for double-comparison
(5) 90-days
(6) 3-months

Late toxicity

Study or Subgroup	hypofractionated Events	Total	Conventional Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Genitourinary						
Aluwini 2016 (HYPRO) (1)	163	395	151	387	25.3%	1.06 [0.89, 1.26]
Arcangeli 2017 (IRE) (2)	11	83	17	85	2.8%	0.66 [0.33, 1.33]
Catton 2017 (PROFIT) (3)	136	608	134	598	22.4%	1.00 [0.81, 1.23]
Dearnaley 2016 (CHHiP 57gy) (4)	57	1057	33	520	7.3%	0.85 [0.56, 1.29]
Dearnaley 2016 (CHHiP 60gy) (5)	88	1049	33	520	7.3%	1.32 [0.90, 1.94]
Hoffman 2014 (6)	15	102	16	102	2.6%	0.94 [0.49, 1.79]
Lee 2016 (RTOG 0415) (7)	161	545	121	534	20.2%	1.30 [1.06, 1.60]
Pollack 2013 (FCCC)	68	151	73	152	12.1%	0.94 [0.74, 1.19]
Subtotal (95% CI)		**3990**		**2898**	**100.0%**	**1.07 [0.97, 1.18]**
Total events	699		578			
Heterogeneity: Chi² = 9.52, df = 7 (P = 0.22); I² = 26%						
Test for overall effect: Z = 1.40 (P = 0.16)						
1.10.2 Gastrointestinal						
Aluwini 2016 (HYPRO)	87	395	68	387	15.8%	1.25 [0.94, 1.67]
Arcangeli 2017 (IRE)	11	83	12	85	2.7%	0.94 [0.44, 2.01]
Catton 2017 (PROFIT)	54	608	83	598	19.2%	0.64 [0.46, 0.88]
Dearnaley 2016 (CHHiP 57gy)	95	1057	55	520	16.9%	0.85 [0.62, 1.16]
Dearnaley 2016 (CHHiP 60gy)	105	1049	56	520	17.2%	0.93 [0.68, 1.26]
Hoffman 2014	11	102	5	102	1.1%	2.20 [0.79, 6.11]
Lee 2016 (RTOG 0415)	121	545	75	534	17.4%	1.58 [1.22, 2.05]
Marzi 2009 (8)	7	81	8	81	1.8%	0.88 [0.33, 2.30]
Pollack 2013 (FCCC)	27	151	34	152	7.8%	0.80 [0.51, 1.26]
Subtotal (95% CI)		**4071**		**2979**	**100.0%**	**1.03 [0.91, 1.16]**
Total events	518		396			
Heterogeneity: Chi² = 25.76, df = 8 (P = 0.001); I² = 69%						
Test for overall effect: Z = 0.45 (P = 0.65)						



Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%

Footnotes

(1) 3 years
(2) up to 10 years (although only small number of participants still alive)
(3) 5 years (from 6 months post-RT)
(4) 5-years
(5) 5-years
(6) 5 years (anything after 90days)
(7) 5-years
(8) 30-month

Appendix G: GRADE tables

Conventional versus hypofractionated radiotherapy: survival and adverse events outcomes

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall freedom from biochemical failure- RR >1 favours hypofractionated										
4 studies RENCI: Arcangeli 2017 Lee 2016 PROFIT: Catton 2017 HYPRO: Incrocci 2016	RCTs	3,270	RR 1.03 (1.00, 1.06)	840 per 1000 people[6]	866 per 1000 people (from 26 fewer to 25 more)[6]	Not serious	Not serious	Not serious	Not serious	High
Time to biochemical failure– HR >1 favours hypofractionated										
2 studies RENCI: Arcangeli 2017 Lee 2016	RCTs	1,260	HR 1.39 (0.99, 1.96)	-	-	Not serious	Serious[4]	Not serious	Serious[2]	Low
Overall freedom from biochemical-clinical failure- RR >1 favours hypofractionated										
6 studies FCCC: Pollack 2013* HYPRO: Incrocci 2016 Lee 2016** PROFIT: Catton 2017	RCTs	6,621	RR 1.01 (0.99, 1.03)	896 per 1000 people[5]	905 per 1000 people (from 18 fewer to 18 more)[5]	Not serious	Not serious	Not serious	Serious[2]	Moderate

CHHiP Dearnaley 2016***										
Time to biochemical-clinical failure- HR <1 favours hypofractionated										
6 studies FCCC: Pollack 2013* HYPRO: Incrocci 2016 Lee 2016** PROFIT: Catton 2017 CHHiP Dearnaley 2016***	RCTs	6,621	HR 1.03 (0.93, 1.14)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
Subgroup analysis patients aged ≥75 years										
CHHiP Dearnaley 2016***	RCTs	491	HR 0.59 (0.38, 0.92)	-	-	Not serious	N/A	Not serious	Not Serious	High
Subgroup analysis patients aged <75 years										
CHHiP Dearnaley 2016***	RCTs	2,725	1.11 (0.92, 1.33)	-	-	Not serious	n/a	Not serious	Serious[2]	Moderate
Overall survival (5 to 10 years)- RR >1 favours hypofractionated										
7 studies RENCI: Arcangeli 2017 FCCC: Pollack 2013	RCTs	6,789	RR 1.01 (0.99, 1.03)	922 per 1000 people at 5 years[5]	932 per 1000 people (from 18 fewer to 18 more) at 5 years[5]	Not serious	Not serious	Not serious	Not serious	High

