

# Prostate Cancer: Diagnosis and management

## Evidence reviews for radical radiotherapy

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## Contents

|                                                                                              |           |
|----------------------------------------------------------------------------------------------|-----------|
| <b>Radical radiotherapy</b> .....                                                            | <b>6</b>  |
| Review question .....                                                                        | 6         |
| Introduction .....                                                                           | 6         |
| Methods and process .....                                                                    | 7         |
| Clinical evidence .....                                                                      | 8         |
| Summary of clinical studies included in the evidence review .....                            | 9         |
| Quality assessment of clinical studies included in the evidence review .....                 | 10        |
| Economic evidence .....                                                                      | 10        |
| Summary of studies included in the economic evidence review.....                             | 10        |
| Economic model.....                                                                          | 12        |
| Evidence statements .....                                                                    | 12        |
| Recommendations .....                                                                        | 14        |
| Rationale and impact.....                                                                    | 14        |
| The committee’s discussion of the evidence.....                                              | 15        |
| <b>Appendices</b> .....                                                                      | <b>18</b> |
| <b>Appendix A– Review protocols</b> .....                                                    | <b>18</b> |
| Review protocol for radical therapy.....                                                     | 18        |
| <b>Appendix B – Methods</b> .....                                                            | <b>24</b> |
| Quality assessment .....                                                                     | 24        |
| Methods for combining intervention evidence .....                                            | 24        |
| Minimal clinically important differences (MIDs) .....                                        | 25        |
| GRADE for pairwise meta-analyses of interventional evidence .....                            | 25        |
| Evidence statements .....                                                                    | 26        |
| <b>Health economics</b> .....                                                                | <b>27</b> |
| <b>Appendix C– Literature search strategies</b> .....                                        | <b>29</b> |
| Search summary .....                                                                         | 29        |
| Clinical searches .....                                                                      | 29        |
| Study design filters and limit.....                                                          | 30        |
| Health Economics search strategy .....                                                       | 31        |
| Health Economics filters.....                                                                | 31        |
| <b>Appendix D – Study selection</b> .....                                                    | <b>32</b> |
| <b>Appendix E– Evidence tables</b> .....                                                     | <b>35</b> |
| <b>Appendix F - Forest plots</b> .....                                                       | <b>53</b> |
| Conventional versus hypofractionated radiation therapy.....                                  | 53        |
| <b>Appendix G: GRADE tables</b> .....                                                        | <b>57</b> |
| Conventional versus hypofractionated radiotherapy: survival and adverse events outcomes..... | 57        |

|                                                                                                        |           |
|--------------------------------------------------------------------------------------------------------|-----------|
| External beam radiotherapy (EBRT) alone versus EBRT plus low-dose-rate<br>brachytherapy (LDR-BT) ..... | 65        |
| <b>Appendix H – Excluded studies .....</b>                                                             | <b>68</b> |
| Clinical studies .....                                                                                 | 68        |
| Economic studies .....                                                                                 | 79        |
| <b>Appendix I – References .....</b>                                                                   | <b>82</b> |

# 1 Radical radiotherapy

## 2 Review question

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

## 5 Introduction

6 The aim of the review was to determine the optimal dose of radiotherapy for people  
7 with localised prostate cancer. This question was identified for update during the  
8 2016 exceptional surveillance review. The update will determine the optimal dose  
9 and fractionation schedule for people with localised prostate cancer (T1b–T3a N0  
10 M0) who are treated with radical radiotherapy.

11 The protocol defined the comparator of interest as ‘conventional external beam  
12 fractionation’. For the purposes of this review, the committee defined conventional  
13 fractionation as 70 – 80 Gy in 2 Gy fractions or similar. Therefore, studies were  
14 included providing there was a conventional fractionation arm giving between 70 and  
15 80 Gy total dose of external beam radiotherapy in 1.8–2.0 Gy fractions.

16 This review aims to determine the effectiveness of:

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

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

28 Brachytherapy involves the placement of a sealed radiation source into the prostate  
29 gland, either in the form of radioactive seeds (low-dose-rate brachytherapy) or thin  
30 tubes (high-dose-rate brachytherapy), both of which supply the prostate with  
31 radioactive material. Brachytherapy requires just one or two days in hospital. This  
32 review identified studies that fulfilled the conditions specified in Table 1. For full  
33 details of the review protocol, see appendix A.

34 **Table 1: PICO for radical radiotherapy**

|                      |                                                                                                                                                                                                   |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population</b>    | People with localised prostate cancer (T1b–T3a N0 M0)                                                                                                                                             |
| <b>Interventions</b> | <ul style="list-style-type: none"><li>• Hypofractionated radiotherapy to the prostate</li><li>• Brachytherapy plus external beam radiotherapy</li><li>• Brachytherapy alone<sup>1</sup></li></ul> |
| <b>Comparator</b>    | Conventional fractionation with external beam therapy                                                                                                                                             |
| <b>Outcomes</b>      | <ul style="list-style-type: none"><li>• Prostate cancer-specific mortality</li><li>• Overall survival</li></ul>                                                                                   |

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<sup>1</sup> 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)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|            | <ul style="list-style-type: none"><li>• Metastasis-free survival</li><li>• Treatment-related morbidity for example<ul style="list-style-type: none"><li>○ 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</li><li>○ 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)</li><li>○ 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.</li></ul></li><li>• Health-related quality of life - for example:<ul style="list-style-type: none"><li>○ European Organisation for Research and Treatment of Cancer quality of life,</li><li>○ EPIC instrument</li></ul></li></ul> |

1

## 2 **Methods and process**

3 This evidence review was developed using the methods and process described in  
4 [Developing NICE guidelines: the manual 2014](#). Methods specific to this review  
5 question are described in the review protocol in appendix A and the methods section  
6 Appendix B.

7 Declarations of interest were recorded according to [NICE's 2014 and 2018 conflicts](#)  
8 [of interest policies](#).

## 9 **Protocol deviation**

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

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

- 15 • There was variability between included studies in the reporting of gastrointestinal  
16 (GI) and genitourinary (GU) toxicity, therefore, the present analysis focused on the  
17 frequency of participants reporting maximum toxicity of grade 2 or greater,  
18 according to the Radiation Oncology/Toxicity Grading (RTOG), at any point during  
19 follow-up. For studies reporting multiple measures of toxicity, RTOG was  
20 prioritised.
- 21 • Acute toxicity was defined as toxicity following completion of radiotherapy up until  
22 18 weeks. Originally, a 3-month limit was used; however a key trial (CHHiP) used  
23 an acute period of 18 weeks.

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

## 18 **Clinical evidence**

### 19 **Included studies**

20 This review was conducted as part of a larger update of the [NICE Prostate Cancer](#)  
21 [guideline \(CG175\)](#).

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

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

30 Multiple papers reporting results of the same study were identified and collated, so  
31 that each study rather than individual reports was the unit of interest in the review;  
32 therefore there were 11 unique studies.

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

40 For study selection process please see Appendix D.

41 For the full evidence tables, forest plots and GRADE profiles for included studies,  
42 please see [appendices E, F](#) and [G](#).



1 **Excluded studies**

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

4 **Summary of clinical studies included in the evidence review**

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

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

12 The overall evidence was as follows:

- 13 • Conventional versus hypofractionated radiation therapy – 10 RCTs reported in  
14 21 papers:
  - 15 ○ HYPRO (Netherlands): Aluwini (2015, 2016), Incrocci (2016) and Wortel (2016)
  - 16 ○ RENCi (Italy): Arcangeli (2010, 2011, 2012 and 2017)
  - 17 ○ CHHiP (United Kingdom): Dearnaley (2012, 2016, 2018) and Wilkins  
18 (2015)
  - 19 ○ PROFIT (Canada, Australia and France): Catton (2017)
  - 20 ○ RTOG 0415 (United States): Lee (2016)
  - 21 ○ FCCC (United States): Pollack (2006 and 2013) and Shaikh (2017)
  - 22 ○ Hoffman (2014 and 2016) (United States)
  - 23 ○ Marzi (2009) (Italy)
  - 24 ○ Norkus (2009) (Lithuania)
  - 25 ○ Norkus (2013) (Lithuania)
- 26 • External beam therapy alone versus external beam therapy plus low-dose-rate  
27 brachytherapy boost – 1 RCT reported in 2 papers:
  - 28 ○ ASCENDE-RT (Canada): Morris (2016) and Rodda (2017)
- 29 • Brachtherapy alone
  - 30 ○ No studies met the inclusion criteria

31 **Outcomes and sample sizes**

32 The reported outcomes where data were extractable were:-

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

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

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

1

## 2 **Quality assessment of clinical studies included in the evidence review**

3 See evidence tables in appendix E for quality assessment of individual studies and  
4 appendix G for GRADE tables

## 5 **Economic evidence**

### 6 **Included studies**

7 Standard health economics filters were applied to the clinical search strategy for this  
8 question. Details are provided in Appendix C. In total, 1,541 references were  
9 returned, of which 1,508 could be confidently excluded on screening of titles and  
10 abstracts. The remaining 33 studies were reviewed in full text, and 28 were found not  
11 to be relevant. One US study was identified subsequently by reference searching  
12 from one of the reviews obtained from our search. One additional study was  
13 identified after the search date. This left 7 unique cost–utility analyses.

