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Review

A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer

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Abstract ***Background:*** Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males. A systematic review of randomised controlled trials (RCTs) of radiotherapy and other non-pharmacological management options for localised prostate cancer was undertaken.

Methods: A search of thirteen databases was carried out until March 2014. RCTs comparing radiotherapy (brachytherapy (BT) or external beam radiotherapy (EBRT)) to other management options i.e. radical prostatectomy (RP), active surveillance, watchful waiting, high intensity focused ultrasound (HIFU), or cryotherapy; each alone or in combination, e.g. with adjuvant hormone therapy (HT), were included.
Methods followed guidance by the Centre for Reviews and Dissemination and the Cochrane Collaboration. Indirect comparisons were calculated using the Bucher method.

Results: Thirty-six randomised controlled trials (RCTs, 134 references) were included. EBRT, BT and RP were found to be effective in the management of localised prostate cancer. While

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higher doses of EBRT seem to be related to favourable survival-related outcomes they might, depending on technique, involve more adverse events, e.g. gastrointestinal and genitourinary toxicity. Combining EBRT with hormone therapy shows a statistically significant advantage regarding overall survival when compared to EBRT alone (Relative risk 1.21, 95% confidence interval 1.12–1.30). Aside from mixed findings regarding urinary function, BT and radical prostatectomy were comparable in terms of quality of life and biochemical progression-free survival while favouring BT regarding patient satisfaction and sexual function.
There might be advantages of EBRT (with/without HT) compared to cryoablation (with/without HT). No studies on HIFU were identified.
Conclusions: Based on this systematic review, there is no strong evidence to support one therapy over another as EBRT, BT and RP can all be considered as effective monotherapies for localised disease with EBRT also effective for post-operative management. All treatments have unique adverse events profiles. Further large, robust RCTs which report treatment-specific and treatment combination-specific outcomes in defined prostate cancer risk groups following established reporting standards are needed. These will strengthen the evidence base for newer technologies, help reinforce current consensus guidelines and establish greater standardisation across practices.

1. Background

Worldwide, prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 [1]. It is currently estimated that 1 in 7 men in the USA will be diagnosed with prostate cancer at some time in their lives (15.3% of men, based on 2008–2010 data), with an estimated prevalence in 2011 of 2,707,821 men living with prostate cancer and an estimated 233,000 new cases for 2014. For those who have the disease, chances of surviving 5 years after diagnosis are good (98.9% based on data from 2004–2010). Nevertheless, it is estimated that 29,480 American men will die from prostate cancer in 2014 [2,3]. Aside from reducing life expectancy, prostate cancer is associated with reduced quality of life in terms of decreased sexual functioning, urinary incontinence and changes in bowel function, all of which may occur prior to treatment and/or worsen after treatment [4].

Prostate cancer also affects society as a whole through premature death and disability as well as resulting human and economic consequences. It has been estimated that approximately $11.9 billion is spent each year in the United States on prostate cancer treatment, with $4.6bn, $6.2bn and $1.1bn spent on initial treatment, continuing care and last year of life, respectively [5,6]. It is clearly important to ensure that, for those in need of treatment, expenditure is targeted so that the right patients are in receipt of the most effective treatment at the correct time.

Current widely accepted management options include active surveillance, watchful waiting, radical prostatectomy (RP), hormone therapy (HT), radiotherapy, (i.e. external beam radiotherapy (EBRT) or brachytherapy (BT)) and chemotherapy. These approaches are applied individually, sequentially or in combination. High intensity focused ultrasound (HIFU) and cryotherapy are also used but to a lesser degree [7].

However, there is a lack of systematic reviews of randomised controlled trials assessing these options for prostate cancer, i.e. RP, radiotherapy (EBRT and BT), HIFU and cryotherapy.

In this systematic review, we aim to assess the efficacy [8] and adverse events associated with radiotherapy (EBRT and/or BT) compared with other non-pharmacological management options in patients with localised prostate cancer.

2. Methods

The systematic review process followed published guidelines [9,10].

2.1. Inclusion criteria

Our review was focused on non-pharmacological interventions. Pharmacological management of patients was only considered if it was an adjunct to main treatment. Published and unpublished randomised controlled trials were included when they reported on adult men (>18 years) with prostate cancer, treated with any form of radiotherapy (EBRT and/or BT), alone or in combination with HT or RP, in comparison to other relevant management options, i.e. RP, active surveillance, watchful waiting, HIFU and cryotherapy. Outcomes considered relevant for our review included mortality outcomes (overall survival, disease-specific survival), progression outcomes (clinical, biochemical and mixed progression-free survival), adverse events (AE; including

genitourinary and gastrointestinal toxicities and sexual functioning), patient satisfaction, treatment failure (TF) and quality of life (QoL). The main outcome was overall survival (OS).

2.2. Literature search

Searches were undertaken to identify all relevant randomised controlled trials (RCTs), regardless of language or publication status (published, unpublished, in press and in progress). The following databases were searched up to February 2014: MEDLINE, MEDLINE In-Process Citations and Daily Updates, EMBASE (all via OvidSP) and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, a search of PubMed was conducted in March 2014. The search strategies (keywords) were developed specifically for each database. Appendix 1 presents the search strategy developed to search MEDLINE.

Additional reference checking in retrieved articles and systematic reviews was undertaken and supplementary searches for secondary publications were conducted: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews or Effects (DARE), Health Technology Assessment (HTA) database (via CRD website), International Prospective Register of Systematic Reviews (PROSPERO), National Institute for Health and Care Excellence (NICE) guidance, Guidelines International Network (GIN), National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme and National Guidelines Clearinghouse (NGC).

2.3. Methods of study selection, quality assessment and data extraction

Two reviewers independently inspected the titles and abstracts identified by the search. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected and pre-specified inclusion criteria applied.

For each study, data were extracted by one reviewer and checked for accuracy by a second reviewer. A quality assessment based on the methods described in the Cochrane Handbook was performed [11]. Study characteristics and quality were presented in tables. Where details on the risk group (i.e. D'Amico classification) were missing, a surrogate was created which was based on the reported baseline characteristics of included patients. The choice of risk stratification system is considered in the discussion section. D'Amico classified prostate cancer patients into 3 groups: low-risk (prostate-specific antigen [PSA] < 10 ng/ml and clinical stage T1c-T2a and Gleason score $\leqslant 6$), intermediate risk (PSA $\geqslant 10$ ng/ml, but $\leqslant 20$ ng/mL or clinical stage T2b or Gleason score $= 7$) and high-risk (PSA > 20 ng/ml or clinical stage $\geqslant$ T2c or Gleason score $\geqslant 8$) [12]. Three pre-specified categories were agreed with clinical experts following consideration of the literature and used to allow the comparison of different dosages of EBRT as monotherapy: low dose ($<$75 Gy), intermediate dose (75–78 Gy), high dose ($\geqslant$78 Gy).

Any disagreement during data extraction was resolved through discussion. Abstracts were also included where full manuscripts were unavailable, in line with current guidance [9,10].

2.4. Study analyses

Tables were used to present relevant results for all studies. All 'head-to-head' comparisons of comparator treatments were performed in line with the Cochrane Handbook [9]. Pooled effect sizes (relative risks (RR)) and 95% confidence intervals (95%-CIs) using random effects (inverse–variance, I–V) methods were only reported where trials were considered to be clinically and statistically homogeneous.

3. Results

Literature searches yielded 25,867 references. Additionally, searches were undertaken to identify relevant systematic reviews, technology appraisals, guidance and guidelines. These additional searches, aimed to identify supplementary primary studies, retrieved a total number of 826 hits. After removing 9,143 duplicates, a total of 17,550 references were available for screening (see Fig. 1).

Titles and abstracts were screened and 492 potentially relevant papers ordered as full texts. Of these, 134 references (relating to 36 individual studies) were included. A list of excluded studies is available on request.

3.1. Characteristics and risk of bias of included studies

Nearly all of the included studies have been conducted in Europe or North America, (34 out of 36) and two studies were carried out in Australia and New Zealand as well as China, respectively. On average, the 36 studies included 345 patients (median 212, total 11,731; two abstracts did not report patient numbers).