HYPRO: Incrocci 2016 Lee 2016 PROFIT: Catton 2017 CHHiP Dearnaley 2016***										
Time to any-cause death- HR >1 favours hypofractionated										
6 studies RENCI: Arcangeli 2017 FCCC: Pollack 2013 HYPRO: Incrocci 2016 Lee 2016 PROFIT: Catton 2017 CHHiP Dearnaley 2016***	RCTs	6,486	HR 1.13 (0.97, 1.33)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
Freedom from prostate cancer-related death – RR>1 favours hypofractionated										
5 studies RENCI: Arcangeli 2017 FCCC: Pollack 2013 HYPRO: Incrocci 2016 Lee 2016 PROFIT: Catton 2017	RCTs	3,553	RR 1.00 (0.99, 1.01)	984 per 1000 people at 5 years[6]	984 per 1000 people (from 10 fewer to 10 more) at 5 years[6]	Not serious	Not serious	Not serious	Not serious	High
Time to prostate cancer-related death – HR>1 favours hypofractionated										

2 studies RENCI: Arcangeli 2017 PROFIT: Catton 2017	RCTs	1,374	HR 1.66 (0.84, 3.28)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
Acute genitourinary toxicity - RR<1 favours hypofractionated										
9 studies HYPRO: Aluwini 2015 RENCI: Arcangeli 2011 PROFIT: Catton 2017 CHHiP: Dearnaley 2016*** Lee 2016 Norkus 2009 Norkus 2013 FCCC: Pollack 2006	RCTs	5,710	RR 1.01 (0.95, 1.07)	398 per 1000 people	402 per 1000 people (from 24 fewer to 24 more)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Acute gastrointestinal toxicity - RR<1 favours hypofractionated										
9 studies HYPRO: Aluwini 2015 RENCI: Arcangeli 2011 PROFIT: Catton 2017	RCTs	5,709	RR 1.42 (1.29, 1.56)	190 per 1000 people	270 per 1000 people (from 25 fewer to 26 more)	Serious[1]	Not serious	Not serious	Not serious	Moderate

CHHiP: Dearnaley 2016*** Lee 2016 Norkus 2009 Norkus 2013 FCCC: Pollack 2006										
Late genitourinary toxicity - RR<1 favours hypofractionated										
8 studies HYPRO: Aluwini 2016 RENCI: Arcangeli 2017 PROFIT: Catton 2017 CHHiP: Dearnaley 2016*** Hoffman 2014 Lee 2016 FCCC: Pollack 2006	RCTs	6,888	RR 1.07 (0.97, 1.18)	199 per 1000 people	213 per 1000 people (from 20 fewer to 22 more)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Late gastrointestinal toxicity - RR<1 favours hypofractionated										
9 studies HYPRO: Aluwini 2016 RENCI: Arcangeli 2017	RCTs	7,050	RR 1.03 (0.91, 1.16)	133 per 1000 people	137 per 1000 people (from 16 fewer to 17 more)	Serious[1]	Serious[4]	Not serious	Not serious	Low

PROFIT: Catton 2017 CHHiP: Dearnaley 2016*** Hoffman 2014 Lee 2016 FCCC: Pollack 2006 Marzi 2009 ****										

1. Blinding procedures were not possible/attempted and this may have affected the reporting and/or scoring of this outcome
2. 95% confidence intervals for the effect size crossed the line of no effect – downgraded once
3. 95% confidence intervals for the effect size crossed one line of the MID – downgraded once
4. $I^2 > 33.3\%$
5. Follow-up length 5 years with exception of one study (RENCI: 10-years). A 5-year estimate was calculated using CHHiP study as a control
6. Follow-up length 5 years with exception of one study (RENCI: 10-years). A 5-year estimate was calculated using PROFIT study as a control

* Considered the start of any salvage therapy (ADT, cryosurgery or prostatectomy) as evidence of clinical failure.