### 14 **Excluded studies**

15 Details of studies excluded after consideration at the full-text stage are provided in  
16 [appendix H](#).

## 17 **Summary of studies included in the economic evidence review**

18 Four studies adopting a US focus were included:

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

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

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

5 Sher et al (2014) compared SBRT (35 Gy in 5 fractions) with IMRT (75.6 Gy in  
6 42 fractions). The authors developed a Markov decision model with a 4-month cycle  
7 length predicting lifetime costs and QALYs of 65-year-old man with low-risk prostate  
8 cancer. Probabilities of recurrence and toxicity (sexual, rectal and urinary) were  
9 obtained by reviewing published observational studies. The SBRT cohort had a  
10 higher probability of rectal and urinary dysfunction than IMRT, whereas sexual  
11 dysfunction probabilities were similar. Costs were taken from 2012 prices adopting  
12 the US payer perspective (Medicare). The study showed that QALYs were slightly  
13 higher with IMRT than SBRT (9.96 vs 9.93), reflecting the higher toxicity rate in the  
14 SBRT group. However, SBRT was deemed cost effective, as it was shown to be  
15 considerably cost saving compared with IMRT (\$10,109 vs \$27,564), suggesting over  
16 \$500,000 could be saved for every QALY forgone. Treatment efficacy estimates,  
17 rectal toxicity and sexual dysfunction, and the uncertain potential for late effects from  
18 SBRT were significant drivers of the cost effectiveness. Applying the extreme values  
19 of these favouring IMRT did not change the base-case conclusion. The study was  
20 judged to be partially applicable with potentially serious limitations.

21 Ollendorf et al. (2008) developed an economic model to assess the cost  
22 effectiveness of brachytherapy, delivered as 100 iodine-125 at dose of 145 Gy  
23 compared with proton beam therapy (PBT) and IMRT (each 74–78 Gy in 39  
24 fractions), to treat people with low-risk localised prostate cancer. Assuming that the  
25 3 modalities have the same efficacy, the study's focus was on different toxicities.  
26 Acute and late GI and/or GU toxicities and sexual dysfunction were modelled. GI  
27 toxicity was higher with IMRT than brachytherapy in the short term. Costs were  
28 included adopting public payer perspective for the base case including capital  
29 expenditures in its reimbursement framework and patient time in therapy cost.  
30 Scenario analysis excluding patients' time costs was performed. The three  
31 techniques have comparable toxicity in the long run. The authors found that  
32 brachytherapy was dominant compared with IMRT and PBT, delivering higher  
33 QALYs and saving costs. The study was judged to be partially applicable with  
34 potentially serious limitations.

35 Ramsay et al. (2015) performed a UK economic evaluation based on a modified  
36 Markov modelling approach to predict lifetime costs and QALYs for patients with  
37 localised prostate cancer receiving brachytherapy (80 seeds with an average of  
38 28 needles used per patient) or IMRT (74 - 78 Gy in 37 fractions). Additional  
39 comparators – cryotherapy, high-intensity focused ultrasound and radical  
40 prostatectomy – are beyond the scope of this review question and excluded from  
41 consideration, here. Recurrence events were represented by health states where  
42 patients received further active or palliative treatments. Treatment-related acute and  
43 late toxicities (urinary incontinence, erectile dysfunction and bowel dysfunction) were  
44 modelled. The base case assumed identical efficacy in terms of biochemical  
45 recurrence. Utility values were drawn from multiple sources by literature review;  
46 when the authors found multiple values for particular parameters, median values  
47 were used, which were then calibrated to the EQ-5D. Costs adopted an NHS  
48 perspective. Short- and long-term toxicity rates were higher for IMRT for erectile and  
49 bowel dysfunction, and higher for brachytherapy for urinary incontinence. The  
50 authors found that brachytherapy is slightly more effective than IMRT (3.75 vs 3.69  
51 QALYs), but also incurs higher costs (£24,456 vs £19,363), resulting in an ICER of  
52 around £85,000 per QALY gained. In sensitivity analysis, the finding that  
53 brachytherapy is more expensive than IMRT was maintained, but there was much

1 greater uncertainty about whether it is more effective. The study was judged to be  
2 directly applicable with potentially serious limitations.

3 Sanyal et al. (2016), a Canadian study, developed a Markov model to predict lifetime  
4 direct costs and QALYs of 65-year-old men with local prostate cancer, stratified into  
5 low-, intermediate- and high-risk groups. Transition probabilities, AEs associated with  
6 treatment options, health state utility values and costs were derived from informal  
7 searches of the literature. The relevant comparators for low- and for the intermediate-  
8 risk groups were conventional IMRT (38 fractions), brachytherapy (using palladium-  
9 103 seeds) and IMRT plus brachytherapy (delivered over 19 fractions overall).  
10 Interventions used for the high-risk groups were out of the scope, as they did not  
11 include conventional IMRT. Annual probabilities of moving to the recurrence state  
12 were assumed identical between the comparators. Short- and long-term toxicities  
13 were modelled. The authors found that, for the low-risk group, IMRT and  
14 brachytherapy delivered equal effectiveness, but brachytherapy was associated with  
15 lower costs. For intermediate-risk group, conventional IMRT was slightly more  
16 effective than a combination of IMRT and brachytherapy and was associated with  
17 lower costs; this reflects the high toxicity assigned to the combination of IMRT plus  
18 brachytherapy. One-way sensitivity analysis was performed but not PSA; the results  
19 seemed to be consistent with the base-case ones. The study was judged to be  
20 partially applicable with very serious limitations.

21 Zemplényi et al. (2018), a Hungarian study, developed a 10-year Markov decision  
22 model evaluating the cost effectiveness of hypo-fractionated IMRT (HF-IMRT;  
23 25 fractions) compared with conventional fractionation IMRT or three dimensional  
24 conformal radio-therapy (3DCRT), each 38 fractions, for 70-year-old men with  
25 localised prostate cancer. Based on data from a large cohort study, 3DCRT was  
26 assigned inferior recurrence-free survival to IMRT; HF-IMRT was assumed to have  
27 identical recurrence-free survival to IMRT. Health state utility values were obtained  
28 from an existing literature using the standard gamble technique. Treatment-related  
29 acute and late toxicities were obtained from existing literature; values assigned to the  
30 HF-IMRT acute toxicity were lower than the IMRT; however, HF-IMRT was  
31 associated with higher late GU toxicity than the IMRT and 3DCRT. Sexual  
32 dysfunction was ignored in the model, since no studies could be identified presenting  
33 relevant comparative data. The authors found that HF-IMRT was slightly more  
34 effective and less expensive compared with both IMRT and 3DCRT. Probabilistic  
35 sensitivity analysis showed that HF-IMRT was dominant and cost effective in 99% of  
36 the 1000 iterations, considering the threshold of €20,000 per QALY gain. Results  
37 from different scenarios using progression rates from different publications did not  
38 alter the base-case conclusion. The study was judged to be partially applicable with  
39 potentially serious limitations.

#### 40 **Economic model**

41 Original health economic modelling was not prioritised for this review question.

#### 42 **Evidence statements**

43 The format of the evidence statements is explained in the methods in [appendix B](#).

#### 44 **Conventional versus hypofractionated radiation therapy**

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

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

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

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

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

#### 17 **Economic evidence**

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

#### 22 **Extremely hypofractionated radiotherapy (stereotactic body radiotherapy; 23 SBRT) versus conventional fractionation**

#### 24 **Economic evidence**

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

#### 30 **External beam radiation therapy (EBRT) alone versus external radiation beam 31 therapy plus low-dose-rate brachytherapy**

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

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

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

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

#### 5 **Economic evidence**

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

#### 10 **Brachytherapy versus conventional fractionated external beam RT**

##### 11 **Economic evidence**

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

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

#### 18 **Recommendations**

19 C1. For people having radical external beam radiotherapy for localised prostate  
20 cancer:

- 21 • Offer hypofractionated radiotherapy (60 Gy in 20 fractions) using image-  
22 guided intensity modulated radiation therapy (IMRT), unless  
23 contraindicated **or**
- 24 • Offer conventional radiotherapy (74 Gy in 37 fractions) to people who  
25 cannot have hypofractionated radiotherapy. **[2019]**

26 C2. Consider brachytherapy in combination with external beam radiotherapy for  
27 people with intermediate- and high-risk localised prostate cancer. **[2019]**

#### 28 **Rationale and impact**

##### 29 **Why the committee made the recommendations**

30 A large body of evidence showed that hypofractionated radiotherapy and  
31 conventional radiotherapy were equally effective. The committee noted that  
32 hypofractionated radiotherapy is associated with higher rates of acute gastrointestinal  
33 toxicity, but overall it could enable people to have a better quality of life because  
34 people would need to make fewer clinic visits. Fewer clinic visits for hypofractionated  
35 radiotherapy would also mean fewer resources were needed compared with  
36 conventional radiotherapy treatment. Therefore, hypofractionated radiotherapy was  
37 recommended as the first option.

38 The committee agreed that 60 Gy in 20 fractions was the optimal dose for people  
39 having hypofractionated radiotherapy. This was the dosage used in the large UK  
40 CHHiP trial that was associated with greater efficacy compared with a 57 Gy  
41 schedule, although the 60 Gy schedule did also show slightly greater toxicity.

1 The committee considered evidence from a large trial that showed a reduction in  
2 biochemical failure (for example, local recurrence or distant metastases) associated  
3 with the use of low-dose brachytherapy in combination with external beam radiation  
4 therapy for people with high-risk localised prostate cancer. As a result, the committee  
5 amended the previous recommendation so it was not limited to high-dose  
6 brachytherapy.

## 7 **Impact of the recommendations on practice**

8 As hypofractionated radiotherapy is already routinely used in practice, alongside  
9 other non-radiotherapy treatment options for people with localised prostate cancer,  
10 these recommendations are unlikely to have an impact on resources.

11 For brachytherapy, the committee agreed that only a small number of people  
12 (typically those with high-risk prostate cancer) would currently have brachytherapy,  
13 so the changes to the recommendations are unlikely to have a significant impact on  
14 current practice.