As detailed in Table 2, few studies reported patient risk stratification and those that did used a variety of classifications. Five studies [46,53,68,83,159] (including one with follow-up < 5 years) based risk stratification on the D'Amico classification (see Table 1); in one study [49] patients were stratified according to risk as defined by the National Comprehensive Cancer Network (NCCN); another two studies [96,82] (including one small study $n < 50$ patients) used the Partin classification while Holmberg et al. [146] defined low risk patients

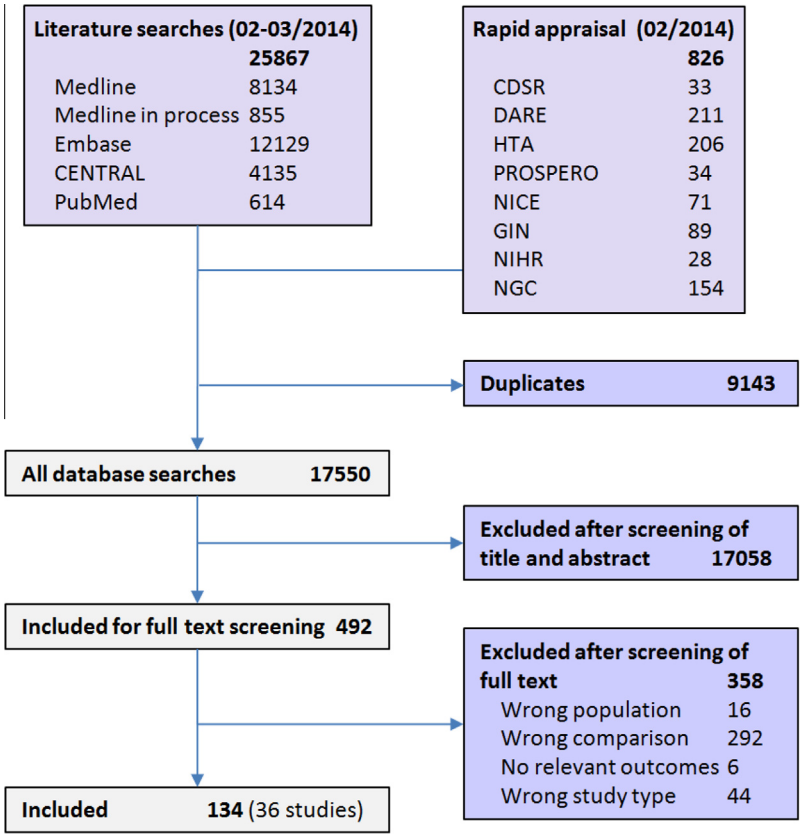

Fig. 1. Flow diagram of study searches and inclusion based on PRISMA.

based on Gleason score and WHO grade. In order to allow a more transparent way of comparing the risk grouping of included patients, a D'Amico surrogate was extracted based on the baseline characteristics reported by each study (see Table 1). Two studies included patients stratified to a single risk group ([14] (small study) [83]). The other studies assigned patients to two ($n = 10$) or three risk groups ($n = 22$), while two studies provided insufficient baseline data which prevented assignment of their patients to risk groups [157,123] (one study: unknown size and follow-up).

None of the studies fulfilled all pre-specified quality criteria [11]. Common sources for potential risk of bias included missing or insufficient details on randomisation procedure, allocation concealment and the lack of blinding of patients, physicians and outcome assessors.

3.2. Summary of direct comparisons

Key survival-related findings for each treatment are presented in Table 2. Relative effects are grouped as 'greater than' (i.e. statistically significant difference ($p \leqslant 0.05$) in favour of A), 'no significant difference' ($p > 0.05$) and 'worse than' (i.e. statistically significant difference ($p \leqslant 0.05$) in favour of B; see columns). A full version of the table, including all assessed outcomes, is available as an online Appendix.

These results are also presented in a network diagram showing the survival-related relative effects of all included studies for each identified comparison (see Fig. 2). Endpoints for which no statistically significant differences were reported are represented by the grey double lines. In contrast, endpoints for which a statistically significant effect was found are represented by the coloured lines where the arrow points to the treatment with the higher relative effect. The numbers of studies reporting on each outcome are given in brackets while letters refer to the risk grade of patients included in the studies (D'Amico surrogate). A full version of the network is available as an online Appendix. Outcomes relevant to mortality and/or disease progression are highlighted in bold.

3.3. Summary of pooled estimates

For some comparisons of overall survival, available data allowed pooling. Comparisons of EBRT (low dose) with: (1) EBRT (low dose) combined with HT; (2) EBRT (low dose) + BT, i.e. combined dose escalation; as well as (3) EBRT (high dose) were all possible. Furthermore, pooling was possible for two studies comparing RP with watchful waiting and RP with RP followed by EBRT. Only one of these comparisons showed a statistically significant advantage, as shown

Table 1
Summary of characteristics of included studies.

Study	Participants	Risk of bias*	D'Amico surrogate	Intervention	Comparison	Extracted outcome
Brachytherapy vs. radical prostatectomy						
Crook [14–18] Canada, 09/2002–07/2005 SPIRIT	$n = 34$ Stage: T1c/T2a PSA at baseline (ng/ml): ⩽10 Gleason score: ⩽6 Age: 60 years (entire cohort) TRUS volume ⩽ 60 cm^3	?/?/?/?/?/?	Low risk	Brachytherapy (no further details)	RP	Bowel function (EPIC), patient satisfaction (EPIC), sexual function (EPIC), urinary function (EPIC)
Giberti [19] Italy, 05/1999–10/2002	$n = 174$ Stage: cT1c-cT2a PSA at baseline (ng/ml, mean): 7.8 (RP), 7.5 (brachytherapy) Gleason score: 5.8 (mean) Age: 65 years (mean)	☺/?/?/☺/?/☺	Low-intermediate risk	Brachytherapy (no further details)	RP	Bowel function (EORTC-QLQ-PR25), bPFS, QoL (EORTC-QLQ-C30), sexual function (IIEF), urinary function (EORTC-QLQ-PR25)
Brachytherapy vs. Brachytherapy + hormone therapy						
Cui [41] China, NR (Abstract only)	$n = 165$ Stage: T1c-T3b PSA at baseline (ng/ml, median): 26.5 Gleason score: not reported Age: 79 years (median)	?/?/?/?/☺/☺	low–high risk	Brachytherapy (I-125)	Brachytherapy (I-125) after 3 month neoadjuvant HT (no further details)	bPFS
Cryoablation vs. external beam radiation therapy (low dose)						
Al-Zahrani [42–45] Canada, 1999–2002 (Abstract only)	$n = 62$ Stage: cT2c-cT3b PSA at baseline (ng/ml): <25 Gleason score: not reported Age: not reported Negative metastatic evaluation on CT and bone scan	?/?/?/?/?/☺	Intermediate-high risk	EBRT (66 Gy in 33 fractions)	Cryoablation	bPFS, DSS, OS
Donnelly [46,47] Canada, 12/1997–02/2003	$n = 231$ Stage: pT2-pT3N0M0 PSA at baseline (ng/ml, median): 8.1 (cryoablation), 9.0 (EBRT) Gleason score: 35% ⩽6, 55% 7, 10% 8–10 Age: 69 years (median) Risk (D'Amico): 8% low, 26% intermediate, 66% high Prostate volume ⩽ 60 cm^3	?/?/?/?/☺/☺	Low–high risk	EBRT (68 Gy-73.5 Gy)	Cryoablation	Bowel function (PCI), DSS, mPFS, OS, QoL (EORTC-QLQ-C30), sexual function (intercourse at 36 months), urinary function (PCI)
External beam radiation therapy (low dose) vs. external beam radiation therapy (low dose) + brachytherapy						
Hoskin [48–52] UK, 12/1997–08/2005	$n = 218$ Stage: T1-T3M0 PSA at baseline (ng/ml): 33% <10, 41% 10–19.9, 26% ⩾20 Gleason score: 42% ⩽6, 42% 7, 16% 8–10 Age: 68.9 years (mean) Risk (NCCN): 4% low, 42% intermediate, 54% high	?/?/☹/☹/☹/☺	Low–high risk	EBRT (55 Gy in 20 fractions)	EBRT (35.75 Gy in 13 fractions) + HDR-BT (2× 8.5 Gy)	Bowel function (modified Dische Scales), bPFS, mPFS, OS, QoL (FACT-P), urinary function (modified Dische Scales)

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Table 1 (*continued*)