** considered death by any cause as evidence of clinical failure.

*** Study was split in analysis to 57Gy and 60Gy arms. Conventional fractionation data was halved to account for this.

**** Study period of 30-months.

Conventional versus hypofractionated radiotherapy: Quality of life outcomes over time

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Time to worsening of IPSS overall- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	303	HR 0.90 (0.46, 1.78)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of IPSS Quality of life- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	303	HR 1.47 (0.62, 3.48)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of urinary incontinence (EPIC) – HR<1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	225	HR 1.91 (0.97, 3.76)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening urinary irritative/obstructive (EPIC)- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	225	HR 0.40 (0.10, 1.55)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening sexual bother (EPIC)- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	225	HR 2.27 (0.68, 4.91)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening hormonal bother (EPIC)- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	225	HR 1.22 (0.59, 2.55	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low

Time to worsening bowel bother (EPIC)- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	225	HR 0.77 (0.25, 2.36)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening visual analogue scale scores (EQ5D)- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	215	HR 1.61 (0.42, 6.18)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening EQ5D Index scores- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study FCCC: Shaikh (2017)	RCTs	215	HR 2.13 (0.60, 7.56)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall urinary bother- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study CHHiP: Wilkins 2015 (60Gy)*	RCTs	1560 across all three arms	HR 1.03 (0.72 – 1.48	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low
1 Study CHHiP: Wilkins 2015 (57Gy)*	RCTs		HR 0.85 (0.58 – 1.24)	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall bowel bother- HR <1 favours better outcomes associated with hypofractionated over time										
1 Study CHHiP: Wilkins 2015 (60Gy)*	RCTs	1762 across all three arms	HR 1.10 (0.80 – 1.48)	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low
1 Study CHHiP: Wilkins 2015 (57Gy)*	RCTs		HR 0.90 (0.65 – 1.24)	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall sexual bother- HR <1 favours better outcomes associated with hypofractionated over time										

1 Study CHHiP: Wilkins 2015 (60Gy)*	RCTs	997 across all three arms	HR 1.19 (0.92 – 1.55)	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low
1 Study CHHiP: Wilkins 2015 (57Gy)*	RCTs		HR 1.14 (0.88 – 1.48)	-	-	Very serious[1, 4]	N/A	Not serious	Serious[2]	Very low

1. Blinding was not attempted/possible and this had a high risk of biasing the outcome, there is also variability between questionnaires in response rate.
2. 95% confidence intervals for the effect size crossed the line of no effect – downgraded once

* Measured using a combination of both EPIC and UCLA-PCI QoL instruments

External beam radiotherapy (EBRT) alone versus EBRT plus low-dose-rate brachytherapy (LDR-BT)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Time to biochemical failure- HR >1 favours brachytherapy										
1 study ASCENDE-RT (Morris, 2016)	RCTs	398	HR 2.04* (1.25, 3.33)	-	-	Not serious	N/A	Not serious	Not serious	High
Time to any-cause death– HR >1 favours brachytherapy										
1 study ASCENDE-RT (Morris, 2016)	RCTs	398	HR 1.13** (0.69, 1.85)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
Freedom from prostate cancer-related death– RR >1 favours brachytherapy										

1 study ASCENDE-RT (Morris, 2016)	RCTs	398	RR 1.02 (0.98, 1.06)	945 per 1000 people	948 per 1000 people (7 fewer to 5 more)	Not serious	N/A	Not serious	Not serious	High
Acute GU toxicity– RR <1 favours brachytherapy										
1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	RR 2.24 (1.55, 3.23)	164 per 1000 people	368 per 1000 people (from 114 fewer to 162 more)	Serious[1]	N/A	Not serious	Not serious	Moderate
Acute GI toxicity– RR <1 favours brachytherapy										
1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	RR 1.01 (0.82, 1.25)	143 per 1000 people	145 per 1000 people (from 26 fewer to 35 more)	Serious[1]	N/A	Not serious	Not serious	Moderate
5-year urinary toxicity: Usage of pads– RR < favours brachytherapy										
1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	RR 2.95 (1.58, 5.51)	60 per 1000 people	177 per 1000 people (from 82 fewer to 153 more)	Serious[1]	N/A	Not serious	Not serious	Moderate
5-year catheterization– RR <1 favours brachytherapy										
1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	RR 3.70 (1.53, 8.94)	30 per 1000 people	111 per 1000 people (from 65 fewer to 157 more)	Serious[1]	N/A	Not serious	Not serious	Moderate
Time to grade 2 late GU toxicity– HR >1 favours brachytherapy										
1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	HR 0.51 (0.33, 0.77)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Time to grade 2 late GI toxicity– HR >1 favours brachytherapy										

1 study ASCENDE-RT (Rodda, 2017)	RCTs	383	HR 0.75 (0.48, 1.17)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low

1. Blinding procedures were not possible/attempted and this had the potential to impact on the reporting and/or scoring of this outcome
2. 95% confidence intervals crosses the line of no effect – downgraded once

*Taken from multivariate analysis controlling for log pre-treatment PSA, percentage of positive cores, clinical T stage, and Gleason sum: HR 2.17 in univariate analysis.

**Taken from multivariate analysis controlling for age, disease status (relapse vs. no relapse) and log pre-treatment PSA: HR 1.29 in univariate analysis.