## 15 **The committee's discussion of the evidence**

### 16 **Interpreting the evidence**

#### 17 ***The outcomes that matter most***

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

24 Quality of life is an important factor related to radiotherapy. In particular, convenience  
25 of treatment is of critical importance. Conventional radiotherapy takes an average of  
26 7.5 weeks to deliver whereas hypofractionated radiotherapy is given over a shorter  
27 time. The committee noted that this needed to be balanced against the greater short-  
28 term toxicity of hypofractionated radiotherapy when discussing treatment options with  
29 patients.

#### 30 ***The quality of the evidence***

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

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

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

1 **Benefits and harms**

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

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

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

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

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

27 **Cost effectiveness and resource use**

28 The committee reviewed the included economic evidence. It agreed that the cost–  
29 utility analysis performed by Zempenyi et al. (2018) provided partially applicable  
30 evidence. The committee noted that, given the clinical evidence provided in the  
31 clinical review showing no inferiority for hypofractionated external beam radiotherapy  
32 compared with conventional fractionation in terms of efficacy and toxicity, the  
33 reduction in the number of radiotherapy sessions would lead to cost saving. Thus,  
34 the economic evidence provided by Zempenyi et al. was agreed to be sufficient to  
35 underpin strong recommendations in favour of offering external beam radiotherapy at  
36 a dose of 60 Gy in 20 fractions to people receiving radiotherapy for localised prostate  
37 cancer.

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

46 The committee reviewed the included economic evidence provided by a Canadian  
47 study (Sanyal et al. 2016), judged as partially applicable with very serious limitations,  
48 on the comparison between a combination of external beam radiotherapy plus



1 brachytherapy and external beam radiotherapy only for the treatment of intermediate-  
2 risk localised prostate cancer. It noted that this study made the assumption of equal  
3 efficacy measured by time to recurrence, which was not realistic based on evidence  
4 provided by a UK RCT (ASCENDE-RT) included in the clinical review. This trial  
5 showed that patients on a combination of brachytherapy and EBRT experience half  
6 the rate of recurrence of people receiving EBRT alone. The committee noted that the  
7 improved efficacy associated with the combination of brachytherapy and EBRT would  
8 result in overall improved QALYs that were not captured in the economic evidence.  
9 The committee agreed that the clinical evidence provided by ASCENDE-RT was  
10 sufficient to consider this combination for this population, as this would not change  
11 the current practice, affecting a small population, and hence not having a significant  
12 resource impact.

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

#### 20 **Other considerations**

21 The committee agreed that the new recommendations are consistent with the  
22 recommendations made by NHS England, who encourage the use of  
23 hypofractionated image-guided IMRT for the treatment of localised prostate cancer.  
24

# 1 Appendices

## 2 Appendix A– Review protocols

### 3 Review protocol for radical therapy

| ID  | Field (based on <a href="#">PRISMA-P</a> )                              | 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) | <ul style="list-style-type: none"> <li>• Hypofractionated radiotherapy to the prostate</li> <li>• Brachytherapy plus external beam radiotherapy</li> </ul> |
| VI  | Eligibility criteria – comparator(s)/control or                         | Conventional fractionation with external beam therapy                                                                                                      |

|     | reference (gold) standard   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VII | Outcomes and prioritisation | <ul style="list-style-type: none"> <li>• Prostate cancer-specific mortality</li> <li>• Overall survival</li> <li>• Metastasis-free survival</li> <li>• Treatment-related morbidity for example <ul style="list-style-type: none"> <li>○ 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</li> <li>○ 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)</li> <li>○ 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.</li> </ul> </li> <li>• Health-related quality of life - for example: <ul style="list-style-type: none"> <li>○ European Organisation for Research and Treatment of Cancer quality of life,</li> <li>○ EPIC instrument</li> </ul> </li> </ul> <p><i>If reported – <u>psychological aspects</u> of quality of life to be reported separately</i></p> |

|      |                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| VIII | Eligibility criteria – study design                         | <ul style="list-style-type: none"> <li>• RCTs</li> <li>• Systematic reviews of RCTs</li> </ul>                                                                                                                                                                                                                                                                                                                                                              |
| IX   | Other inclusion exclusion criteria                          | Non English- language papers                                                                                                                                                                                                                                                                                                                                                                                                                                |
| X    | Proposed sensitivity/sub-group analysis, or meta-regression | <ul style="list-style-type: none"> <li>• Total dose</li> <li>• Different hypo-fractionation schedules.</li> </ul>                                                                                                                                                                                                                                                                                                                                           |
| 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<br><br>Searches from 2008, this question is an update from a previous guideline, committee agreed to limit searches to 2008                                                                                                                                                                                                                                                                                              |

|       |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| XIV   | Identify if an update                             | <p>This is an update.</p> <p>Original question: from 2008, no question located.</p> <p><b>Recommendations affected:</b></p> <p>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. <b>[2008]</b></p> <p>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. <b>[2008]</b></p> <p>Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. <b>[new 2014]</b></p> |
| XV    | Author contacts                                   | Guideline updates team                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| XVI   | Highlight if amendment to previous protocol       | For details please see section 4.5 of <a href="#">Developing NICE guidelines: the manual</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 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                        | <p>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 <a href="#">Developing NICE guidelines: the manual</a>.</p> <p>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 <a href="#">Developing NICE guidelines: the manual</a>.</p> |

|        |                              |                                                                  |
|--------|------------------------------|------------------------------------------------------------------|
| 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                                                              |

1

# 1 **Appendix B – Methods**

## 2 **Evidence of effectiveness of interventions**

### 3 **Quality assessment**

4 Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Each individual  
5 study was classified into one of the following three groups:

6 Low risk of bias – The true effect size for the study is likely to be close to the estimated effect  
7 size.

8 Moderate risk of bias – There is a possibility the true effect size for the study is substantially  
9 different to the estimated effect size.

10 High risk of bias – It is likely the true effect size for the study is substantially different to the  
11 estimated effect size.

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

16 Direct – No important deviations from the protocol in population, intervention, comparator  
17 and/or outcomes.

18 Partially indirect – Important deviations from the protocol in one of the population,  
19 intervention, comparator and/or outcomes.

20 Indirect – Important deviations from the protocol in at least two of the following areas:  
21 population, intervention, comparator and/or outcomes.

### 22 **Methods for combining intervention evidence**

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

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

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

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

40 Significant between study heterogeneity in methodology, population, intervention or  
41 comparator was identified by the reviewer in advance of data analysis. This decision was  
42 made and recorded before any data analysis was undertaken.



- 43 The presence of significant statistical heterogeneity in the meta-analysis, defined as  $I^2 \geq 50\%$ .  
 44 In any meta-analyses where some (but not all) of the data came from studies at high risk of  
 45 bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results  
 46 from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses  
 47 where some (but not all) of the data came from indirect studies, a sensitivity analysis was  
 48 conducted, excluding those studies from the analysis.
- 49 Meta-analyses were performed in Cochrane Review Manager v5.3.

## 50 Minimal clinically important differences (MIDs)

51 The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to  
 52 identify published minimal clinically important difference thresholds relevant to this guideline.  
 53 Identified MIDs were assessed to ensure they had been developed and validated in a  
 54 methodologically rigorous way, and were applicable to the populations, interventions and  
 55 outcomes specified in this guideline. In addition, the Guideline Committee were asked to  
 56 prospectively specify any outcomes where they felt a consensus MID could be defined from  
 57 their experience. In particular, any questions looking to evaluate non-inferiority (that one  
 58 treatment is not meaningfully worse than another) required an MID to be defined to act as a  
 59 non-inferiority margin.

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

## 64 GRADE for pairwise meta-analyses of interventional evidence

65 GRADE was used to assess the quality of evidence for the selected outcomes as specified in  
 66 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high  
 67 quality and the quality of the evidence for each outcome was downgraded or not from this  
 68 initial point based on the criteria given in Table 2

69 **Table 2: Rationale for downgrading quality of evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk of bias   | <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p> |
| Indirectness   | <p>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.</p> <p>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.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.</p>                                                                                                                                                                                                                   |

| 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  | <p>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 <math>I^2</math> statistic.</p> <p>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.</p> <p>Not serious: If the <math>I^2</math> was less than 33.3%, the outcome was not downgraded.</p> <p>Serious: If the <math>I^2</math> was between 33.3% and 66.7%, the outcome was downgraded one level.</p> <p>Very serious: If the <math>I^2</math> was greater than 66.7%, the outcome was downgraded two levels.</p> <p>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.</p> |
| Imprecision    | <p>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.</p> <p>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.</p> <p>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.</p>                                                                                                                     |

70 The quality of evidence for each outcome was upgraded if any of the following three  
71 conditions were met:  
72 Data from non-randomised studies showing an effect size sufficiently large that it cannot be  
73 explained by confounding alone.  
74 Data showing a dose-response gradient.  
75 Data where all plausible residual confounding is likely to increase our confidence in the effect  
76 estimate.

## 77 Evidence statements

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

- 79 • Situations where the data are only consistent, at a 95% confidence level, with an  
80 effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of  
81 that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the  
82 zone of equivalence). In such cases, we state that the evidence showed that there is  
83 an effect.
- 84 • Situations where the data are only consistent, at a 95% confidence level, with an  
85 effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of  
86 that effect is most likely to be less than the MID (i.e. the point estimate is in the zone  
87 of equivalence). In such cases, we state that the evidence could not show a  
88 meaningful difference.
- 89 • Situations where the data are consistent, at a 95% confidence level, with an effect in  
90 either direction (i.e. one that is not 'statistically significant') but the confidence limits

91 are smaller than the MIDs in both directions. In such cases, we state that the  
 92 evidence showed that there is no difference.  
 93 • In all other cases, we state that the evidence could not differentiate between the  
 94 comparators.