Study	Participants	Risk of bias*	D'Amico surrogate	Intervention	Comparison	Extracted outcome
Sathya [53] Canada, 05/1992–12/1997	$n = 104$ Stage: T2-T3N0M0 (TNM 1992) PSA at baseline (ng/ml): 37% <10, 28% 10–19.9, 35% ⩾20 Gleason score: 36% ⩽6, 49% 7, 15% 8–10 Age: 65 years (mean) Risk (D'Amico): 40% intermediate, 60% high	?/☺/ ?/☺/ ☺/☺	Low–high risk	EBRT (40 Gy in 20 fractions) + BT (iridium implant, 35 Gy)	EBRT (66 Gy in 33 fractions)	mPFS, OS, toxicity
Zapatero-Ortuno [54] Spain, NR (Abstract only)	$n = 30$ Intermediate risk localised disease. Stage: T1c-T2c PSA at baseline (ng/ml, median): 9.76 Gleason score: 57% ⩽6, 43% 7 Age: 68.57 years (mean)	?/?/?/ ?/?/?	Low–high risk	3DCR/EBRT (46 Gy) + brachytherapy boost with LDR-BT of 108 Gy)	3DCR/EBRT (76 Gy)	bPFS, OS, sexual function (IIEF), toxicity
External beam radiation therapy (low dose) vs. external beam radiation therapy (low dose) + hormone therapy						
Bolla [55–59] European MC, 05/1987–10/1995 EORTC trial 22863	$n = 401$ Stage: T1–T4 PSA at baseline (ng/ml, median): 6% ⩽4, 11% 4.1–10, 16% 10.1–20, 24% 20.1–40, 34% >40, 9% unknown Gleason score: 6% 2–4, 22% 5–6, 34% 7–10, 38% unknown Age: 71 years (median) WHO performance status 0–2	☺/☹/ ☹/☹/ ☺/☺	Low–high risk	EBRT (70 Gy in 7 weeks)	EBRT (70 Gy in 7 weeks) + adjuvant HT	AE, bPFS, DSS, OS
D'Amico [60–62] USA, MC, 12/1995–04/2001	$n = 206$ Stage: cT1b–cT2b (AJCC 1992) PSA at baseline (ng/ml, median): 11 Gleason score: 28% 5–6, 35% 3 + 4, 23% 4 + 3, 14% 8–10 Age: 73 years (median)	☺/?/ ☹/☹/ ☺/☹	Low–high risk	EBRT (70.35 Gy in 36 fractions)	EBRT (70.35 Gy in 36 fractions) + 6 month HT	DSS, OS, Toxicity
Denham [63–67] Australia and New Zealand MC, 06/1996–02/2000 TROG 96.01	$n = 802$ Stage: T2b–T4 PSA at baseline (ng/ml): 4% <4, 24% ⩾ 4 and <10, 34% ⩾10 and <20, 30% ⩾20 and <50, 7% ⩾50 and <100, 1% ⩾100 Gleason score: 44% 2–6, 38% 7, 17% 8–10, 1% missing Age: 68 years (median)	☺/?/ ☹/☹/ ☺/☺	Intermediate-high risk	EBRT (66 Gy in 33 fractions)	(1) EBRT (66 Gy in 33 fractions) + 3 months neoadjuvant HT (2) EBRT (66 Gy in 33 fractions) + 6 months neoadjuvant HT	bPFS, cPFS, DSS, OS, TF

Jones [68–72] USA MC, 10/1994–04/2001 RTOG 94–08	$n = 1979$ Stage: T1b–T2b (AJCC 1992) PSA at baseline (ng/ml): 11% <4, 89% 4–20 Gleason score: 62% 2–6, 27% 7, 9% 8–10, 2% unknown Age: 71 years (median) Risk (D'Amico): 35% low, 54% intermediate, 11% high	☺/?/ ?/?/ ☺/☺	Low–high risk	EBRT (66.6 Gy in 37 fractions)	EBRT (66 Gy in 37 fractions) after 2 months neoadjuvant HT and 2 months adjuvant HT	bPFS, cPFS, DSS, OS, sexual function
Laverdière [73] Canada, 1991–1994	$n = 120$ Stage: T2a–T3c PSA at baseline (ng/ml): 14% <4, 40% 4–10, 23% 10–20, 23% >20 Gleason score: 42% ⩽3, 42% 4–6, 16% ⩾7 Age: 70 years (mean)	?/?/?/ ?/☺/ ☺	Low–high risk	EBRT (64 Gy in 32 fractions)	(1) 3 months neoadjuvant HT + EBRT (64 Gy in 32 fractions) (2) 3 months neoadjuvant HT + EBRT (64 Gy in 32 fractions) + 6 months HT	bPFS, cPFS
Pilepich [74–78] USA MC, 04/1987–06/1991 RTOG 86–10	$n = 456$ Stage: T2–T4 PSA at baseline (ng/ml, median): 22.6 (EBRT + HT), 33.8 (EBRT) Gleason score: 15% 2–5, 56% 6–7, 28% 8–10, 1% missing Age: 71 years	?/?/?/ ?/☺/ ☺	Low–high risk	EBRT (65–70 Gy in daily doses of 1.8–2.0 Gy)	EBRT (65–70 Gy in daily doses of 1.8–2.0 Gy) + neoadjuvant HT	bPFS, cPFS, DSS, OS, TF
Zagars [79,80]USA, 11/1967–12/1973	$n = 78$ Stage: not reported PSA at baseline: not reported Gleason score: not reported Age: 64 years (mean/median)	?/?/?/ ?/☺/ ☺	Low–high risk	EBRT (70 Gy in 35 fractions)	EBRT (70 Gy in 35 fractions) + HT (oestrogens)	DSS, OS
External beam radiation therapy (low dose) vs. external beam radiation therapy (low–high dose)						
Spagnoletti [81,82] Italy, 09/2008–07/2009 (Abstract only)	$n = 40$ Stage: cT1-T2N0M0 PSA at baseline: not reported Gleason score: not reported Risk: intermediate (Partin classification)	?/?/?/ ?/☺/ ☺	Low-intermediate risk	CFRT (72–78 Gy in 36–39 fractions)	HFRT (64.8–70.2 Gy in 24–26 fractions)	Toxicity
External beam radiation therapy (low–high dose) vs. external beam radiation therapy (low–high dose) + hormone therapy						
Mok [83] Canada, 1999–2006 (Abstract only)	$n = 243$ Risk (D'Amico): (T1–T2, Gleason score 7, PSA < 20 ng/ml; T1-T2, Gleason score ⩽ 6, PSA 10–20 ng/ml) Age: not reported	?/?/?/ ?/☺/ ☺	Intermediate risk	EBRT (75.6 or 79.8 Gy in 42 fractions)	EBRT (75.6 or 79.8 Gy in 42 fractions)+ 3 neoadjuvant HT	bPFS, toxicity
External beam radiation therapy (low dose) vs. external beam radiation therapy (intermediate dose)						
Norkus [84] Lithuania, 01/2010–05/2012	$n = 124$ Stage: 19% < T2c, 81% ⩾ T2c PSA at baseline (ng/ml): 78% ⩽ 20, 22% > 20 Gleason score: 91% ⩽ 7, 9% > 7 Age: 65 years (median)	☺/?/ ☹/☹/ ☺/☺	Low–high risk	CFRT (76 Gy in 38 fractions)	HFRT (63 Gy in 20 fractions)	QoL, toxicity, urinary function

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Table 1 (*continued*)