Appendix H – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Abdel-Wahab (2009)	Radiotherapy: Encouraging early data for SBRT in prostate cancer	Conference abstract
Abramowitz (2012)	Hypofractionated radiotherapy for prostate cancer: Has the time come?	Review article but not a systematic review
Al-Mamgani (2008)	Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer	Dose-escalation or high vs low dose
Aluwini (2012)	Acute toxicity of the randomized phase III Dutch Hypofractionation Trial (hypro)for prostate cancer	Conference abstract
Amini (2016)	Survival Outcomes of Dose-Escalated External Beam Radiotherapy versus Combined Brachytherapy for Intermediate and High Risk Prostate Cancer Using the National Cancer Data Base	Not a relevant study design Non-randomised, retrospective
Annamalai (2015)	Combined HDR brachytherapy boost plus external beam radiotherapy by IMRT versus external beam radiotherapy alone IMRT in intermediate-and high-risk prostate cancer: dosimetric analysis from a randomized control trial	Conference abstract
Annamalai (2016)	Randomized control trial between HDR brachytherapy and intensity modulated radiotherapy in localized prostate cancer: analysis of acute and late toxicity and health related quality of life	Conference abstract Full text paper not available
Anonymous (2008)	Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial (Journal of the American Medical Association (2005) 294, 10, (1233-1239))	Conference abstract
Beckendorf (2011)	70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial	Dose-escalation or high vs low dose
Botrel (2013)	Hypofractionated external-beam radiation therapy (HEBRT) versus conventional external-beam radiation (CEBRT) in patients with localized prostate cancer: a systematic review and meta-analysis (Provisional abstract)	Conference abstract
Bychkova (2015)	Radiosensitivity of bone metastases according to different histogenesis	Conference abstract Full text paper not available

Short Title	Title	Reason for exclusion
Bychkova (2017)	Clinical features of bone metastases and their importance for radiotherapy	Conference abstract Full text paper not available
Cameron (2014)	Palliative pelvic radiotherapy of symptomatic incurable prostate cancer - a systematic review	Study does not contain any of the outcomes of interest
Cao (2017)	Moderate hypofractionated radiotherapy is more effective and safe for localized prostate cancer patients: A meta-analysis	Systematic review
Chatzikonstantinou (2017)	High-dose-rate brachytherapy as salvage modality for locally recurrent prostate cancer after definitive radiotherapy : A systematic review	Comparator in study does not match that specified in protocol
Cozzarini (2017)	Patient-reported urinary incontinence after radiotherapy for prostate cancer: Quantifying the dose-effect	Conference abstract
D'Ambrosio (2008)	Assessment of External Beam Radiation Technology for Dose Escalation and Normal Tissue Protection in the Treatment of Prostate Cancer	Review article but not a systematic review
Datta (2017)	Conventional Versus Hypofractionated Radiation Therapy for Localized or Locally Advanced Prostate Cancer: A Systematic Review and Meta-analysis along with Therapeutic Implications	Systematic review
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
Di Franco (2017)	Rectal/urinary toxicity after hypofractionated vs. conventional radiotherapy in high risk prostate cancer: systematic review and meta-analysis	Systematic review
El-Ghamrawi (2015)	Hypofractionated Simultaneous Integrated Boost (SIB) versus Conventional Fractionation in Localized Prostate Cancer: A Randomized Pilot Study	Hypo boost versus conventional
Felix (2012)	Morbidity results in a prospective randomized trial of hypofractionation versus standard fractionation for prostate cancer using conformal radiation therapy	Conference abstract Full text paper not available
Gardner (2008)	Brachytherapy for prostate cancer	Conference abstract
Goldner (2014)	MRC RT01 randomized trial on 64 Gy vs. 74 Gy in localized primary prostate cancer: significant improvement in biochemical control, but still no significant improvement in long-term survival	Study not reported in English
Guix (2016)	Dose escalation with high-dose-3D-conformal/ IMRT (HD-3D-CRT/IMRT) compared with low-dose 3D-conformal/IMRT plus HDR	Conference abstract

Short Title	Title	Reason for exclusion
	brachytherapy (LD-3D-CRT/IMRTDHDR-B) for intermediate- or high-risk prostate cancer: higher disease control and survival with lower toxicity	Full text paper not available
Gulliford (2010)	A comparison of dose-volume constraints derived using peak and longitudinal definitions of late rectal toxicity	Study does not contain any relevant interventions
Hannan (2016)	Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial	Comparator in study does not match that specified in protocol Not a relevant study design - cohort study
Hannoun-Levi (2017)	Brachytherapy for prostate cancer: present and future	Study not reported in English
Heemsbergen (2010)	Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics	Dose-escalation or high vs low dose
Heemsbergen (2014)	Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival	Dose-escalation or high vs low dose
Helou (2014)	A comparative study of quality of life in patients with localized prostate cancer treated at a single institution: stereotactic ablative radiotherapy or external beam+high dose rate brachytherapy boost	Study does not contain any relevant interventions
Helou (2015)	High dose-rate brachytherapy boost for intermediate risk prostate cancer: Long-term outcomes of two different treatment schedules and early biochemical predictors of success	Comparison of differing brachytherapy doses
Helou (2017)	Stereotactic ablative radiotherapy in the treatment of low and intermediate risk prostate cancer: Is there an optimal dose?	Not a relevant study design - non-randomised
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 Full text paper not available
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 Full text paper not available
Hoskin (2007)	High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial	Pre-2008 and not linked to later study
Hoskin (2012)	Quality of Life after radical radiotherapy for prostate cancer: results from a randomised trial of EBRT + HDR-BT	Conference abstract