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

97 • We state that the evidence showed that there is an effect if the 95% CI does not  
 98 cross the line of no effect.

99 • We state the evidence could not differentiate between comparators if the 95% CI  
 100 crosses the line of no effect.

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

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

## 111 Health economics

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

121 Economic studies identified through a systematic search of the literature are appraised using  
 122 a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014).  
 123 This checklist is not intended to judge the quality of a study per se, but to determine whether  
 124 an existing economic evaluation is useful to inform the decision-making of the committee for  
 125 a specific topic within the guideline.

126 There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the  
 127 relevance of the study to the specific guideline topic and the NICE reference case);  
 128 evaluations are categorised according to the criteria in Table 3.

129 **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 |

130 In the second step, only those studies deemed directly or partially applicable are further  
 131 assessed for limitations (that is, methodological quality); see categorisation criteria in Table  
 132 4.

133 **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 |

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

137

138

## 139 Appendix C– Literature search strategies

### 140 Search summary

141 The search strategies were based on the review protocol provided and the previous  
142 strategies used in [CG175](#) (pages 11&16).

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

### 146 Clinical searches

147 Source searched for this review question:

- 148 • Cochrane Database of Systematic Reviews – CDSR (Wiley)
- 149 • Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- 150 • Database of Abstracts of Reviews of Effects – DARE (Wiley)
- 151 • Health Technology Assessment Database – HTA (Wiley)
- 152 • EMBASE (Ovid)
- 153 • MEDLINE (Ovid)
- 154 • MEDLINE In-Process (Ovid)

155 The clinical searches were conducted in December 2017

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

158

#### 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

159 **Study design filters and limit**

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

163

**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

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

## 167 **Health Economics search strategy**

168 Economic evaluations and quality of life data.

169 Sources searched:

- 170 • NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- 171 • Health Technology Assessment (HTA Database)
- 172 • EconLit (Ovid)
- 173 • Embase (Ovid)
- 174 • MEDLINE (Ovid)
- 175 • MEDLINE In-Process (Ovid)