Study	Participants	Risk of bias*	D'Amico surrogate	Intervention	Comparison	Extracted outcome
External beam radiation therapy (low dose) vs. external beam radiation therapy (high dose)						
Aluwini [85] The Netherlands MC, 04/2007–01/2011 (Abstract only)	$n = 820$ Stage: "localised prostate cancer" PSA at baseline (ng/ml): not reported Gleason score: not reported Age: not reported	?/?/?/?/☺/☹	Low–high risk	CFRT (78 Gy in 39 fractions)	HFRT (64.6 Gy in 19 fractions)	Toxicity
Arcangeli [86–92] Italy, 01/2003–12/2007	$n = 114$ Stage: T2c-T4 PSA at baseline (ng/ml, mean/median): 19/13 (CFRT); 26/16 (HFRT) Gleason score: 49% $\leqslant 3+4$; 51% $\geqslant 4+3$ Age: 75 years (median)	?/?/?/?/☺/☺	Intermediate-high risk	CFRT (80 Gy in 40 fractions) after 9 months HT	HFRT (62 Gy in 20 fractions) after 9 months HT	bPFS, cPFS, Toxicity
Beckendorf [93–95] France MC, 09/1999–02/2002 GETUG-06	$n = 306$ Stage: T1–T3a (UICC 1997) PSA at baseline (ng/ml): 39% <10, 45% 10 $\leqslant$20, 16% >20 Gleason score: 63% <7, 37% $\geqslant$7 Age: 67 years (mean)	?/?/?/?/☺/☺	Low–high risk	EBRT (46 Gy in 23 fractions + 24 Gy = 70 Gy)	EBRT (46 Gy in 23 fractions + 34 Gy = 80 Gy)	AE, bPFS, DSS, OS, QoL, sexual function, toxicity
Peeters [96–104] The Netherlands MC, 06/1997–02/2003 CKTO 96–10	$n = 664$ Stage: T1–T4 PSA at baseline: 7% $\leqslant$4, 32% 4–10, 38% 10–20, 23% 20–60 Gleason score: 30% 2–4, 55% 5–7, 15% 8–10 Age: 68.7 years (mean) Risk: low–high (Partin classification)	?/?/?/?/☺/☺	Low–high risk	EBRT (68 Gy in 34 fractions, 22% of patients with neoadjuvant HT)	EBRT (78 Gy in 39 fractions, 21% of patients with neoadjuvant HT)	bPFS, cPFS, OS, QoL, TF, toxicity, urinary function
Pollack [105–113] USA, 1993–1998	$n = 301$ Stage: T1–3NxN0M0 PSA at baseline (ng/ml): 11% $\leqslant$4; 54% 4–10; 35% >10 Gleason score: 50% 2–6, 33% 7, 17% 8–10 Age: not reported	?/?/?/?/☺/☺	Low–high risk	EBRT (78 Gy; conventional 46 Gy in 23 fractions + 32 Gy 3DCR boost)	EBRT (70 Gy in 35 fractions)	bPFS, complications, cPFS, QoL, OS, toxicity
Zietman [114–117] USA MC, 01/1996–12/1999	$n = 393$ Stage: T1b–T2b (AJCC 1992) PSA at baseline (ng/ml): 11% <4, 74%, 4–10, 15% 10–15 Gleason score: 75% 2–6, 15% 7, 9% 8–10, 1% unknown Age: 67 years (median)	☺/☺/?/?/☺/☺	Low-intermediate risk	EBRT (70.2 Gy in 1.8 Gy fractions)	EBRT (79.2 Gy in 1.8 Gy fractions)	bPFS, cPFS, OS, QoL, toxicity

External beam radiation therapy (low dose) vs. radical prostatectomy						
Paulson [118,119] USA, NR	$n = 90$ Stage: T1-T2N0M0 (clinical stage A2 or B) PSA at baseline: not reported Gleason score: not reported Age: not reported Normal prostatic acid phosphatase levels, negative isotopic bone scans, no pelvic nodal extension	?/?/?/ ?/?/☺	Low-intermediate risk	RP	EBRT (no further details)	TF
External beam radiation therapy (low dose) vs. watchful waiting						
Fransson [120–122] Sweden MC, 1986–1996 UMEÅ 1	$n = 72$ Stage: T1b–T2, G1–G2, N0, M0 PSA at baseline (ng/ml): 38% < 10, 18% 10–19.9, 44% ⩾ 20 Gleason score: not reported Age: 72 years (mean)	?/?/?/ ?/☺/ ☺	Low–high risk	EBRT (64–68 Gy in 32 fractions)	WW	Bowel function (PCSS), QoL (QLQ-C30), sexual function (PCSS), urinary function (PCSS)
External beam radiation therapy (unclear dose) vs. external beam radiation therapy (unclear dose) + hormone therapy						
Porter [123] Canada, NR (Abstract only)	No information available (Paper unobtainable)	?/?/?/ ?/?/?	Not estimable	EBRT (no further information)	EBRT + neoadjuvant HT (no further information)	No information available
External beam radiation therapy (unclear dose) vs. radical prostatectomy						
Stasi [124] Italy, 01/1997–09/2001 (Abstract only)	$n = 137$ "Clinically localised" prostate cancer (no further information)	?/?/?/ ?/☺/ ☺	Low–high risk	EBRT (no further details)	RP	Bowel function, bPFS, cPFS, DSS, sexual function, urinary function
External beam radiation therapy (unclear dose) + brachytherapy vs. external beam radiation therapy (unclear dose) + brachytherapy + hormone therapy						
García Blanco [125] Spain, 01/2007–11/2008 (Abstract only)	$n = 62$ "Intermediate to high risk" No further information	?/?/?/ ?/☺/ ☺	Intermediate-high	EBRT + HDR-BT (no further information)	EBRT + HDR-BT + HT (no further information)	bPFS, cPFS, toxicity
Radical prostatectomy vs. radical prostatectomy + EBRT						
Bolla [126–133] European MC, 11/1992–12/2001 EORTC trial 22911	$n = 1005$ Stage: cT0–cT3N0 (UICC 1989) PSA at baseline (ng/ml, median): 12.4 Gleason score: not reportedvAge: ⩽75 years Untreated. WHO performance status 0–2	☺/?/ ?/?/ ☺/☺	Low–high risk	RP	RP + EBRT (60 Gy in 30 fractions)	AE, bPFS, DSS, mPFS, OS, toxicity, urinary function (pad test)
Thompson [134–137] Canada, USA, MC, 08/1988–01/1997	$n = 425$ Stage: pT3N0M0 PSA at baseline (ng/ml): 50% < 10, 50% ⩾ 10 Gleason score: 50% ⩽ 6, 36% 7, 13% 8–10 Age: 65 years (median) RP 16 months prior to study. Negative bone scan.	☺/?/ ☹/☹/ ☺/☺	Intermediate-high risk	RP	RP + EBRT (60–64 Gy in 30–32 fractions)	AE, bPFS, cPFS, OS, urinary function

(*continued on next page*)

Table 1 (*continued*)

Study	Participants	Risk of bias*	D'Amico surrogate	Intervention	Comparison	Extracted outcome
Wiegel [138–141] Germany MC, 04/1997–09/2004 ARO 96–02/AUO AP 09/95	$n = 307$ Stage: pT3-pT4N0 (IUAC 1992) PSA at baseline (ng/ml, median): 10.4 Gleason score: 32% ⩽6, 54% 7, 14% 8–9 Age: 64 years (median) WHO performance status 0–1.	☺/?/ ?/?/ ☺/☺	Intermediate-high risk	RP	RP + EBRT (60 Gy in 30 fractions)	mPFS, OS
Radical prostatectomy vs. watchful waiting						
Holmberg [142–153] Finland, Iceland, Sweden, MC, 01/1989–02/1999 SPCG-4	$n = 695$ Stage: T0c/d-2 (IUAC 1978/1987) PSA at baseline (ng/ml): <50 Gleason score: not reported Age: 64 years (mean) Life expectance > 10 years. Untreated. Negative bone scan. Risk (Gleason/WHO): 38% low, no further details	☺/?/ ?/☺/ ☺/☺	Low–high risk	RP	WW	cPFS, DSS, OS, sexual function, urinary function
Madsen 1988 [154–156] USA, 05/1967–03/1975	$n = 142$ Stage: T0-T2 (stage I and II adenocarcinoma of prostate) PSA at baseline: not reported Gleason score: 87% ⩽ 6, 13% 7–10 Age (median): 67 years (stage I), 61 years (stage II)	?/?/?/ ?/☹/ ☹	Low–high risk	RP	WW	OS
Norlen [157] Sweden, NR (Abstract only)	No information available	?/?/?/ ?/?/?	Not estimable	RP	WW	No information available
Wilt [158–167] USA MC, 11/1994–01/2002 Wilt 2012	$n = 731$ Stage: T1a-T2cNxM0 PSA at baseline (ng/ml, mean): 10.2 Gleason score: 74% ⩽6, 19% 7, 7% 8–10 Age: 66.9 years (mean) Risk (D'Amico): 42% low, 36% intermediate, 22% high	☺/?/ ?/?/ ☺/☺	Low–high risk	RP	WW	Bowel function, cPFS, DSS, OS, QoL, sexual function, urinary function