Short Title	Title	Reason for exclusion
Hoskin (2012)	High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence	Comparison of differing brachytherapy doses
Hoskin (2012)	Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer	Brachytherapy plus hypofractionated EBRT vs hypofractionated EBRT alone
Hoskin (2013)	Quality of life after radical radiotherapy for prostate cancer: longitudinal study from a randomised trial of external beam radiotherapy alone or in combination with high dose rate brachytherapy	Brachytherapy plus hypofractionated EBRT vs hypofractionated EBRT alone
Hoskin (2017)	Single-dose high-dose-rate brachytherapy compared to two and three fractions for locally advanced prostate cancer	Comparison of differing brachytherapy doses
Hou (2014)	High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up (Provisional abstract)	Study does not contain any relevant interventions
Hu (2011)	Genetic polymorphisms of DNA repair and inflammatory responses as determinants of late toxicity in prostate cancer patients who received radiotherapy in a randomized trial	Conference abstract Full text paper not available
Hurwitz (2011)	Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: long-term results of CALGB 99809	Comparison of differing brachytherapy doses
Johnson (2016)	Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized prostate cancer	Comparison of hypofractionated arms without interventional arm
Kim (2013)	A phase II study of hypofractionated proton therapy for prostate cancer	Conventional arm under 70gy
Konski (2015)	Quality adjusted survival comparing standard versus hypofractionated radiation therapy in the treatment of prostate cancer	Conference abstract Full text paper not available
Koontz (2015)	A systematic review of hypofractionation for primary management of prostate cancer	Systematic review
Kotecha (2016)	Dose-Escalated Stereotactic Body Radiation Therapy for Patients With Intermediate- and High-Risk Prostate Cancer: Initial Dosimetry Analysis and Patient Outcomes	Comparison of hypofractionated arms without interventional arm
Koukouraki s (2011)	Treatment of low-risk prostate cancer with radical hypofractionated accelerated radiotherapy with cytoprotection (HypoARC): an interim analysis of toxicity and efficacy	Not a relevant study design - non-randomised

Short Title	Title	Reason for exclusion
Kozuka (2017)	Acute and late complications after hypofractionated intensity modulated radiotherapy in prostate cancer	Waiting for paper
Kuban (2008)	Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer	Dose-escalation or high vs low dose
Kumbhaj (2013)	Single v/s multiple fraction radiotherapy for palliation of painful vertebral bone metastases in prostate cancer: a prospective study	Comparator in study does not match that specified in protocol Study does not contain any of the outcomes of interest
Landoni (2015)	Macroscopic hematuria after conventional or hypofractionated radiation therapy: results from a prospective phase 3 study	Conference abstract Full text paper not available
Liao (2010)	Hypofractionation: what does it mean for prostate cancer treatment?	Not a relevant study design - Non-randomised
Lieng (2017)	Long-term outcomes of a phase II trial of moderate hypofractionated image-guided intensity modulated radiotherapy (IG-IMRT) for localized prostate cancer	Study does not contain any relevant interventions Not a relevant study design - cohort study
Liu (2016)	Hypofractionated Helical Tomotherapy for Older Aged Patients With Prostate Cancer: Preliminary Results of a Phase I-II Trial	Not a relevant study design - non-randomised
Lukka (2005)	Randomized trial comparing two fractionation schedules for patients with localized prostate cancer.	Pre-2008 and not linked to later study
Manikandan (2014)	Dosimetric analysis of external beam radiotherapy plus HDR brachytherapy boost vs. External beam radiotherapy alone (IMRT) in intermediate and high risk prostate cancer: early results of biologically equivalent dose-volume parameters from a randomized control trial	Conference abstract
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 prospectiverandomized control trial	Conference abstract Full text paper not available
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 Full text paper not available

Short Title	Title	Reason for exclusion
Massaccesi (2013)	Hypofractionated intensity-modulated radiotherapy with simultaneous integrated boost after radical prostatectomy: Preliminary results of a phase II trial	Comparator in study does not match that specified in protocol
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	Comparison of differing brachytherapy doses
Michalski (2013)	Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial	Study does not contain any relevant interventions
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)	Dose-escalation or high vs low dose
Michalski (2015)	A randomized trial of 79.2Gy versus 70.2Gy radiation therapy (RT) for localized prostate cancer	Conference abstract Full text paper not available
Miralbell (2012)	Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9-2.2) Gy	Uses pooled results from several studies, some of which do not meet inclusion criteria
Mohammed (2012)	Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer	Not a relevant study design - Non-randomised
Moningi (2017)	Consideration of patient characteristics and comorbidity in selecting candidates for moderately hypofractionated radiation: secondary analysis from a randomized trial	Conference abstract Full text paper not available
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)	LDR brachytherapy is superior to 78 Gy of EBRT for unfavourable risk prostate cancer: the results of a randomized trial	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 Full text paper not available
Morton (2010)	Single-Fraction High-Dose-Rate Brachytherapy and Hypofractionated External Beam Radiotherapy for Men With Intermediate-Risk Prostate Cancer: Analysis of Short- and Medium-Term Toxicity and Quality of Life	Comparator in study does not match that specified in protocol
Murgic (2017)	Comparison of conventionally fractionated and hypofractionated schedule for post-	Conference abstract