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

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

181 The economic searches were conducted in December 2017.

## 182 **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 (pharmac adj economic\$)).tw.  
 26 or/1-25

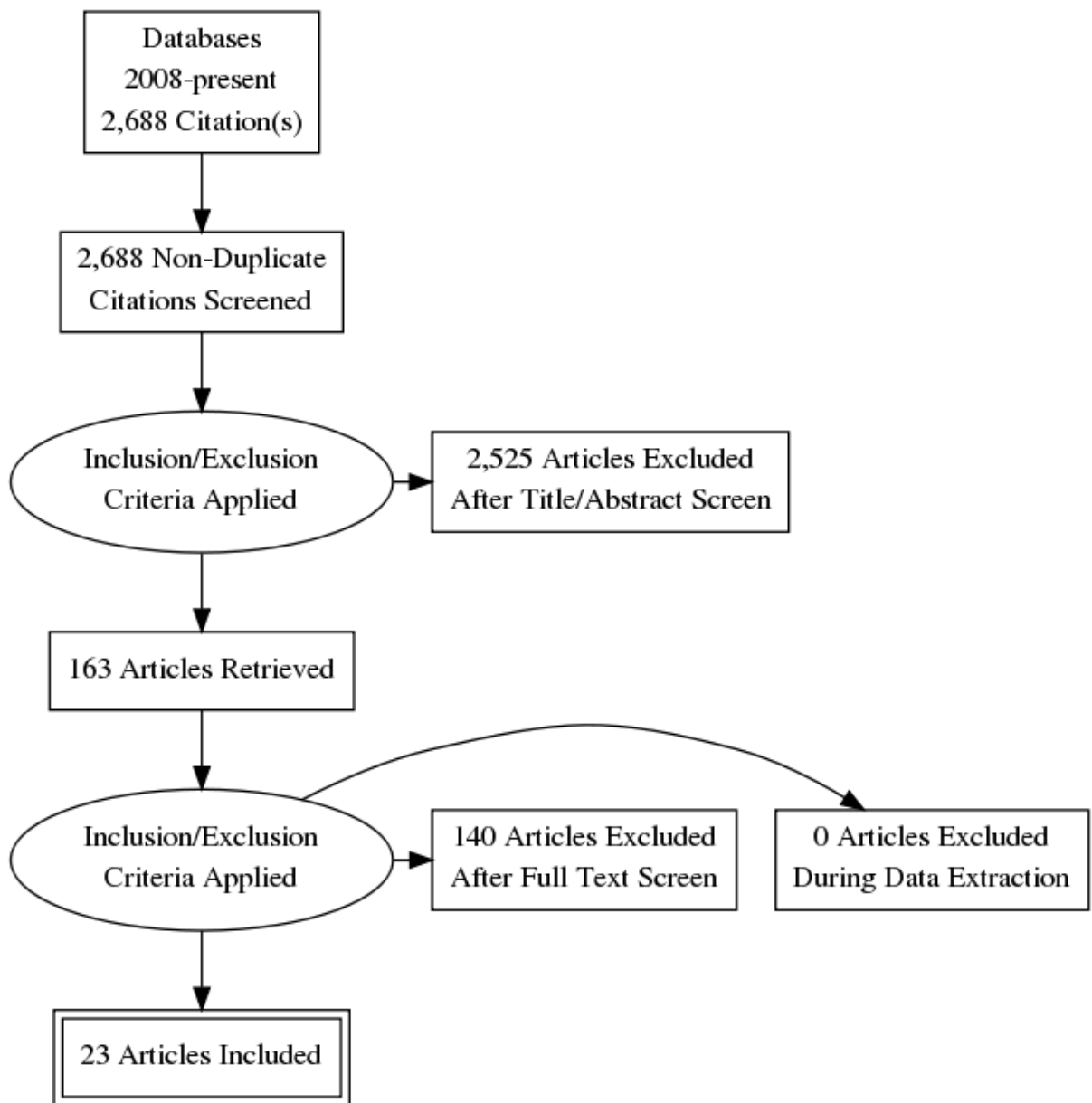
#### **Quality of life**

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

## 183 **Appendix D – Study selection**

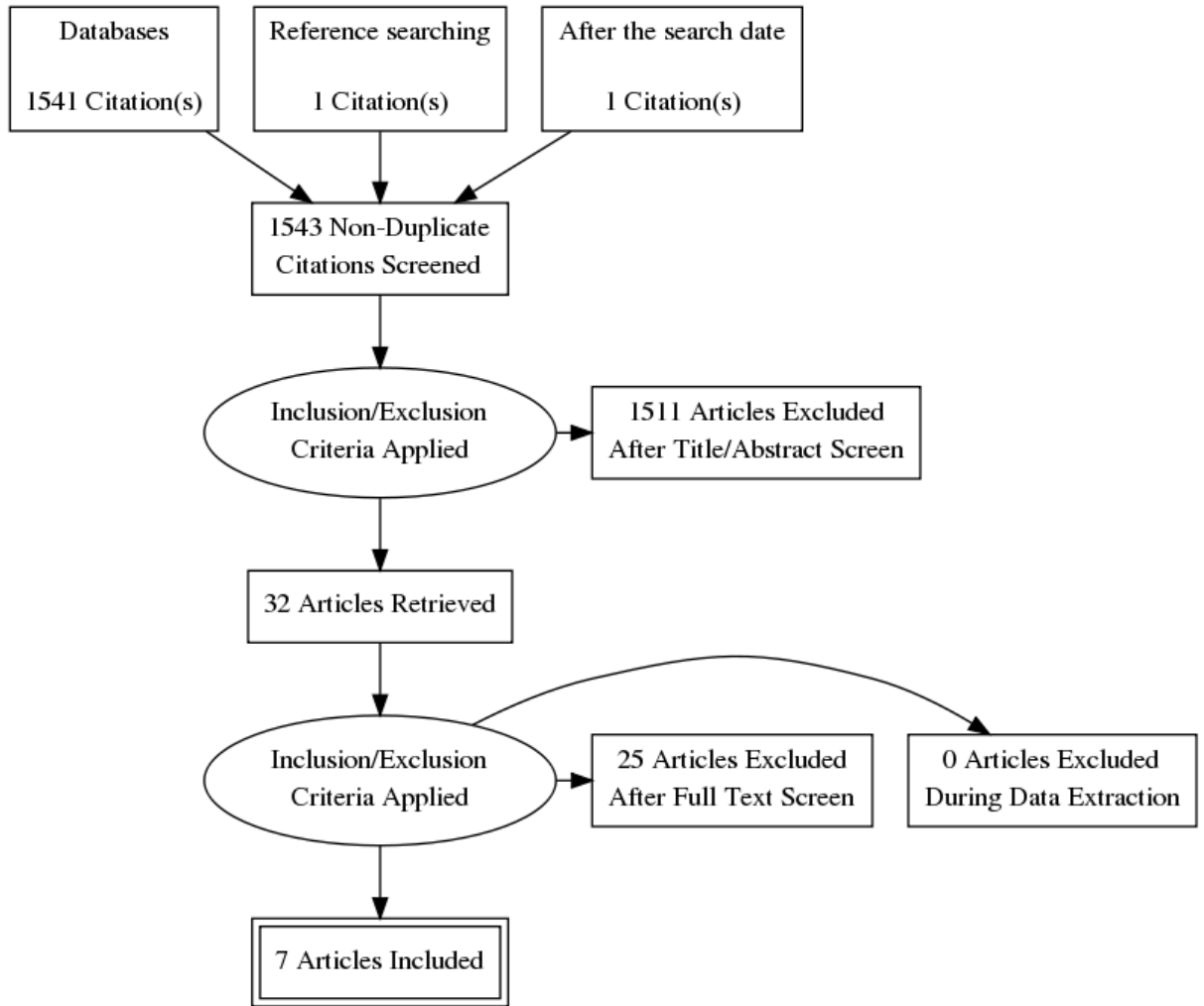
### 184 **Clinical evidence**





185  
186

187 **Economic evidence**



188

189

## 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 | <p>Study type</p> <p>Randomised control trials</p> <p>Associated studies</p> <p>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</p> <p>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</p> <p>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</p> <p>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)</p> <p>Randomised controlled trial</p> <p>Study details</p> <p>Study location</p> <p>The Netherlands</p> | <p>Random sequence generation</p> <p>Low risk of bias</p> <p>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 stratification factors (ie, treatment centre and risk group).</p> <p>Allocation concealment</p> <p>Unclear risk of bias</p> <p>Unclear if outcome assessor was blinded</p> <p>Blinding of participants and personnel</p> <p>High risk of bias</p> <p>"The local investigators were treating physicians, so they were not masked to treatment."</p> <p>Blinding of outcome assessment</p> <p>Unclear risk of bias</p> <p>Unclear if outcome assessor was blinded</p> <p>Incomplete outcome data</p> <p>Low risk of bias</p> <p>38/820 lost to follow up (less than 10%)</p> |

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

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

| Short Title | Title | Study characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Quality Assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             |       | <p>telephone assessments to week 14 and again every 6m follow-up visit for 5 years. HRQoL assessed at baseline, 24m and 48m.</p> <p>Sources of funding<br/>Several contributors received funding and/or are affiliated to pharmaceutical companies</p> <p>Inclusion criteria<br/>Prostate cancer<br/>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.</p> <p>Exclusion criteria<br/>Prior radiology<br/>Prior PCa therapy other than biopsy or transurethral resection<br/>Comorbidities<br/>malignancy diagnosed within 5 years of entry other than non-melanoma skin cancer, or inflammatory bowel disease<br/>Other<br/>PCa diagnosis 6 months or more before study entry</p> <p>Sample characteristics<br/>Sample size<br/>1206 randomly assigned, 1192 completed treatment, 1116 analysed.<br/>Split between study groups<br/>598 conventional; 608 hypofractionated<br/>Loss to follow-up<br/>76 lost to follow-up<br/>Median age (IQR)</p> | <p>Blinding of participants and personnel<br/>Unclear risk of bias<br/>Unclear whether any blinding was attempted</p> <p>Blinding of outcome assessment<br/>Unclear risk of bias<br/>Unclear if assessor was blind</p> <p>Incomplete outcome data<br/>Low risk of bias<br/>Similar attrition between groups</p> <p>Selective reporting<br/>Low risk of bias</p> <p>Other sources of bias<br/>Low risk of bias<br/>Balanced baseline characteristics</p> <p>Overall risk of bias<br/>Moderate<br/>Likely no blinding procedures. This will have a relatively small impact on bias risk for biochemical outcomes and moderate risk for physician assessed toxicity.</p> <p>Directness<br/>Directly applicable</p> |

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

| Short Title | Title | Study characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Quality Assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             |       | <p>(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.</p> <p>Associated studies<br/>Dearnaley 2012: Preliminary data Wilkins 2015: QoL</p> <p>Inclusion criteria<br/>Prostate cancer<br/>T1b–T3aN0M0 and WHO performance status 0-1. Until Aug 1, 2006 participants must have had a PSA concentration &lt; 40 ng/mL and &lt; 30% risk of lymph node involvement. After Aug 1, 2006 this was revised to PSA concentration &lt; 30 ng/mL and &lt; 30% risk of senubak vesicle involvement.</p> <p>Age<br/>Older than 16</p> <p>Exclusion criteria<br/>prior surgery<br/>Radical prostatectomy<br/>Prior radiology<br/>Prior pelvis radiotherapy<br/>Comorbidities<br/>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).<br/>Other<br/>T3 tumors and Gleason score of 8+.<br/>Life expectancy<br/>&lt;10 years<br/>Androgen suppression</p> | <p>Likely non-blinded</p> <p>Incomplete outcome data<br/>Low risk of bias<br/>Less than 10% lost to follow-up</p> <p>Selective reporting<br/>Low risk of bias<br/>All reported</p> <p>Other sources of bias<br/>Low risk of bias</p> <p>Overall risk of bias<br/>Moderate<br/>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.</p> <p>Directness<br/>Directly applicable</p> |



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

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

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

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

| Short Title   | Title                                                                                                                                                                                                                                                                                                         | Study characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Quality Assessment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               |                                                                                                                                                                                                                                                                                                               | <p>Interventions</p> <p>hypofractionated radiotherapy<br/>62gy in 20 x 3.1gy fractions (over 5 weeks)</p> <p>Conventional radiotherapy<br/>80gy in 40 x 2gy fractions (over 8 weeks)</p> <p>Type of radiotherapy used<br/>3DCRT</p> <p>Outcome measure(s)<br/>Toxicity<br/>Late rectal toxicity using RTOG scale</p>                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 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 | <p>Study type<br/>Randomised controlled trial</p> <p>Associated studies<br/>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</p> <p>Study details<br/>Study location<br/>Study dates<br/>2002-2014<br/>Duration of follow-up<br/>median 6.5 years<br/>Sources of funding<br/>Received unrestricted educational grants from Oncura corporation and Sanofi-Aventis Canada.</p> | <p>Random sequence generation<br/>Low risk of bias<br/>Participants were randomized</p> <p>Allocation concealment<br/>Unclear risk of bias<br/>Unlikely to have been concealed</p> <p>Blinding of participants and personnel<br/>Unclear risk of bias<br/>Unlikely to be blinded however at data lockdown trial investigators only had knowledge of median follow-up length and total number of biochemical events</p> <p>Blinding of outcome assessment<br/>Unclear risk of bias<br/>Unlikely blinded</p> <p>Incomplete outcome data<br/>Low risk of bias</p> |

| Short Title | Title | Study characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Quality Assessment                                                                                                                                                                                                                                                                                                                                                      |
|-------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             |       | <p>Inclusion criteria<br/>Prostate cancer<br/>Intermediate to high risk</p> <p>Exclusion criteria<br/>None reported</p> <p>Sample characteristics<br/>Sample size<br/>398 participants<br/>Split between study groups<br/>200 allocated to EBRT (187 received intervention) 198 allocated to LDR-BT (182 received intervention)<br/>Loss to follow-up<br/>1 lost to follow-up 29 did not receive allocated intervention<br/>All included in ITT 15 not included in toxicity assessment follow-up<br/>Median age (IQR)<br/>68 (range 45-86) years<br/>Androgen deprivation therapy<br/>All patients received 8 months ADT prior to RT</p> <p>Interventions<br/>Type of radiotherapy used<br/>3D-CRT<br/>External beam therapy (Mono)<br/>Dose-escalated 46Gy in 23 fractions plus 32 Gy boost in 16 fractions<br/>External beam + brachytherapy<br/>46Gy in 20 fractions plus LDR-BT boost of 1125 brachytherapy implant of 116Gy</p> <p>Outcome measure(s)<br/>Toxicity<br/>Rodda 2017: Acute (within 6 months) and late (after 6</p> | <p>Selective reporting<br/>Low risk of bias</p> <p>Other sources of bias<br/>Low risk of bias</p> <p>Overall risk of bias<br/>Moderate<br/>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.</p> <p>Directness<br/>Directly applicable</p> |

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

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



| Short Title    | Title                                                                               | Study characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Quality Assessment                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |                                                                                     | <p>Conventional arm median: 65 years (range 50-78)<br/> Hypofractionated arm median: 63 years (range 53-75)</p> <p>Interventions<br/> hypofractionated radiotherapy<br/> 57gy in 13 x 3gy fractions (over 3.5 weeks) plus 4 x 4.5gy fractions<br/> Conventional radiotherapy<br/> 74gy in 37 x 2 gy fractions (over 7.5 weeks)<br/> Type of radiotherapy used<br/> 3DCRT</p> <p>Outcome measure(s)<br/> Toxicity<br/> GI+GU measured using RTOG/EORTC toxicity scale</p>                                                                                                                                                                                                                                                                           | <p>Directness<br/> Partially directly applicable<br/> Study took place in 2004</p>                                                                                                                                                                                                                                                                                                                                               |
| Pollack (2013) | Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer | <p>Study type<br/> Main study<br/> Associated studies<br/> 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<br/> 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<br/> Randomised controlled trial</p> <p>Study details<br/> Study location<br/> USA</p> | <p>Random sequence generation<br/> Low risk of bias<br/> Patients were randomised</p> <p>Allocation concealment<br/> Unclear risk of bias<br/> Unlikely to have been concealed</p> <p>Blinding of participants and personnel<br/> Unclear risk of bias<br/> Likely non-blinded</p> <p>Blinding of outcome assessment<br/> Unclear risk of bias<br/> Likely non-blinded</p> <p>Incomplete outcome data<br/> High risk of bias</p> |