*Risk of bias items [Cochrane Handbook]: Randomisation; Allocation concealment; Patient/personnel blinding; Outcome assessor blinding; Incomplete outcome reporting; Selective outcome reporting. ☺ = low risk of bias; ☹ = high risk of bias; ? = unclear of bias; 3DCR = Three-Dimensional Conformal Radiotherapy; AE = Adverse event; bPFS = Biochemical progression-free survival; BT = Brachytherapy; CFRT = Conventionally fractionated radiotherapy; cPFS = Clinical progression-free survival; CT = Computer tomography; DSS = Disease-specific survival; EBRT = External Beam Radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; EPIC = Expanded Prostate Cancer Index Composite; FACT-P = Functional Assessment of Cancer Therapy specific for prostate cancer; GETUG = Groupe d'Etude des Tumeurs Uro-Génitales; Gy = Gray (SI unit of absorbed radiation); HDR = High-dose radiation; HFRT = Hypofractionated radiotherapy; HT = Hormone therapy; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IUAC = International union against cancer; MC = Multicentre; ml = Millilitre; mPFS = Mixed (biochemical and clinical) progression-free survival; months = Months; NCCN = National Comprehensive Cancer Network; ng = Nanogram; NR = Not reported; OS = Overall survival; PCI = Prostate Cancer Index; PCSS = Prostate Cancer Symptom Scale; PR25 = Prostate-specific module of QLQ-C30; PSA = Prostate-Specific Antigen; QLQ-C30 = EORTC Quality of Life Questionnaire 30-item cancer-specific module; QoL = Quality of life; RP = Radical prostatectomy; SPCG-4 = Scandinavian Prostate Cancer Group study number 4; SPIRIT = Surgical Prostatectomy versus Interstitial Radiotherapy Intervention Trial; TF = Treatment failure; TROG = Trans-Tasman Radiation Oncology Group; UICC = Union for International Cancer Control; UK = United Kingdom; USA = United States of America; WHO = World Health Organization; WW = Watchful Waiting.

Table 2
Key survival-related findings by comparator. (Please note that a full version of this table is available as an online Appendix.)

Intervention	Relative effect		
	Effect greater than	No significant difference	Effect worse than
Brachytherapy		*RP:* bPFS, (Giberti, 2009, $n = 174$, low-intermediate risk)	
Cryoablation		*EBRT (low dose):* mPFS (36 months, difference 3.9%, 95%-CI −5.3 to 13.2) (Donnelly, 2010, $n = 231$, low–high risk); DSS, OS (Al-Zahrani, 2011; Donnelly, 2010), $n = 293$, low–high risk)	*EBRT (low dose):* bPFS (8 yrs: 17.4% vs. 59.1%, $p = 0.01$) (Al-Zahrani, 2011, $n = 62$, intermediate-high risk)
EBRT (low dose)	*Cryoablation:* bPFS (8 yrs: 17.4% vs. 59.1%, $p = 0.01$) (Al-Zahrani 2011, $n = 62$, intermediate-high risk) *EBRT (high dose, CFRT) [vs. EBRT (low dose, HFRT)]:* bPFS (79% vs. 87%, $p = 0.035$) (Arcangeli, 2010, $n = 114$, intermediate-high risk)	*Cryoablation:* mPFS (36 months, difference 3.9%, 95%-CI −5.3 to 13.2) (Donnelly 2010, $n = 231$, low–high risk); DSS, OS (2 studies (Al-Zahrani, 2011; Donnelly, 2010), $n = 293$, low–high risk) *EBRT (low dose) ± BT:* bPFS ($n = 0$ after mean FUP 22.7 months, PSA after 17.5 months: 0.68 ng/ml vs. 0.88 ng/ml, $p = 0.44$) (Zapatero-Ortuno, 2010, $n = 30$, low-intermediate risk); OS ($n = 0$ after mean FUP 22.7 months; HR 1.36, 95%-CI 0.50–3.65, $p = 0.54$; 10 yrs, $p = 0.2$) (3 studies (Hoskin, 2007; Sathya, 2005; Zapatero-Ortuno, 2010), $n = 352$, low–high risk) *EBRT (low dose) ± HT:* bPFS (2 yrs) (Laverdière, 1997, $n = 120$, low–high risk); OS (10 yrs, 8.7 vs. 7.3 yrs, $p = 0.12$; 15 yrs, no significant difference) (2 studies (Pilepich, 1995; Zagars, 1988), $n = 534$, low–high risk) *EBRT (high dose):* cPFS (clinical failure, HR 0.89, 95%-CI 0.69–1.15) (Peeters, 2006, $n = 664$, low–high risk); DSS (54 months, $p = 0.61$; 110 months, HR 0.96, 95%-CI 0.63–1.45) (2 studies (Beckendorf, 2004; Peeters, 2006), $n = 968$, low–high risk); bPFS (5 yrs, Phoenix, 23.5 vs. 32%; 10 yrs, Phoenix, $p = 0.001$) (2 studies (Beckendorf, 2004; Zietman, 2005), $n = 699$, low–high risk); OS (54 months, $p = 0.52$; 110 months, HR 0.99, 95%-CI 0.75–1.3; 8 yrs, no overall difference) (4 studies (Beckendorf, 2004; Peeters, 2006; Pollack, 2000; Zietman), $n = 1662$, low–high risk)	*EBRT (low dose) ± BT:* bPFS (Hoskin, 2007, $n = 218$, low–high risk); mPFS (HR 0.42, 95%–CI 0.23–0.75, $p = 0.0024$; Median FUP 7.1 yrs: $p = 0.01$) (2 studies (Hoskin, 2007; Sathya, 2005), $n = 312$, low–high risk) *EBRT (low dose) ± HT:* bPFS (10 yrs. $p = 0.003$/ $p < 0.001$; 10 yrs, HR 1.74, 95%-CI 1.48–2.04, 1 yr, $p < 0.0001$; 10 yrs, $p < 0.01$), cPFS (10 yrs, $p = 0.002$/ $p < 0.001$; 10 yrs, HR 1.45, 95%-CI 1.03–2.06, 2 yrs; $p < 0.01$; 10 yrs, distant metastases, $p = 0.006$) (4 studies (Denham, 2008; Jones, 2011; Laverdière, 1997; Pilepich, 1995), $n = 3357$, low–high risk); OS (10 yrs, HR 0.60, 95%-CI 0.45–0.80; 7.6 yrs. HR 1.8, 95%-CI 1.1–2.9; 10 yrs, HR 0.63, 95%-CI 0.48–0.83; 10 years, HR 1.17, 95%-CI 1.01–1.35) (4 studies (Bolla, 2002; D'Amico, 2004; Denham, 2008; Jones, 2011). $n = 3388$, low–high risk); DSS (10 yrs, HR 0.42, 95%-CI 0.33–0.55; 4.5 yrs, $p = 0.02$; 10 yrs, HR 0.49, 95%-CI 0.32–0.74; 10 yrs, HR 1.87, 95%-CI 1.27–2.74; 10 yrs, $p = 0.01$; 15 yrs, $p = 0.008$) (5 studies (Bolla, 2002; D'Amico, 2004; Denham, 2008; Jones, 2011; Pilepich, 1995; Zagars, 1988). $n = 3922$, low–high risk) *EBRT (high dose):* bPFS (Phoenix, HR 0.80, 95%-CI 0.64–0.97), mPFS (110 months, HR 0.79, 95%-CI 0.64–0.97; 6 yrs, 64% vs. 70%, $p = 0.03$) (Peeters, 2006, $n = 664$, low–high risk); cPFS (10 yrs, HR 0.57, 95%-CI 0.43–0.74) (Zietman, 2005, $n = 393$, low-intermediate risk) *RP:* mPFS (Time to first event, $p = 0.037$) (Paulson, 1982, $n = 90$, low-intermediate risk)
EBRT (low dose) + BT	*EBRT (low dose):* bPFS (Hoskin 2007, $n = 218$, low–high risk); mPFS (HR 0.42, 95%-CI 0.23–0.75, $p = 0.0024$; Median FUP 7.1 yrs: $p = 0.01$) (2 studies (Hoskin, 2007; Sathya, 2005), $n = 312$, low–high risk)	*EBRT (low dose):* bPFS ($n = 0$ after mean FUP 22.7 months, PSA after 17.5 months: 0.68 ng/ml vs. 0.88 ng/ml, $p = 0.44$) (Zapatero-Ortuno, 2010, $n = 30$, low-intermediate risk); OS ($n = 0$ after mean FUP 22.7 months; HR 1.36, 95%-CI 0.50–3.65, $p = 0.54$; 10 yrs, $p = 0.2$) (3 studies (Hoskin, 2007; Sathya, 2005; Zapatero-Ortuno, 2010), $n = 352$, low–high risk)	

(*continued on next page*)

Table 2 (*continued*)