Short Title	Title	Reason for exclusion
	prostatectomy salvage radiotherapy: early results from non-randomized observational study	Full text paper not available
Murray (2016)	Effect of dose and image guided radiation therapy (IGRT) on patient-reported sexual function in prostate radiation therapy	Conference abstract Full text paper not available
Nabid (2015)	A phase III trial of short-term androgen deprivation therapy in intermediate-risk prostate cancer treated with radiotherapy	Dose-escalation or high vs low dose
Naismith (2014)	Forward and inverse-planned intensity-modulated radiotherapy (IMRT) in the CHHiP trial: a comparison of dosimetry and normal tissue toxicity	Conference abstract Full text paper not available
Nakajima (2017)	Acute toxicity of image-guided hypofractionated proton therapy for localized prostate cancer	Not a relevant study design - Cohorts treated at different time points
Nguyen (2010)	Rectal dose-volume histogram parameters are associated with long-term patient-reported gastrointestinal quality of life after conventional and high-dose radiation for prostate cancer: a subgroup analysis of a randomized trial	dose-escalation or high vs low dose
Niazi (2017)	Phase 3 study of hypofractionated, dose escalation radiation therapy for high-risk adenocarcinoma of the prostate	Conference abstract Full text paper not available
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 of the outcomes of interest
Orio (2016)	The decreased use of brachytherapy boost for intermediate and high-risk prostate cancer despite evidence supporting its effectiveness	Not a relevant study design - Non-RCT
Palorini (2016)	Multi-variable models of large International Prostate Symptom Score worsening at the end of therapy in prostate cancer radiotherapy	
Pellizzon (2011)	High-dose-rate brachytherapy combined with hypofractionated external beam radiotherapy for men with intermediate or high risk prostate cancer: Analysis of short- and medium-term urinary toxicity and biochemical control	Not a relevant study design - Non-randomised
Pieters (2009)	Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: a systematic review	Systematic review
Pinkawa (2009)	Impact of the target volume (prostate alone vs. prostate with seminal vesicles) and fraction dose	Not a relevant study design

Short Title	Title	Reason for exclusion
	(1.8 Gy vs. 2.0 Gy) on quality of life changes after external-beam radiotherapy for prostate cancer	- Non-randomised
Prada (2008)	High-dose-rate intensity modulated brachytherapy with external-beam radiotherapy improves local and biochemical control in patients with high-risk prostate cancer	Comparator in study does not match that specified in protocol
Pugh (2017)	NRG Oncology/RTOG 0415, hypofractionation in patients with low-risk prostate cancer: are patient reported outcomes the practice change tipping point?	Conference abstract Full text paper not available
Quon (2012)	Quality of life after hypofractionated concomitant intensity-modulated radiotherapy boost for high-risk prostate cancer	Study does not contain any relevant interventions Not a relevant study design - non-randomised
Rodda (2015)	Quality of life outcomes: ascende-RT a multicenter randomized trial of radiation therapy for prostate cancer	Conference abstract Full text paper not available
Rodda (2015)	GU and GI toxicity in ASCENDE-RT*: a multicentre randomized trial of dose-escalated radiation for prostate cancer	Conference abstract Full text paper not available
Rodda (2015)	Toxicity outcomes in ascende-RT: a multicenter randomized trial of dose-escalation trial for prostate cancer	Conference abstract Full text paper not available
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	Data not reported in an extractable format
Royce (2017)	Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer: A Meta-analysis of Randomized Noninferiority Trials	Systematic review
Sanchez-Gomez (2015)	Hypofractionated radiation therapy versus conventional radiation therapy in prostate cancer: A systematic review of its safety and efficacy	More recent systematic review included that covers the same topic
Sathya (2005)	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.	Pre-2008 and not linked to later study
Schulz (2011)	Dose escalation in the radiation therapy of prostate cancer	Review article but not a systematic review
Serrano (2015)	Permanent prostate brachytherapy using high V150	Comparison of differing

