Comparative Efficacy and Safety of Treatments for Localized Prostate Cancer: An Application of Network Meta-Analysis.

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COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR LOCALIZED PROSTATE CANCER: AN APPLICATION OF NETWORK META-ANALYSIS

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ABSTRACT

Context: There is ongoing uncertainty about the optimal management of patients with localized prostate cancer.

Objective: To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Design: Systematic review with Bayesian network meta-analysis to estimate comparative odds ratios, and a score (0-100%) that, for a given outcome, reflects average rank order of superiority of each treatment compared against all others, using the surface under the cumulative ranking curve (SUCRA) statistic.

Data sources: Electronic searches of Medline without language restriction.

Study selection: Randomized trials comparing the efficacy and safety of different primary treatments (48 papers from 21 randomized trials included 7,350 men).

Data extraction: Two reviewers independently extracted data and assessed risk of bias.

Results: Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU). There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiotherapy (SUCRA: 99% and 77% for gastrointestinal and genitourinary toxicity, respectively).

Conclusions: The limited available evidence suggests that different treatments may be optimal for different efficacy and safety outcomes. These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes. More trial evidence is required to reduce uncertainty. Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

ARTICLE SUMMARY

Article focus

- To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Key messages

- Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU).
- There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Different treatments may be optimal for different efficacy and safety outcomes.
- Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

Strengths and limitations of this study

- The novel method of network meta-analysis enabled us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).
- This network meta-analysis only included randomised controlled trials and the risk of bias in each included study had been comprehensively assessed by using the Cochrane Collaboration's Risk of Bias tool, which strengthens the robustness of evidence synthesis.
- The number of available randomized controlled trials was small which could be a limitation of the study.

BACKGROUND

Prostate cancer is a worldwide major public health issue.[1] Nearly 75% of diagnosed cases, however, occur in developed countries,[2] where it is typically the most common cancer in men.[3-4] In the UK, about 40,000 men are diagnosed with prostate cancer and 10,000 men die from it every year.[3] In the US, there are 240,000 new diagnoses of prostate cancer, with 34,000 associated deaths every year.[5] Most patients with prostate cancers are diagnosed at an early stage,[6-7] and many diagnoses are made in asymptomatic men.[8-10]

The main treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy and observational management (that is, regular testing of clinical, biochemical or radiological markers or as prompted by occurrence of symptoms).[8] Because some of these treatments are associated with substantial risk of side effects, it is important to try to resolve the current uncertainty about the optimal treatment options.

Some randomized trials have compared the efficacy and safety of two or three treatments. For example, the SPCG-4 trial in Europe and the PIVOT study in the US compared radical prostatectomy with observational management.[11-12] The UK Prostate Testing for Cancer and Treatment (ProtecT) trial is evaluating treatment effectiveness of active monitoring, radical prostatectomy and external beam radiotherapy for clinically localized prostate cancer in men aged 50-69 years identified through population-based PSA testing.[13] The recruitment phase for the ProtecT trial, which began in 1999, has been completed, but outcomes will not be available until a minimum follow-up period has been accrued.

It is unlikely that any single trial will compare all available treatment options. We therefore performed a network meta-analysis based on a systematic review of completed randomized trials comparing different interventions for patients with localized prostate cancer. The network meta-analysis allowed us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).[14-16]

METHODS

Eligibility criteria

We sought completed randomized trials in men with localized prostate cancer that had compared two or more of the following interventions (as primary treatment, with or without the same adjuvant therapy in all arms): prostatectomy; radiotherapy including brachytherapy; cryotherapy; high-intensity focused ultrasound (HIFU) and observational management. Observational management is characterized by testing of clinical, biochemical or radiological markers of disease progression at regular intervals (typically every 6 months) or as prompted by the occurrence of new symptoms, possibly leading to either radical or palliative treatment. We opted to use the term 'observational management' in preference to active surveillance or active monitoring because the latter terms typically aim to keep men in a window of curability so that only those who require it undergo radical treatment.

Eligible trials had to have reported any of the following efficacy and safety outcomes: all-cause mortality, prostate cancer mortality and gastrointestinal or genitourinary toxicity. Studies comparing treatment combinations or sequences (e.g. per protocol management by surgery with subsequent radiotherapy) were excluded.

Identification of studies

We adopted the search strategy of a systematic review that supported the development of clinical guidelines on the diagnosis and treatment of prostate cancer by the UK's National Institute for Health and Clinical Excellence (NICE) in 2008.[8] Studies had been identified by searching Medline (in 2006) and scanning reference list of papers. We retrieved all relevant randomized trials identified in the NICE guideline and implemented the same search strategies to update the collection of trials. We restricted the search to the period from January 2005 to September 2012.