Intervention	Relative effect		
	Effect greater than	No significant difference	Effect worse than
EBRT (low dose) + HT	*EBRT (low dose):* bPFS (10 yrs. $p = 0.003/p < 0.001$; 10 yrs, HR 1.74, 95%-CI 1.48–2.04, 1 yr, $p < 0.0001$; 10 yrs, $p < 0.01$), cPFS (10 yrs, $p = 0.002/p < 0.001$; 10 yrs, HR 1.45, 95%-CI 1.03–2.06, 2 yrs; $p < 0.01$; 10 yrs, distant metastases, $p = 0.006$) (4 studies (Denham, 2008; Jones, 2011; Laverdière, 1997; Pilepich, 1995), $n = 3357$, low–high risk); OS (10 yrs, HR 0.60, 95%-CI 0.45–0.80; 7.6 yrs. HR 1.8, 95%-CI 1.1–2.9; 10 yrs, HR 0.63, 95%-CI 0.48–0.83; 10 years, HR 1.17, 95%-CI 1.01–1.35) (4 studies (Bolla, 2002; D'Amico, 2004; Denham, 2008; Jones, 2011). $n = 3388$, low–high risk); DSS (10 yrs, HR 0.42, 95%-CI 0.33–0.55; 4.5 yrs, $p = 0.02$; 10 yrs, HR 0.49, 95%-CI 0.32–0.74; 10 yrs, HR 1.87, 95%-CI 1.27–2.74; 10 yr, $p = 0.01$; 15 yrs, $p = 0.008$) (5 studies (Bolla, 2002; D'Amico, 2004; Denham, 2008; Jones, 2011; Pilepich, 1995; Zagars, 1988). $n = 3922$, low–high risk)	*EBRT (low dose):* bPFS (2 yrs) (Laverdière, 1997, $n = 120$, low–high risk); OS (10 yrs, 8.7 vs. 7.3 yrs, $p = 0.12$; 15 yrs, no significant difference) (2 studies (Pilepich, 1995; Zagars, 1988), $n = 534$, low–high risk)	
EBRT (low–high dose)		*EBRT (low–high dose) ± HT:* bPFS (82.1 months, HR 0.71, 95%-CI 0.46–1.09) (Mok, 2012, $n = 243$, intermediate risk)	
EBRT (low–high dose) + HT		*EBRT (low–high dose):* bPFS (82.1 months, HR 0.71, 95%-CI 0.46–1.09) (Mok, 2012, $n = 243$, intermediate risk)	
EBRT (high dose)	*EBRT (low dose):* bPFS (Phoenix, HR 0.80, 95%-CI 0.64–0.97), mPFS (110 months, HR 0.79, 95%-CI 0.64–0.97; 6 yrs, 64% vs. 70%, $p = 0.03$) (Peeters, 2006, $n = 664$, low–high risk); cPFS (10 yrs, HR 0.57, 95%-CI 0.43–0.74) (Zietman, 2005, $n = 393$, low-intermediate risk)	*EBRT (low dose):* cPFS (clinical failure, HR 0.89, 95%-CI 0.69–1.15) (Peeters, 2006, $n = 664$, low–high risk); DSS (54 months, $p = 0.61$; 110 months, HR 0.96, 95%-CI 0.63–1.45) (2 studies (Beckendorf, 2004; Peeters, 2006), $n = 968$, low–high risk); bPFS (5 yrs, Phoenix, 23.5 vs. 32%; 10 yrs, Phoenix, $p = p = 0.001$) (2 studies (Beckendorf, 2004; Zietman, 2005), $n = 699$, low–high risk); OS (54 months, $p = 0.52$; 110 months, HR 0.99, 95%-CI 0.75–1.3; 8 yrs, no overall difference) (4 studies (Beckendorf, 2004; Peeters, 2006; Pollack, 2000; Zietman), $n = 1662$, low–high risk)	*EBRT (low dose, HFRT) [vs. EBRT (high dose, CFRT)]:* bPFS (79% vs. 87%, $p = 0.035$) (Arcangeli, 2010, $n = 114$, intermediate-high risk)
EBRT (unclear dose)		*RP:* bPFS (median time to failure: 55.5 vs. 56 months), cPFS (median time to local progression: 65 vs. 64 months), DSS (3/70 vs. 1/67) (Stasi 2006, $n = 137$, low–high risk)	
EBRT (unclear dose) + BT		*EBRT (unclear dose)* ± *BT* ± *HT:* bPFS (60 months, Phoenix, 83 vs. 90%, $p = 0.4$), cPFS (60 months, no significant difference for distal metastases and locoregional control) (García Blanco 2013, $n = 62$, intermediate-high risk)	

EBRT (unclear dose) + BT + HT		*EBRT (unclear dose)±BT:* bPFS (60 months, Phoenix, 83 vs. 90%, $p = 0.4$), cPFS (60 months, no significant difference for distal metastases and locoregional control) (García Blanco, 2013, $n = 62$, intermediate-high risk)	
RP	*EBRT (low dose):* mPFS (Time to first event, $p = 0.037$) (Paulson, 1982, $n = 90$, low-intermediate risk) *Watchful waiting:* DSS (6 yrs: HR 0.50, 95%-CI 0.27–0.91, $p = 0.02$) (Holmberg, 2002, $n = 695$, low-intermediate risk); cPFS (local progression, 15 yrs: RR 0.34, 95%-CI 0.26–0.45; distant metastases: HR 0.63, 95%-CI 0.41–0.96, $p = 0.03$; bone metastases, HR 0.40, 95%-CI 0.22–0.70, $p < 0.001$) (2 studies (Wilt, 2012; Holmberg, 2002), $n = 1426$, low–high risk)	*Brachytherapy:* bPFS (Giberti, 2009, $n = 174$, low-intermediate risk) (Giberti, 2009, Crook, 2011), $n = 208$, low-intermediate risk) *ERBT (unclear dose):* bPFS (median time to failure: 55.5 vs. 56 months), cPFS (median time to local progression: 65 vs. 64 months), DSS (3/70 vs. 1/67) (Stasi 2006, $n = 137$, low–high risk) *RP ± EBRT:* DSS (10 yr, 25/502 vs. 34/503) (Bolla, 2005, $n = 1005$, low–high risk); cPFS (10 yrs, metastasis-free survival, $p = 0.56$) (Wiegel ,2009, $n = 307$, intermediate-high risk) (2 studies (Bolla, 2005; Thompson, 2006)), $n = 532$, low–high risk); OS (HR 1.18, 95%-CI 0.91–1.53; 10 yrs, $p = 0.59$) (2 studies (Bolla, 2005; Wiegel, 2009), $n = 1312$, low–high risk) *Watchful waiting:* OS (10 yrs: HR 0.88, 95%-CI 0.71–1.08, $p = 0.22$; 6 yrs: $p = 0.31$) (3 studies (Madsen, 1988; Wilt, 2012; Holmberg, 2002), $n = 1568$, low–high risk)	*RP ± EBRT:* cPFS (Median FUP 12 yrs: HR 0.71, 95%-CI 0.54–0.94, $p = 0.016$), OS (Median follow-up 12 yrs: HR 0.72, 95%-CI 0.55–0.96, $p = 0.023$) (Thompson, 2006, $n = 425$, intermediate-high risk); mPFS (10 yrs; biochemical, chemical, death: HR 0.49 (95%-CI 0.41–0.59), $p = 0.001$; 5 yrs: HR 0.53, 95%-CI 0.37–0.79, $p = 0.015$) (2 studies (Bolla, 2005; Wiegel, 2009), $n = 1312$, low–high risk); bPFS (10 yr, 105/502 vs. 238/503; Median FUP 10.6 yrs: HR 0.62, 95%-CI 0.46–0.82, $p = 0.001$; 10 yr, $p < 0.01$) (3 studies (Bolla, 2005; Thompson, 2006; Wiegel, 2009), $n = 1737$, low–high risk)
RP + EBRT	*RP:* cPFS (Median FUP 12 yrs: HR 0.71, 95%-CI 0.54–0.94, $p = 0.016$), OS (Median follow-up 12 yrs: HR 0.72, 95%-CI 0.55–0.96, $p = 0.023$) (Thompson 2006, $n = 425$, intermediate-high risk); bPFS (10 yr, 105/502 vs. 238/503; Median FUP 10.6 yrs: HR 0.62, 95%-CI 0.46–0.82, $p = 0.001$) (2 studies (Bolla, 2005; Thompson, 2006), $n = 1430$, low–high risk); mPFS (10 yrs; biochemical, chemical, death: HR 0.49 (95%-CI 0.41–0.59), $p = 0.001$; 5 yrs: HR 0.53, 95%-CI 0.37–0.79, $p = 0.015$) (2 studies (Bolla, 2005; Wiegel, 2009), $n = 1312$, low–high risk)	*RP:* DSS (10 yr, 25/502 vs. 34/503) (Bolla 2005, $n = 1005$, low–high risk); OS (HR 1.18 (95%-CI 0.91–1.53), $p = p = 0.2024$) (2 studies (Bolla, 2005, Wiegel, 2009), $n = 1312$, low–high risk)	
Watchful waiting		*RP:* DSS (10 yrs, HR 0.63, 95%-CI 0.36–1.09, $p = 0.09$) (Wilt, 2012, $n = 731$, low–high risk); OS (10 yrs: HR 0.88, 95%-CI 0.71–1.08, $p = 0.22$; 6 yrs: $p = 0.31$) (3 studies (Madsen, 1988; Wilt, 2012; Holmberg, 2002), $n = 1568$, low–high risk)	*RP:* DSS (6 yrs: HR 0.50, 95%-CI 0.27–0.91, $p = 0.02$) (Holmberg, 2002, $n = 695$, low-intermediate risk); cPFS (local progression, 15 yrs: RR 0.34, 95%-CI 0.26–0.45; distant metastases: HR 0.63, 95%-CI 0.41–0.96, $p = 0.03$; bone metastases, HR 0.40, 95%-CI 0.22–0.70, $p < 0.001$) (2 studies (Wilt, 2012; Holmberg, 2002), $n = 1426$, low–high risk)