Short Title	Title	Reason for exclusion
		brachytherapy doses
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 Full text paper not available
Sivanandan (2016)	Prostate Hypofractionated Radiotherapy Trial Results Need to be Interpreted with Caution due to Undertreatment of the Control Arm in the CHHiP Trial	Not a relevant study design - Comment only
Spagnoletti (2013)	Biochemical control after radiation therapy for prostate cancer: hypofractionation versus conventional fractionation	Conference abstract Full text paper not available
Stock (2017)	Performance of a palladium-103 line source for prostate brachytherapy implants: A Phase I trial	Comparator in study does not match that specified in protocol Not a relevant study design - Non-randomised
Strigari (2009)	Mathematical model for evaluating incidence of acute rectal toxicity during conventional or hypofractionated radiotherapy courses for prostate cancer	Data not reported in an extractable format
Sun (2014)	Erratum to: Who benefits from hypofractionated radiation therapy for clinically localized prostate cancer: evidence from meta-analysis [Tumor Biology, DOI 10.1007/s13277-014-2297-y]	Not a relevant study design - Erratum only
Sun (2014)	Who benefits from hypofractionated radiation therapy for clinically localized prostate cancer: evidence from meta-analysis	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)	Dose-escalation or high vs low dose
Taneja (2014)	Re: Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer	Review article but not a systematic review
Thomson (2012)	Dose-escalated hypofractionated intensity-modulated radiotherapy in high-risk carcinoma of the prostate: Outcome and late toxicity	Comparison of hypofractionated arms without interventional arm
Valdagni (2011)	Long-term biochemical control of prostate cancer after standard or hyper-fractionation: evidence for different outcomes between low-intermediate and high risk patients	Study does not contain any relevant interventions
Vargas (2015)	Hypofractionated Versus Standard Fractionated Proton-beam Therapy for Low-risk Prostate Cancer: Interim Results of a Randomized Trial PCG GU 002	

Short Title	Title	Reason for exclusion
Viani (2009)	Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials	Dose-escalation or high vs low dose
Viani (2012)	High-dose conformal radiotherapy reduces prostate cancer-specific mortality: results of a meta-analysis	Dose-escalation or high vs low dose
Viani (2013)	Acute toxicity profile in prostate cancer with conventional and hypofractionated treatment	Not a relevant study design - non-randomised
Viani (2016)	Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: a randomized clinical trial	Comparator in study does not match that specified in protocol
Vogelius (2011)	A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer: in regard to Arcangeli C, et al. (Int J Radiat Oncol Biol Phys 2010;78: 11-18)	Review article but not a systematic review
Voong (2017)	Long-term economic value of hypofractionated prostate radiation: secondary analysis of a randomized trial	Study does not contain any of the outcomes of interest
Wang (2017)	Clinical outcomes and late toxicity of hypofractionated intensity-modulated radiotherapy for high-risk prostate cancer	Conference abstract
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
Wendling (2010)	Hypofractionated RT effective in high-risk prostate cancer	Full text paper not available
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
Wiegel (2015)	PREFEREnce-based randomized evaluation of treatment modalities in low or early intermediate-risk prostate cancer	Conference abstract
Wilder (2010)	Preliminary results in prostate cancer patients treated with high-dose-rate brachytherapy and intensity modulated radiation therapy (IMRT) vs. IMRT alone	Not a relevant study design - Non-randomised

Short Title	Title	Reason for exclusion
Wilkins (2015)	Patient reported outcomes of overall bowel and urinary bother in the CHHiP trial (CRUK: 8262/A7257)	Conference abstract Full text paper not available
Witte (2010)	Relating dose outside the prostate with freedom from failure in the Dutch trial 68 Gy vs. 78 Gy	Study does not contain any relevant interventions
Wortel (2017)	Local Protocol Variations for Image Guided Radiation Therapy in the Multicenter Dutch Hypofractionation (HYPRO) Trial: impact of Rectal Balloon and MRI Delineation on Anorectal Dose and Gastrointestinal Toxicity Levels	Study does not contain any of the outcomes of interest
Xiang (2015)	Significant association of brachytherapy boost with reduced prostate cancer-specific mortality in contemporary patients with localized, unfavorable-risk prostate cancer	Not a relevant study design - Non-randomised
Xiong (2014)	Comparative efficacy and safety of treatments for localised prostate cancer: An application of network meta-analysis	Systematic review
Xu (2011)	Toxicity analysis of dose escalation from 75.6 gy to 81.0 gy in prostate cancer	Dose-escalation or high vs low dose
Yeoh (2009)	Anorectal function after three- versus two-dimensional radiation therapy for carcinoma of the prostate	Study does not contain any relevant interventions Comparator in study does not match that specified in protocol
Yeoh (2011)	Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial	Conventional arm under 70gy
Zaorsky (2013)	Systematic review of hypofractionated radiation therapy for prostate cancer	Systematic review
Zaorsky (2014)	High dose rate brachytherapy boost for prostate cancer: a systematic review	Systematic review
Zaorsky (2015)	What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation	Dose-escalation or high vs low dose
Zaorsky (2016)	Impact of Radiation Therapy Dose Escalation on Prostate Cancer Outcomes and Toxicities	Study does not contain any relevant interventions
Zapatero (2016)	Late Radiation and Cardiovascular Adverse Effects After Androgen Deprivation and High-Dose Radiation Therapy in Prostate Cancer: results From the DART 01/05 Randomized Phase 3 Trial	Study does not contain any relevant interventions