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

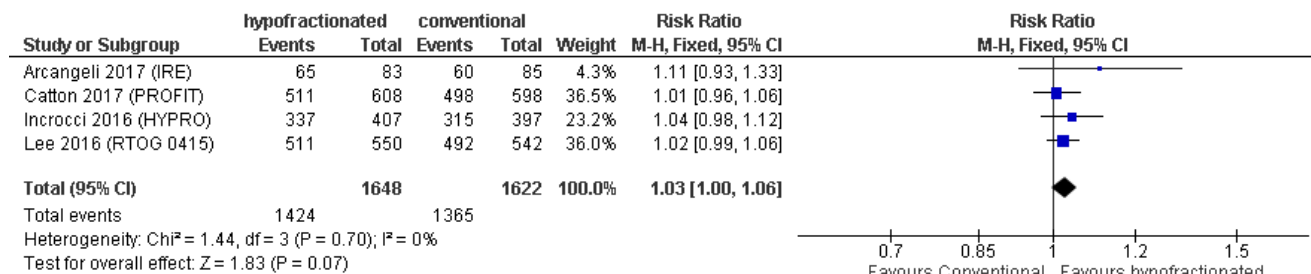
| Short Title | Title | Study characteristics                                                                                                                                                                                                                                                               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



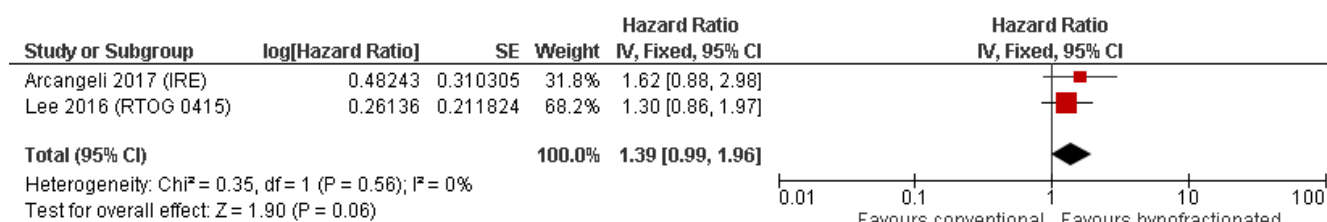
# Appendix F - Forest plots

## Conventional versus hypofractionated radiation therapy

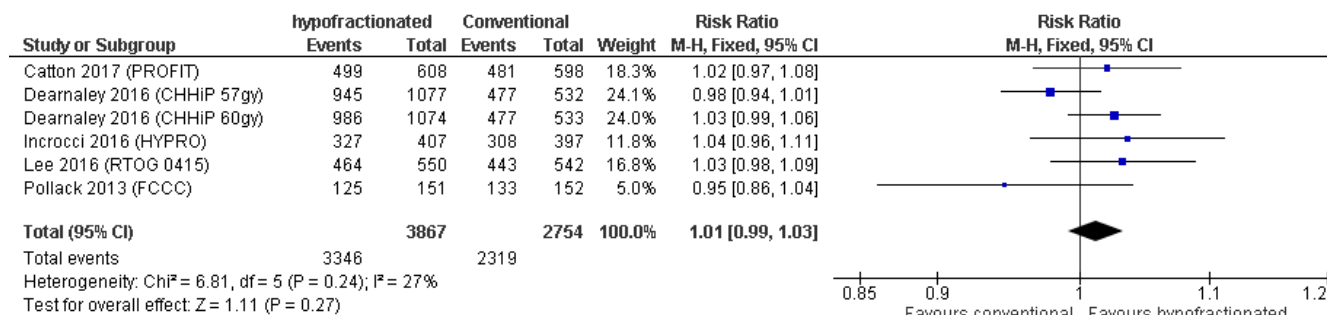
### Freedom from biochemical failure



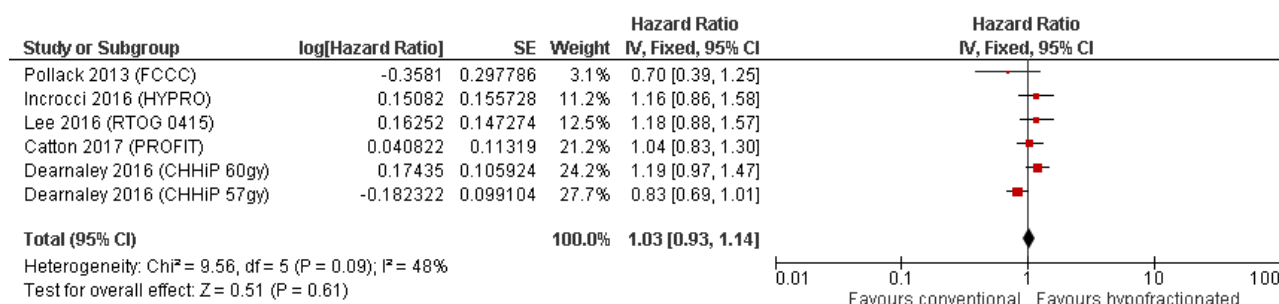
### Time to biochemical failure



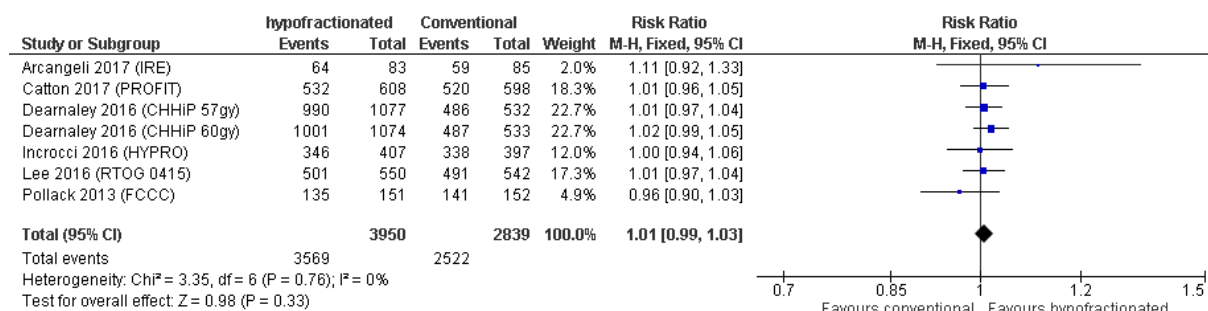
### Freedom from biochemical-clinical failure



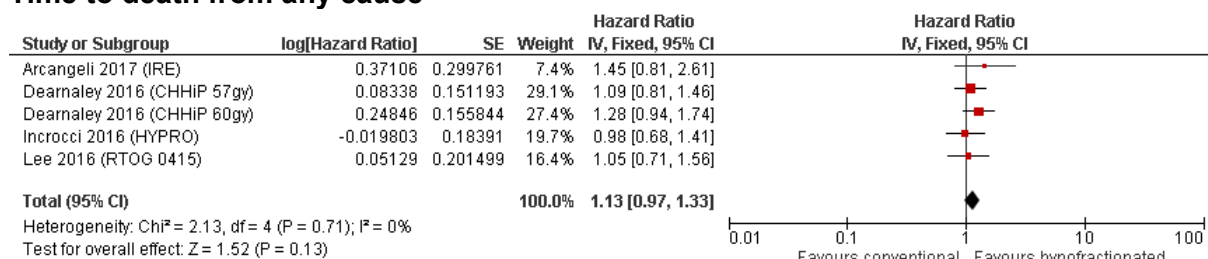
### Time to biochemical-clinical failure