Reading advice: Outcome (follow-up, main finding) (number of studies, number of patients, D'Amico surrogate).

3DCR = Three-Dimensional Conformal Radiotherapy; bPFS = Biochemical progression-free survival; BT = Brachytherapy; CFRT = Conventionally fractionated radiotherapy; CI = Confidence interval; cPFS = Clinical progression-free survival; DSS = Disease-specific survival; EBRT = External Beam Radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; FUP = Follow-up; HDR = High-dose radiation; HFRT = Hypofractionated radiotherapy; HR = Hazard ratio; ml = Millilitre; mPFS = Mixed (biochemical and clinical) progression-free survival; ng = Nanogram; OS = Overall survival; RD = Risk difference; RP = Radical Prostatectomy; RR = Relative risk; wk = Weeks; yrs = Year(s).

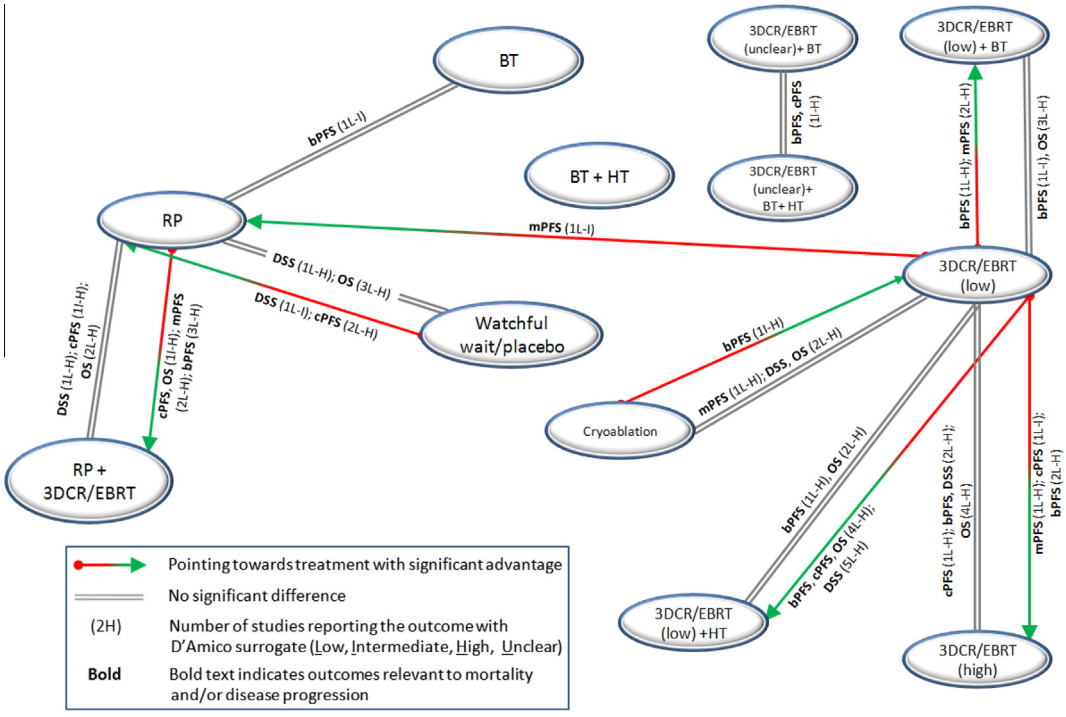

Fig. 2. Network diagram showing all survival-related relative effects. (Please note that a full version of this figure is available as an online Appendix.)

in Fig. 3. Based on six studies, the pooled estimate for comparison of EBRT (low dose) with EBRT (low dose) + HT was RR 1.21 (95%-CI 1.12–1.30) in favour of the combined treatment. Life expectancy for low to high risk patients does appear to improve when HT is added to low dose EBRT, however there is a suggestion that this improvement may be at the cost of a loss of sexual functioning (see information on D'Amico et al. [60] in Table 2).

Where 'head-to-head' trials (i.e. A versus B) were not identified, it was originally planned to perform indirect comparisons. The RRs (with 95%-CIs) for A versus B would have been estimated using 'indirect' methods [13]. However, clinical differences in patient populations prohibited indirect comparisons.

3.4. Findings of the review

Based on an extensive search of the current literature, 36 relevant studies were identified, allowing twelve different pair-wise comparisons.

Findings from direct comparisons suggest that EBRT, BT and RP are effective treatments for localised prostate cancer and that post-operative EBRT is also effective but might be associated with additional toxicity; see Fig. 2 and Table 2.

Evidence from two smaller trials ($n = 208$), comparing BT with RP in patients with low to intermediate risk cancer suggest similar biochemical disease-free survival when compared with RP, with favourable results for BT in terms of sexual functioning [14–19]. The effects on urinary function are unclear. While one study reports statistically significant greater and more short-term urinary problems, the other study suggests late changes (after 5 years) in urinary function in favour of BT. Use of BT in higher risk patients has not been evaluated in any of the included RCTs.

In the light of the specific techniques employed in trials, higher doses of EBRT result in favourable survival-related outcomes (overall and progression-free survival) but might be associated with more side effects (GI- and GU-toxicity), depending on technique. Combining EBRT (low dose) with hormone therapy showed statistically significant advantages in terms of overall survival (see Fig. 2 and Table 2).

4. Discussion

In this systematic review, we aimed to assess the efficacy and adverse events associated with radiotherapy (EBRT and/or BT) compared with other management options in patients with prostate cancer.

4.1. Comparison with other reviews

A number of recently published systematic reviews assessed comparators identified and discussed here. Most of these reviews did not identify any RCTs