No language limits were placed on the searches (see Appendix 1 for full search strategies).

Data extraction

Two reviewers (TX and RT) independently screened all the titles and abstracts of the studies retrieved by the searches for potentially eligible trials, and then independently assessed the full articles of these trials to confirm whether they met the eligibility criteria. The results were checked and discussed by TX and RT to agree upon a final list of included studies. Using a structured and piloted data collection form, all relevant data in each included paper were extracted by two reviewers independently (TX and RT/YW). The data extracted were cross-checked and unresolved discrepancies were referred to a third reviewer; where necessary, problems were discussed in a panel meeting (TX, RT, YW, JH and GL) whilst DN acted as a clinical expert advisor.

For each included study, we extracted characteristics of participants and interventions, outcomes reported and collected, sample size (randomized and analysed) in each arm, numerical results, losses to follow-up and details of patients excluded from the analyses.[17] To inform the appropriateness of including studies in the meta-analysis and facilitate assessment of the strength of the evidence we assessed the risk of bias in each included study using The Cochrane Collaboration's Risk of Bias tool.[18] Two reviewers (TX and either RT or YW) completed this independently and agreed on final assessments. The tool assesses risk of bias arising from inadequacies in processes of generation of the random allocation sequence, concealment of the allocation sequence and blinding, and from incomplete outcome data and selective outcome reporting.

Outcomes

We analysed all-cause mortality and cancer-related mortality at 5 years, late gastrointestinal and late genitourinary toxicity at 3 years. The choice of these follow-up times was pragmatic, as they were the ones most frequently reported in the included trials. Once these time points had been chosen, we extracted the outcome data from the time nearest to these targeted measurement times. Late gastrointestinal and late genitourinary toxicity were defined as scores ≥ 2 measured by the Radiation Therapy Oncology Group (RTOG) questionnaire scale by 3 years follow-up.[19] We have not encompassed biochemical or clinical failure as operational definitions of either of those outcomes tend to be specific to different radical treatment modalities.[20]

Statistical analyses

Initially, we compared each pair of treatments using direct evidence alone, for each outcome. Separate meta-analyses were performed for each pair-wise comparison of interventions: a random-effects model was fitted within each comparison,[21] with a common between-study heterogeneity variance assumed across comparisons to allow for heterogeneity even when only a single study was available. Results are reported as odds ratios with 95% confidence intervals, for every comparison evaluated directly in one or more studies.

Next, we fitted a network meta-analysis model for each outcome separately,[22] combining direct evidence for each comparison (e.g. from studies comparing interventions A with B) with indirect evidence (e.g. from studies comparing A with C and studies comparing B with C), for all pair-wise comparisons simultaneously. The model accounts explicitly for the binary nature of each outcome using a binomial likelihood function; allows for heterogeneity of treatment effects between trials of the

same comparison (assuming the same amount of heterogeneity for each comparison, irrespective of how many trials address it); and enforces an underlying relationship between direct and indirect evidence for a particular comparison, assuming these are consistent between the two sources. For each 'loop' of treatment comparisons from three or more independent sources and for each outcome, we computed the difference between estimates from direct and indirect evidence. This provides a measure of inconsistency between the different sources. We did not implement more sophisticated methods for testing or adjusting for inconsistency, due to the small number of loops in the network.

Results are reported as odds ratios with 95% credible intervals, for all pair-wise comparisons of interventions. All analyses were performed within a Bayesian framework, using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[23] Informative prior distributions were used for the heterogeneity variance, from a published set of distributions for heterogeneity expected in meta-analyses examining particular intervention and outcome types,[24] since heterogeneity is imprecisely estimated when the number of studies is small. For all-cause mortality, a log-normal (-3.93, 1.51^2) distribution was used. For gastrointestinal and genitourinary toxicity, a log-normal (-2.01, 1.64^2) distribution was used. For cancer-related mortality, a log-normal (-2.89, 1.91^2) distribution was used. Vague N (0, 10^4) priors were used for all other model parameters. Results were based on 100,000 iterations, following a burn-in of 20,000 iterations.

For each outcome, we estimated the probability that each intervention is superior to all others, the second best, the third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain. These ranking probabilities were used to calculate a summary numerical value: the SUCRA (surface under the cumulative ranking curve).[25] SUCRA values are expressed as percentages; if an

intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%. If all interventions are equivalent, we would expect all SUCRA values to be near 50%. We also report the median ranks and 95% credible intervals for each intervention.