Short Title	Title	Reason for exclusion
Zhu (2014)	Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis	Systematic review
Zietman (2010)	Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09	Dose-escalation or high vs low dose
Zietman (2013)	RETRACTED: High-dose conformal radiotherapy reduces prostate cancer-specific mortality: results of a meta-analysis Int J Radiat Oncol Biol Phys 2012;83:e619-e625	Study retracted due to mistakes in data
Zilli (2010)	Dose escalation study with two different hypofractionated intensity modulated radiotherapy techniques for localized prostate cancer: acute toxicity	Comparison of hypofractionated arms without interventional arm

Economic **studies**

Short Title	Title	Reason for exclusion
Amin et al. 2014	Systematic Review of the Cost Effectiveness of Radiation Therapy for Prostate Cancer from 2003 to 2013	Reporting findings from other studies, already found in the search
Arabloo et al. 2016	Health technology assessment of image-guided radiotherapy (IGRT): A systematic review of current evidence	Not applicable HTA from Iran
Arcangeli et al. 2016	Hypo-fractionated radiotherapy for organ-confined prostate cancer: is less more?	Reporting findings from other studies, already found in the search
Becerra et al. 2016	Economic evaluation of treatments for patients with localized prostate cancer in Europe: a systematic review	Reporting findings from other studies, already found in the search
Cooperberg et al 2013	Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis	Out of the scope, comparing RT to surgery; doses and number of fractions are not reported
Haque et al 2017	Stereotactic body radiation therapy for prostate cancer-a review	Reporting findings from other studies, already found in the search
Hayes et al 2010	Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis	Not economic evaluation
Musunuru et al 2015	Clinical trials of stereotactic ablative radiotherapy for prostate cancer: updates and future direction	Reporting findings from other studies, already found in the search
Sommers et al. 2008	Predictors of patient preferences and treatment choices for localized prostate cancer	Not economic evaluation
Verma et al 2016	A systematic review of the cost and cost-effectiveness studies of proton radiotherapy	Reporting findings from other studies, already found in the search
Voong et al 2017	Long-term economic value of hypo-fractionated prostate radiation:	Cost analysis comparing CIMRT 42 fractions for 8.4 weeks vs HIMRT 30 fractions for 6 weeks

Short Title	Title	Reason for exclusion
	Secondary analysis of a randomized trial	
Yu et al. 2014	Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity	Cost analysis comparing SBRT to IMRT
Gray et al. 2013	Proton beam radiation therapy for prostate cancer - Is the hype (and the cost) justified?	Proton therapy is out of the scope
Hummel et al 2012	A Model of the Cost-effectiveness of Intensity-modulated Radiotherapy in Comparison with Three-dimensional Conformal Radiotherapy for the Treatment of Localised Prostate Cancer	comparing IMRT with 3DCRT, both delivered with the conventional fractionation
Muralidhar et al. 2017	Maximizing resources in the local treatment of prostate cancer: A summary of cost-effectiveness studies	Reporting findings from other studies, already found in the search
Pistis et al. 2010	External beam radiotherapy plus high-dose-rate brachytherapy for treatment of locally advanced prostate cancer: the initial experience of the Catalan Institute of Oncology	Not economic evaluation
Sharieff et al. 2016	The Technique, Resources and Costs of Stereotactic Body Radiotherapy of Prostate Cancer: A Comparison of Dose Regimens and Delivery Systems	Out of the scope as the study's focus is on the delivery method of the radiation therapy (robotic vs arc-based vs fixed gentry).
Tan et al 2014	Stereotactic body radiotherapy for primary prostate cancer: A systematic review	Reporting findings from other studies, already found in the search
Vigneri et al 2010	The second decade of prostate brachytherapy: evidence and cost based outcomes	Reporting findings from other studies, already found in the search
Yong et al. 2012	Cost-effectiveness of intensity-modulated radiotherapy in prostate cancer	comparing IMRT with 3DCRT, both delivered with the conventional fractionation
Philippou et al. 2014	Localised prostate cancer: clinical and cost-effectiveness of new and emerging technologies	Reporting findings from other studies, already found in the search
El-Ghamrawi et al 2015	Hypo-fractionated Simultaneous Integrated Boost (SIB) versus Conventional Fractionation in Localized Prostate Cancer: A Randomized Pilot Study	Not applicable evidence. Study in Egypt
Shah et al 2012	Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer	Not cost utility analysis
Hayes et al 2013	Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis (Provisional abstract)	QALY not used as an outcome measure

Short Title	Title	Reason for exclusion
Peters et al 2016	Comparative cost-effectiveness of focal and total salvage 125I brachytherapy for recurrent prostate cancer after primary radiotherapy	Compering two types of brachytherapy against each other but not with conventional external beam RT
Helou et al 2017	Stereotactic Body Radiotherapy versus Low Dose Rate Brachytherapy for Localised Prostate Cancer: a Cost-Utility Analysis	Comparing extreme hypo-fractionated RT with brachytherapy but with conventional external beam RT
Kelly et al 2011	The clinical and cost effectiveness of the use of brachytherapy to treat localised prostate cancer (Structured abstract)	Review reporting findings from other studies found to be not relevant
Penson 2013	Re: Active surveillance for prostate cancer compared with immediate treatment: An economic analysis	Only cost-analysis

Appendix I – References

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