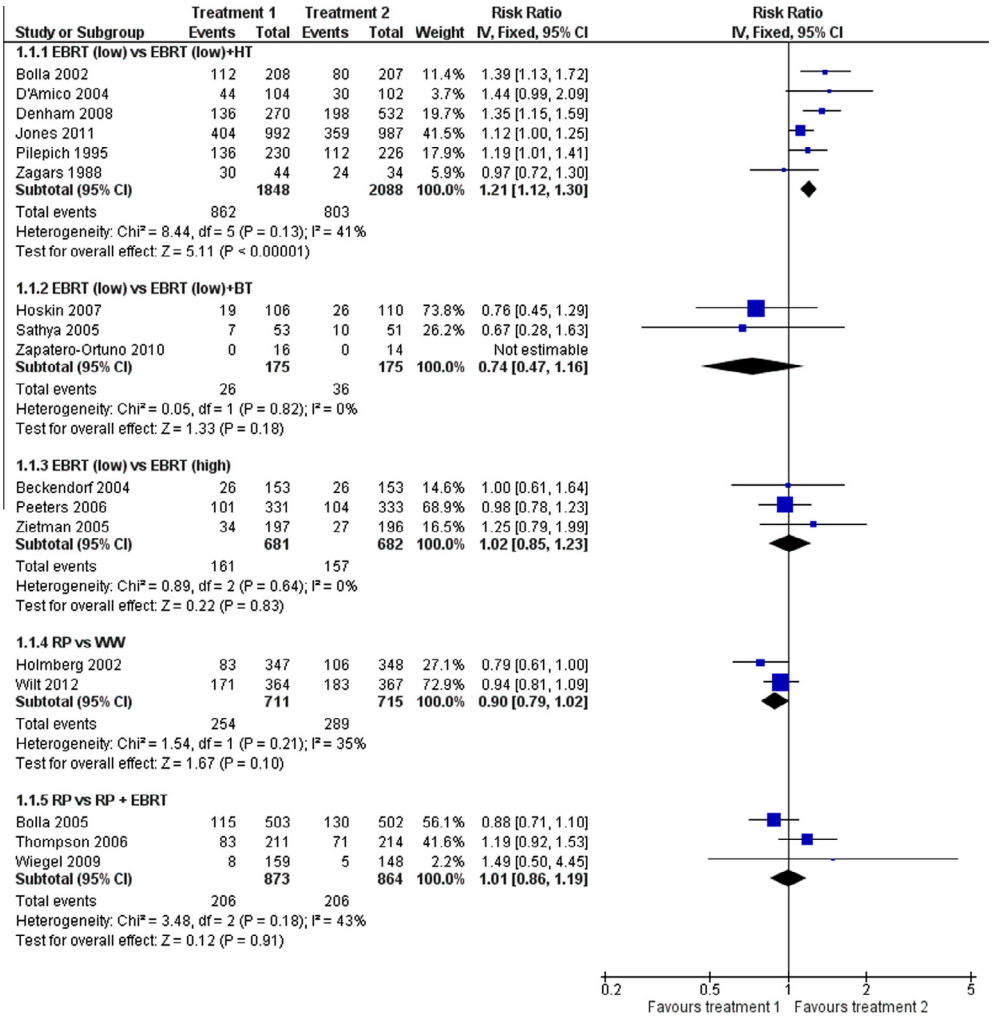

Fig. 3. Forest plots for the endpoint 'overall survival'.

relevant to the respective question which is in agreement with the findings of this report, e.g. Cordeiro 2012 (HIFU) [20] and Dahabreh 2012 (active surveillance) [21]. Stephenson et al. [22] aimed to "review the data concerning the pros and cons of immediate or adjuvant RT, or of an approach involving delayed or salvage RT once BCR [biochemical recurrence] occurs". They identified three RCTs also included in this review [131,136,138]. A systematic review on low-dose-rate brachytherapy for localised prostate cancer by Peinemann et al. [23] included one randomised controlled trial [19] also identified for this report.

Another systematic review included only non-randomised studies [24]. Based on 140 non-randomised studies which assessed 11 different treatment types, Grimm et al. concluded that "in terms of biochemical-free progression, brachytherapy provides superior outcome in patients with low-risk disease". This conclusion is broadly in line with the findings of our review of randomised controlled trials where the study by Giberti et al. [19] including 174 patients showed no significant difference of biochemical progression-free survival between BT and RP. However, the RCT showed a statistically significant advantage of brachytherapy regarding patient satisfaction and self-reported sexual functioning (see Fig. 2 and Table 2).

4.2. Strengths, limitations, uncertainties

The systematic review process followed published guidelines [9,10]. In order to try to identify all potentially relevant evidence relating to the review question as well as to reduce the risk of publication bias, an extensive range of resources was searched. In addition, reference lists of included studies were checked to identify further relevant studies. Published and unpublished trials (such as conference abstracts) irrespective of size or follow up period were eligible for inclusion. However, the size and duration of trials was considered when appraising the evidence.

Although this review sought wherever possible to reduce the risk of bias during the review processes and analyses, the findings may still be subject to certain limitations and uncertainties beyond our control. One such

factor would be the small size of trials which means that important effects, or non-effects cannot necessarily be detected because of underpowering.

The reliability of the findings might be further limited by methodological or reporting weaknesses of the included studies. Results of four studies were only reported in abstracts, which made it difficult to assess the risk of bias and hence comment on the reliability of the findings. Our inclusion criteria are designed to be comprehensive so that no study of potential value is missed. However, this inevitably means that some studies will be included which provide very little evidence of direct use but future researchers can be confident that nothing has been overlooked.

Matching of patients to treatment is facilitated by stratifying patients into risk groups. There is currently a debate as to how patients should be stratified according to risk factors [25]. In this systematic review, the D'Amico risk group classification was used [12] because it was most prevalent within the literature although we are aware that other systems have been used, e.g. the system of the National Comprehensive Cancer Network (NCCN) [26].

However, there was considerable variation in the way eligible populations were described and definitions of patient characteristics were sometimes imprecise, meaning that patients could only be described as having "low to high risk" disease.

We have sought to report on evidence which has already been reported. We are aware that many ongoing studies (e.g. the Prostate Testing for Cancer and Treatment (ProtecT) trial) offer potential to considerably increase the knowledge pool. Keeping abreast of emerging research is a challenge faced by all systematic reviews.

4.3. Implications and recommendations for further research

Further large, methodologically robust randomised controlled trials are needed. These need to be compliant with established reporting standards, use relevant outcome measures collected over long follow-up periods and report data in a form that can be extracted and incorporated into databases and meta-analyses.

It should be noted that such trials are logistically very difficult to complete due to funding issues and patient and physician preferences. However, this review identified ten ongoing studies which might be able to fill gaps in the current evidence base, thereby demonstrating that RCTs are actively being conducted in this area but it should be noted that this list might not be complete [27–40]. The ProtecT trial will help in this regard and should inform which of radiotherapy, radical prostatectomy and active surveillance should be used in daily clinical practice [40].

5. Conclusions

Evidence from this systematic review suggest that, when used appropriately, external beam radiotherapy, brachytherapy and radical prostatectomy can result in improved overall survival, progression-free survival as well as functioning (urinary/bowel/sexual) in localised disease. All treatments have their unique adverse events profiles.

Our ability to make firm recommendations for specific risk-stratified sub-groups or variants of main technologies is limited by the way these issues have been described in the literature. This review provides information as to how such issues might be addressed in future studies.

Further large, methodologically robust, randomised controlled trials are needed to report treatment-specific and treatment combination-specific outcomes in defined prostate cancer risk groups. These will provide the evidence base for the relatively newer therapies, e.g. HIFU, help reinforce current consensus guidelines, establish greater standardisation across practices and point the way towards research gaps.

Authors' contributions

JK developed the concept for the project. SD and Diana Hilmer formulated the search strategy and carried out searches. Study inclusion, quality assessment and data extraction were done by MB, SR and RFW. Statistical analyses were conducted by RFW and GW. In a series of meetings, ABo, ABri, JC, AH, JKa, LP, TdR and NS provided advice on clinical aspects related to study inclusion, quality assessment, data extraction, analyses and results interpretation. The manuscript was prepared by RFW, SR and JK. All authors read and approved the final manuscript.

Conflict of interest statement

Work on this systematic review was sponsored by Elekta. Elekta was given the opportunity to comment on the draft paper, but the authors had full editorial freedom.

Appendix 1. Search strategy for MEDLINE

Medline (OvidSP): 1946-2014/Feb week 4, searched 26/02/2014

(1) ((Prostate or prostatic) adj3 (carcinoma$ or cancer$ or neoplas$ or tumo?r$ or malignan$ or adenocarcinoma$ or adenoma$)).ti,ab,ot. (87042)
(2) Prostatic Neoplasms/(89475)
(3) or/1–2 (104337)
(4) randomised controlled trial.pt. (362550)

(5) controlled clinical trial.pt. (87486)
(6) randomised.ab. (262961)
(7) placebo.ab. (142353)
(8) clinical trials as topic.sh. (167729)
(9) randomly.ab. (187682)
(10) trial.ti. (112719)
(11) or/4–10 (834503)
(12) 3 and 11 (8161)
(13) exp animals/not humans.sh. (3880944)
(14) 12 not 13 (8077)
(15) (201303$ or 201304$ or 201305$ or 201306$ or 201307$ or 201308$ or 201309$ or 20131$ or 2014$).ed,dc. or (2013$ or 2014$).yr. (742841)
(16) **14 and 15 (590)***

Trials filter (best sensitivity and specificity) from:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomised controlled trials in Medline 2008 version; OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

*This search updated a previous search. Therefore the number of references does not match the number reported in the flow chart.

Appendix 2. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.07.019.

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