RESULTS

Included studies and interventions

The NICE systematic review[8] had identified 20 reports relating to 14 randomized trials.[26-45] Our updated searches retrieved 1,740 studies and identified 39 reports of relevant randomized trials, of which 30 had not been included in the NICE review (Figure 1).[46-75] One of these reports was the sole report of a trial providing data only on acute toxicity,[40] two papers only reported the outcomes of biochemical or clinical failure,[38, 56] these 3 studies were then excluded. In addition to the remaining 47 full papers from peer-reviewed journals, we identified and included in the analysis data from a conference abstract, describing a randomized trial comparing external beam radiotherapy versus watchful waiting,[76] and reporting data on long term mortality not previously reported in full-text related publications.[77-78]

Our searches also identified 16 relevant systematic reviews.[79-94] We scrutinized the reference lists of all these as well as any further systematic reviews identified by the NICE review, and found no further relevant randomized trials.

The 48 identified reports described 21 randomized trials comparing the effectiveness of different treatments for localized prostate cancer.[26-37, 39, 41-55, 57-76] Seventeen trials reported all-cause mortality, 16 trials reported cancer-related mortality, 16 trials reported gastrointestinal (GI) toxicity, 15 trials reported genitourinary (GU) toxicity. The characteristics of included studies are summarized in Appendix 2.

The risk of bias assessments for the included trials are illustrated in Figure 2. Most of the evidence was of moderate to good quality. About half of the studies did not report adequate information about allocation sequence generation and allocation sequence concealment. Unblinded designs were used in all trials included; we judged this

unlikely to cause bias for objectively-measured outcomes such as mortality, but generate bias in the reporting and assessment of patient-reported toxicity outcomes. The small number of studies precluded the investigation of potential reporting biases across studies (for example using funnel plots). Our searches were appropriate, but the possibility of publication bias cannot be excluded. It is unclear, however, whether reporting biases would tend to favour any particular treatment (see Appendix 3 for details of bias assessments for included trials).

We categorized the interventions into the following eight categories: observational management; prostatectomy; conventional radiotherapy; conventional radiotherapy-hypofractionated; conformal low dose (LD) radiotherapy; conformal high dose (HD) radiotherapy; conformal LD radiotherapy-hypofractionated; and cryotherapy. Twenty trials had two intervention arms. One trial compared three interventions;[54] since two of the three interventions were very similar and both met our definition of conformal LD radiotherapy-hypofractionated, we combined the data from these two arms and regarded the trial as a two-treatment comparison (conformal LD radiotherapy-hypofractionated versus conformal HD radiotherapy). None of the reviewed studied assessed brachytherapy and HIFU. Figure 3 illustrates the full network of comparisons. There were two closed loops of comparisons, one connecting prostatectomy, observational management and radiotherapy modalities; and the other connecting different radiotherapy modalities. No inconsistency was detected in our estimates of the difference between direct and indirect evidence; however, precision was very low. Cryotherapy only had a single link to the network.

All-cause mortality

All-cause mortality was reported in 17 trials, covering all the eight interventions of interest. There is no evidence of superiority of any treatment for all-cause mortality. For each pairwise comparison of interventions, the 95% intervals for odds ratios were wide and included 1. The lower-left triangle of results in Table 1 presents odds ratios estimated from direct evidence alone, while the upper-right triangle of results presents odds ratios estimated from the network meta-analysis. The intervals are slightly narrower when based on indirect as well as direct evidence rather than direct evidence alone. The SUCRA values presented in Table 2 summarize the ranking information for all interventions. With respect to all-cause mortality, the highest SUCRA values are 69% for conformal LD radiotehrapy-hypofractionated and 63% for conformal HD radiotherapy, indicating that these are most likely to be among the best treatments for this outcome. However, there is very high uncertainty in the rankings of the interventions, as indicated by wide 95% credible intervals.

Cancer-related mortality

Cancer-related mortality was reported in 16 trials, covering eight of the interventions. This was a rare outcome in most treatment groups, as expected for patients with localized prostate cancer with a 5 year end point. Odds ratio estimates had wide 95% credible intervals, particularly in comparisons for which only indirect evidence was available, and there was no evidence of superiority for any of the comparator treatments (Table 3). Based on direct comparisons alone, conformal HD radiotherapy was superior to conventional radiotherapy [odds ratio 0.21 (95% interval 0.03, 0.97)] and prostatectomy was superior to observational management [odds ratio 0.60 (95% interval 0.37, 0.98)].