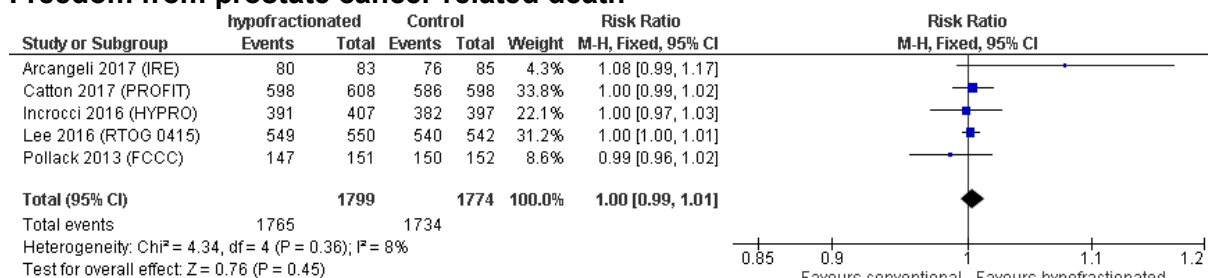
### Overall survival



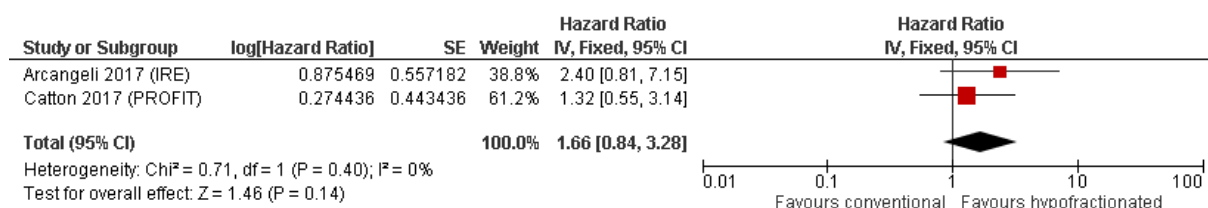
### Time to death from any cause



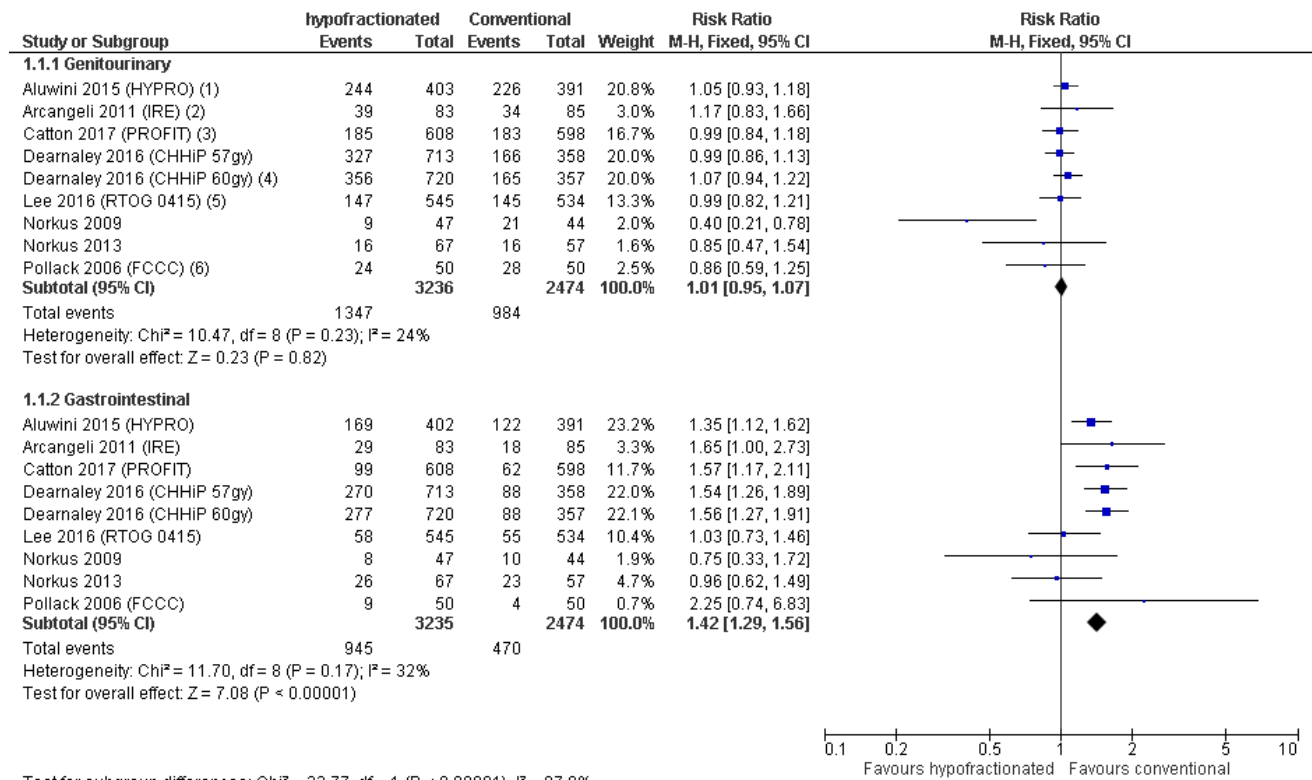
### Freedom from prostate cancer-related death



### Time to prostate cancer-related death



## Acute toxicity

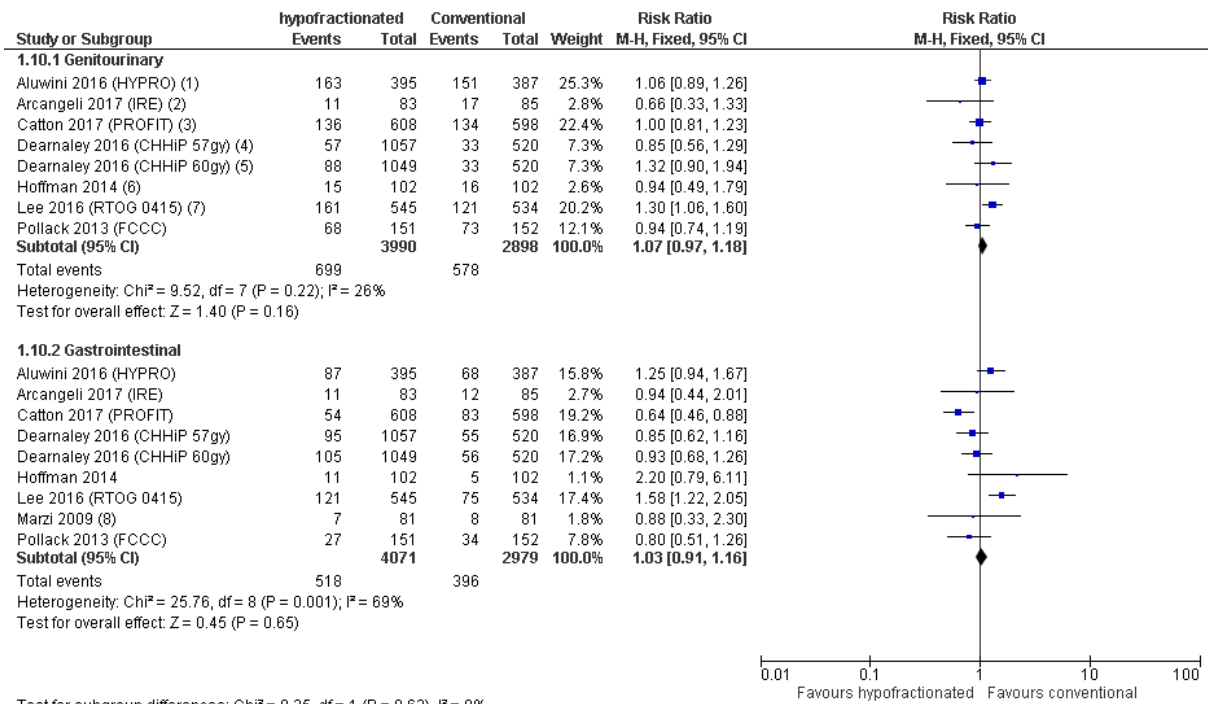


Test for subgroup differences: Chi<sup>2</sup> = 33.77, df = 1 (P < 0.00001), I<sup>2</sup> = 97.0%

### 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



Test for subgroup differences: Chi<sup>2</sup> = 0.25, df = 1 (P = 0.62), I<sup>2</sup> = 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



# 1 Appendix G: GRADE tables

## 2 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  |
|-----------------------------------------------------------------------------------------------|--------------|-------------|----------------------|----------------------------------|-------------------------------------------------------------|--------------|----------------------|--------------|----------------------|----------|
| <b>Overall freedom from biochemical failure- RR &gt;1 favours hypofractionated</b>            |              |             |                      |                                  |                                                             |              |                      |              |                      |          |
| 4 studies<br>RENCI: Arcangeli 2017<br>Lee 2016<br>PROFIT: Catton 2017<br>HYPRO: Incrocci 2016 | RCTs         | 3,270       | RR 1.03 (1.00, 1.06) | 840 per 1000 people <sup>6</sup> | 866 per 1000 people (from 26 fewer to 25 more) <sup>6</sup> | Not serious  | Not serious          | Not serious  | Not serious          | High     |
| <b>Time to biochemical failure– HR &gt;1 favours hypofractionated</b>                         |              |             |                      |                                  |                                                             |              |                      |              |                      |          |
| 2 studies<br>RENCI: Arcangeli 2017<br>Lee 2016                                                | RCTs         | 1,260       | HR 1.39 (0.99, 1.96) | -                                | -                                                           | Not serious  | Serious <sup>4</sup> | Not serious  | Serious <sup>2</sup> | Low      |
| <b>Overall freedom from biochemical-clinical failure- RR &gt;1 favours hypofractionated</b>   |              |             |                      |                                  |                                                             |              |                      |              |                      |          |
| 6 studies<br>FCCC: Pollack 2013*<br>HYPRO: Incrocci 2016<br>Lee 2016**<br>PROFIT: Catton 2017 | RCTs         | 6,621       | RR 1.01 (0.99, 1.03) | 896 per 1000 people <sup>5</sup> | 905 per 1000 people (from 18 fewer to 18 more) <sup>5</sup> | Not serious  | Not serious          | Not serious  | Serious <sup>2</sup> | Moderate |

|                                                                                                                          |      |       |                         |                                             |                                                                        |             |             |             |                      |          |
|--------------------------------------------------------------------------------------------------------------------------|------|-------|-------------------------|---------------------------------------------|------------------------------------------------------------------------|-------------|-------------|-------------|----------------------|----------|
| CHHiP Dearnaley 2016***                                                                                                  |      |       |                         |                                             |                                                                        |             |             |             |                      |          |
| <b>Time to biochemical-clinical failure- HR &lt;1 favours hypofractionated</b>                                           |      |       |                         |                                             |                                                                        |             |             |             |                      |          |
| 6 studies<br>FCCC: Pollack 2013*<br>HYPRO: Incrocci 2016<br>Lee 2016**<br>PROFIT: Catton 2017<br>CHHiP Dearnaley 2016*** | RCTs | 6,621 | HR 1.03<br>(0.93, 1.14) | -                                           | -                                                                      | Not serious | Not serious | Not serious | Serious <sup>2</sup> | Moderate |
| Subgroup analysis patients aged ≥75 years                                                                                |      |       |                         |                                             |                                                                        |             |             |             |                      |          |
| CHHiP Dearnaley 2016***                                                                                                  | RCTs | 491   | HR 0.59<br>(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 <sup>2</sup> | Moderate |
| <b>Overall survival (5 to 10 years)- RR &gt;1 favours hypofractionated</b>                                               |      |       |                         |                                             |                                                                        |             |             |             |                      |          |
| 7 studies<br>RENCI: Arcangeli 2017<br>FCCC: Pollack 2013                                                                 | RCTs | 6,789 | RR 1.01<br>(0.99, 1.03) | 922 per 1000 people at 5 years <sup>5</sup> | 932 per 1000 people (from 18 fewer to 18 more) at 5 years <sup>5</sup> | Not serious | Not serious | Not serious | Not serious          | High     |

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

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

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |  |  |  |  |  |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|--|--|--|--|--|--|--|
| PROFIT: Catton<br>2017<br>CHHiP:<br>Dearnaley<br>2016***<br>Hoffman 2014<br>Lee 2016<br>FCCC: Pollack<br>2006<br>Marzi 2009 ****                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |  |  |  |  |  |  |  |
| <ol style="list-style-type: none"> <li>1. Blinding procedures were not possible/attempted and this may have affected the reporting and/or scoring of this outcome</li> <li>2. 95% confidence intervals for the effect size crossed the line of no effect – downgraded once</li> <li>3. 95% confidence intervals for the effect size crossed one line of the MID – downgraded once</li> <li>4. <math>I^2 &gt; 33.3\%</math></li> <li>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</li> <li>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</li> </ol> <p>* Considered the start of any salvage therapy (ADT, cryosurgery or prostatectomy) as evidence of clinical failure.<br/>                 ** considered death by any cause as evidence of clinical failure.<br/>                 *** Study was split in analysis to 57Gy and 60Gy arms. Conventional fractionation data was halved to account for this.<br/>                 **** Study period of 30-months.</p> |  |  |  |  |  |  |  |  |  |  |

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**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  |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------|----------------------|------------------------|--------------------------------------|---------------------------|---------------|--------------|----------------------|----------|
| <b>Time to worsening of IPSS overall- HR &lt;1 favours better outcomes associated with hypofractionated over time</b>                       |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 303         | HR 0.90 (0.46, 1.78) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |
| <b>Time to worsening of IPSS Quality of life- HR &lt;1 favours better outcomes associated with hypofractionated over time</b>               |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 303         | HR 1.47 (0.62, 3.48) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |
| <b>Time to worsening of urinary incontinence (EPIC) – HR&lt;1 favours better outcomes associated with hypofractionated over time</b>        |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 225         | HR 1.91 (0.97, 3.76) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |
| <b>Time to worsening urinary irritative/obstructive (EPIC)- HR &lt;1 favours better outcomes associated with hypofractionated over time</b> |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 225         | HR 0.40 (0.10, 1.55) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |
| <b>Time to worsening sexual bother (EPIC)- HR &lt;1 favours better outcomes associated with hypofractionated over time</b>                  |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 225         | HR 2.27 (0.68, 4.91) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |
| <b>Time to worsening hormonal bother (EPIC)- HR &lt;1 favours better outcomes associated with hypofractionated over time</b>                |              |             |                      |                        |                                      |                           |               |              |                      |          |
| 1 Study<br>FCCC: Shaikh (2017)                                                                                                              | RCTs         | 225         | HR 1.22 (0.59, 2.55) | -                      | -                                    | Very serious <sup>1</sup> | N/A           | Not serious  | Serious <sup>2</sup> | Very low |

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



|                                                                                                                                                                                                                                                                                                                                                       |      |                                    |                             |   |   |                                |     |             |                      |          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------------------------------------|-----------------------------|---|---|--------------------------------|-----|-------------|----------------------|----------|
| 1 Study<br>CHHiP: Wilkins<br>2015 (60Gy)*                                                                                                                                                                                                                                                                                                             | RCTs | 997<br>across<br>all three<br>arms | HR 1.19<br>(0.92 –<br>1.55) | - | - | Very<br>serious <sup>1,4</sup> | N/A | Not serious | Serious <sup>2</sup> | Very low |
| 1 Study<br>CHHiP: Wilkins<br>2015 (57Gy)*                                                                                                                                                                                                                                                                                                             | RCTs |                                    | HR 1.14<br>(0.88 –<br>1.48) | - | - | Very<br>serious <sup>1,4</sup> | N/A | Not serious | Serious <sup>2</sup> | Very low |
| <p>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.<br/>2. 95% confidence intervals for the effect size crossed the line of no effect – downgraded once</p> <p>* Measured using a combination of both EPIC and UCLA-PCI QoL instruments</p> |      |                                    |                             |   |   |                                |     |             |                      |          |

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10 **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  |
|-----------------------------------------------------------------------------------|--------------|-------------|---------------------------|------------------------|--------------------------------------|--------------|---------------|--------------|----------------------|----------|
| <b>Time to biochemical failure- HR &gt;1 favours brachytherapy</b>                |              |             |                           |                        |                                      |              |               |              |                      |          |
| 1 study<br>ASCENDE-RT<br>(Morris, 2016)                                           | RCTs         | 398         | HR 2.04*<br>(1.25, 3.33)  | -                      | -                                    | Not serious  | N/A           | Not serious  | Not serious          | High     |
| <b>Time to any-cause death– HR &gt;1 favours brachytherapy</b>                    |              |             |                           |                        |                                      |              |               |              |                      |          |
| 1 study<br>ASCENDE-RT<br>(Morris, 2016)                                           | RCTs         | 398         | HR 1.13**<br>(0.69, 1.85) | -                      | -                                    | Not serious  | N/A           | Not serious  | Serious <sup>2</sup> | Moderate |
| <b>Freedom from prostate cancer-related death– RR &gt;1 favours brachytherapy</b> |              |             |                           |                        |                                      |              |               |              |                      |          |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |     |                         |   |   |                      |     |             |                      |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----|-------------------------|---|---|----------------------|-----|-------------|----------------------|-----|
| 1 study<br>ASCENDE-RT<br>(Rodda, 2017)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | RCTs | 383 | HR 0.75<br>(0.48, 1.17) | - | - | Serious <sup>1</sup> | N/A | Not serious | Serious <sup>2</sup> | Low |
| <p>1. Blinding procedures were not possible/attempted and this had the potential to impact on the reporting and/or scoring of this outcome</p> <p>2. 95% confidence intervals crosses the line of no effect – downgraded once</p> <p>*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.</p> <p>**Taken from multivariate analysis controlling for age, disease status (relapse vs. no relapse) and log pre-treatment PSA: HR 1.29 in univariate analysis.</p> |      |     |                         |   |   |                      |     |             |                      |     |

## 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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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<br>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          |
| Koukourakis (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<br>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<br>Full text paper not available                                                                    |
| Liao (2010)       | Hypofractionation: what does it mean for prostate cancer treatment?                                                                                                                                                                                                                        | Not a relevant study design -<br>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<br>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<br>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<br>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<br>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<br>- 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<br>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<br>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<br>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<br>Full text paper not available                      |
| Nakajima (2017)  | Acute toxicity of image-guided hypofractionated proton therapy for localized prostate cancer                                                                                                                                      | Not a relevant study design<br>- 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<br>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<br>- 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<br>- 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<br>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<br>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<br>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<br>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<br>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<br>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<br>- Comment only                                                                    |
| Spagnoletti (2013) | Biochemical control after radiation therapy for prostate cancer: hypofractionation versus conventional fractionation                                                                  | Conference abstract<br>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<br>Not a relevant study design<br>- 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<br>- 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<br>- 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)   | PREFEREence-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<br>- 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<br>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<br>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                                                                                              |



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| 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

### Included studies

- Aluwini S, Pos F, Schimmel E, Lin E, Krol S, Toorn Pp, Jager H, Dirx M, Alemayehu Wg, Heijmen B, and Incrocci L (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, Krol S, Toorn Pp, Jager H, Alemayehu Wg, Heemsbergen W, Heijmen B, and Incrocci L (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
- Arcangeli G, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, Marzi S, Landoni V, Fowler J, and Strigari L (2010) A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer.. *International journal of radiation oncology, biology, and physics* 78(1), 11-8
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- Arcangeli S, Strigari L, Gomellini S, Saracino B, Petrongari Mg, Pinnarò P, Pinzi V, and Arcangeli G (2012) Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *International journal of radiation oncology, biology, and physics* 84(5), 1172-1178
- Arcangeli G, Saracino B, Arcangeli S, Gomellini S, Petrongari Mg, Sanguineti G, and Strigari L (2017) Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: final Results of a Phase III Randomized Trial. *Journal of clinical oncology* 35(17), 1891-1897
- Catton Cn, Lukka H, Gu Cs, Martin Jm, Supiot S, Chung Pwm, Bauman Gs, Bahary Jp, Ahmed S, Cheung P, Tai Kh, Wu Js, Parliament Mb, Tsakiridis T, Corbett Tb, Tang C, Dayes Is, Warde P, Craig Tk, Julian Ja, and Levine Mn (2017) Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *Journal of clinical oncology* 35(17), 1884-1890
- Dearnaley David, Syndikus Isabel, Sumo Georges, Bidmead Margaret, Bloomfield David, Clark Catharine, Gao Annie, Hassan Shama, Horwich Alan, Huddart Robert, Khoo Vincent, Kirkbride Peter, Mayles Helen, Mayles Philip, Naismith Olivia, Parker Chris, Patterson Helen, Russell Martin, Scrase Christopher, South Chris, Staffurth John, and Hall Emma (2012) Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *The Lancet. Oncology* 13(1), 43-54
- Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan Jm, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C, and Hall E (2016) Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *The lancet. Oncology* 17(8), 1047-1060

Hoffman Ke, Voong Kr, Pugh Tj, Skinner H, Levy Lb, Takiar V, Choi S, Du W, Frank Sj, Johnson J, Kanke J, Kudchadker Rj, Lee Ak, Mahmood U, McGuire Se, and Kuban Da (2014) Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *International journal of radiation oncology, biology, and physics* 88(5), 1074-1084

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Prostate cancer: Diagnosis and Management: evidence reviews for Radical Radiotherapy (April 2019)84

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