Gastrointestinal and genitourinary toxicity

Late gastrointestinal toxicity was reported in 16 trials and late genitourinary toxicity was reported in 15 trials. There was evidence that cryotherapy resulted in fewer adverse gastrointestinal events than radiotherapy treatments (estimated odds ratios comparing cryotherapy against the five radiotherapy options ranged from 0.12 to 0.24, whilst all but one of the respective 95% credible intervals excluded 1). The SUCRA value of 99% for cryotherapy and the median rank of 1 (95% interval 1, 2) suggest that cryotherapy is almost certainly superior among the six treatments included in the network meta-analysis in relation to adverse gastrointestinal events (Table 2 and 4). There was also evidence that gastrointestinal toxicity was more likely with conformal HD radiotherapy than with conformal LD radiotherapy. Interpretation of such findings for toxicity should be more cautious than for the other outcomes, due to a concern that lack of blinding could have led to a risk of detection bias. For genitourinary toxicity, there was no evidence favouring one intervention over another (Table 5), although cryotherapy tended to receive better rankings than the five radiotherapy treatments (Table 2), and the odds ratio estimates favour cryotherapy, but the 95% intervals all included 1.

Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis

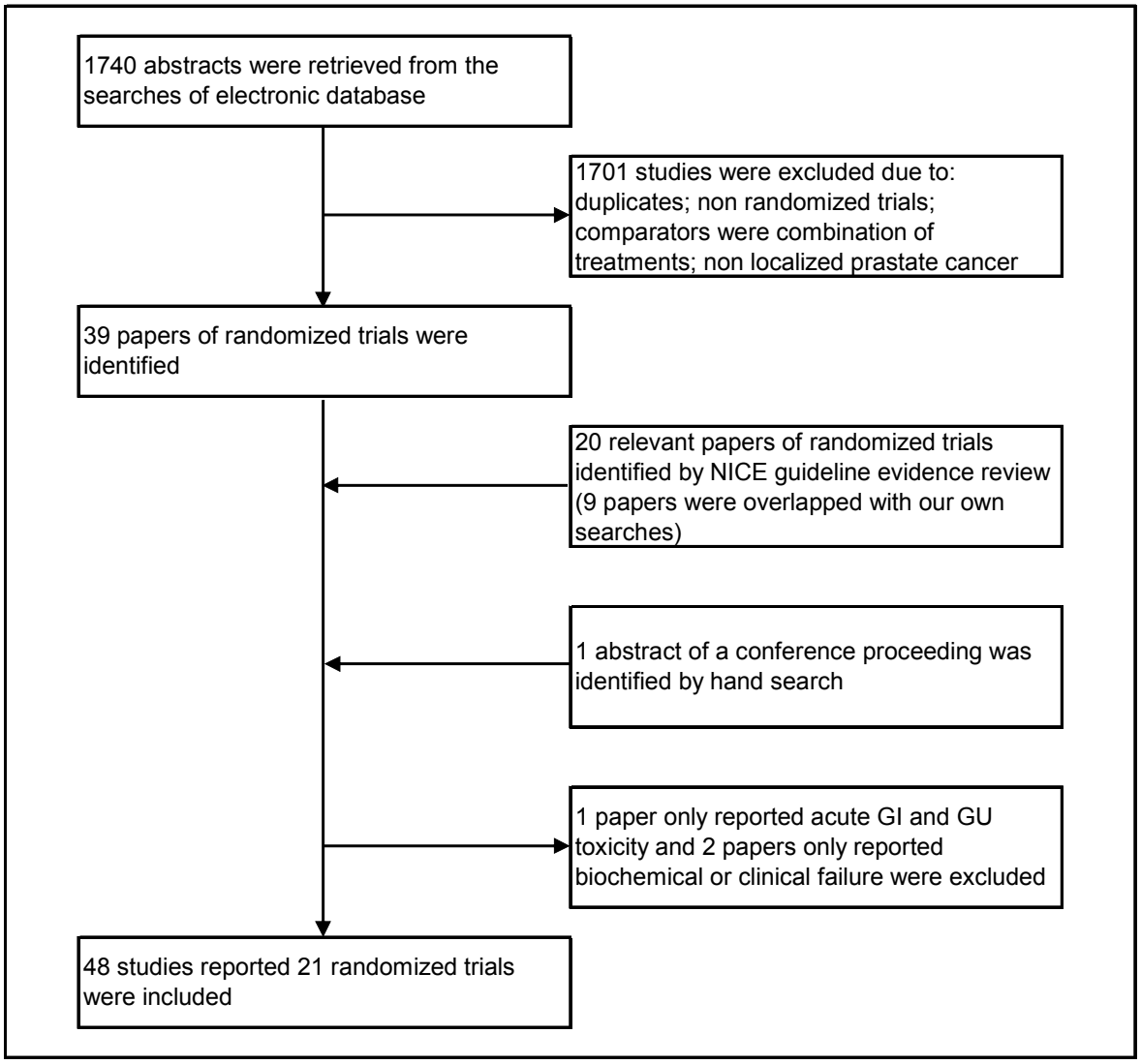


Figure 2. Risk of bias assessments for the included randomized trials

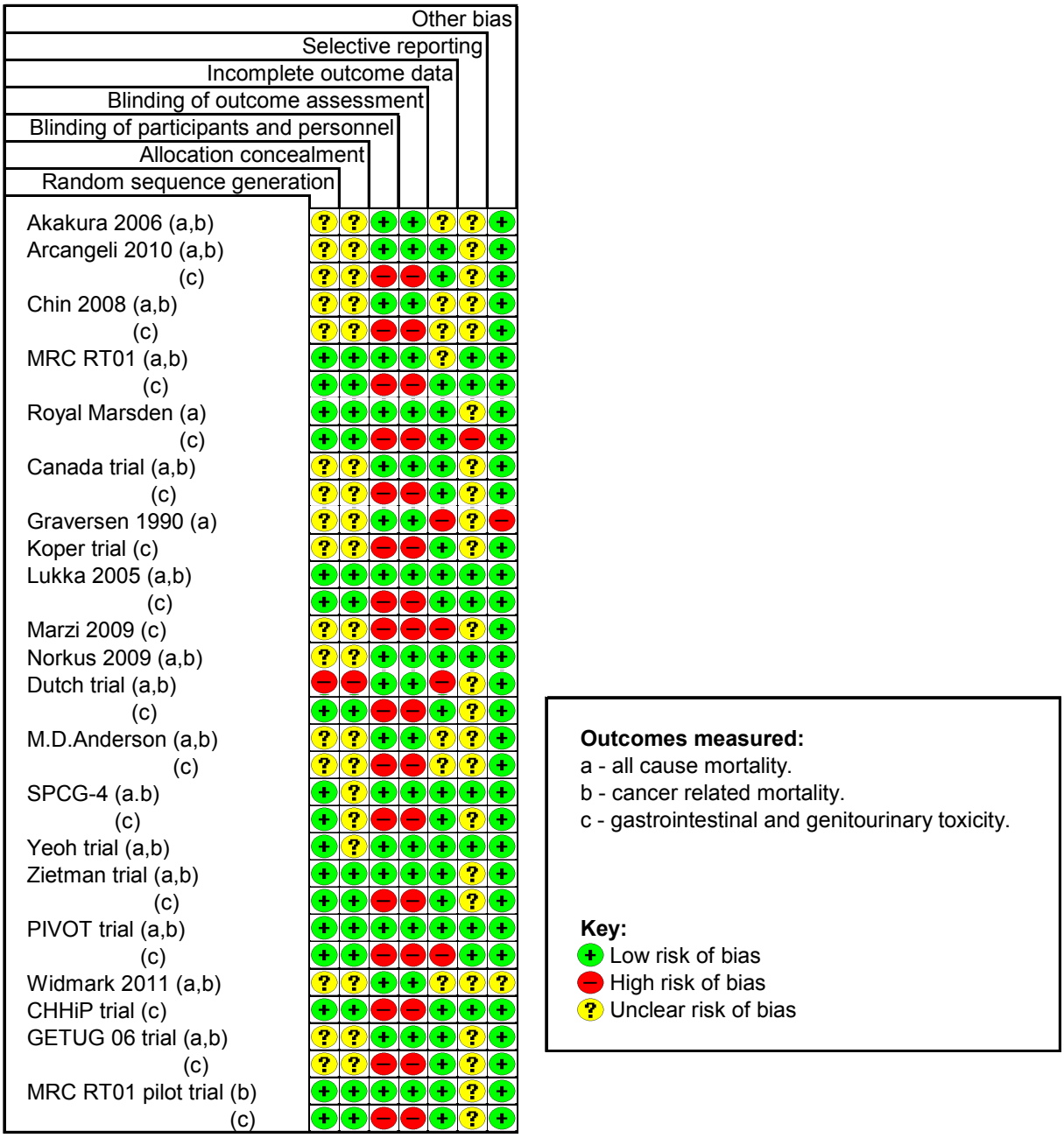
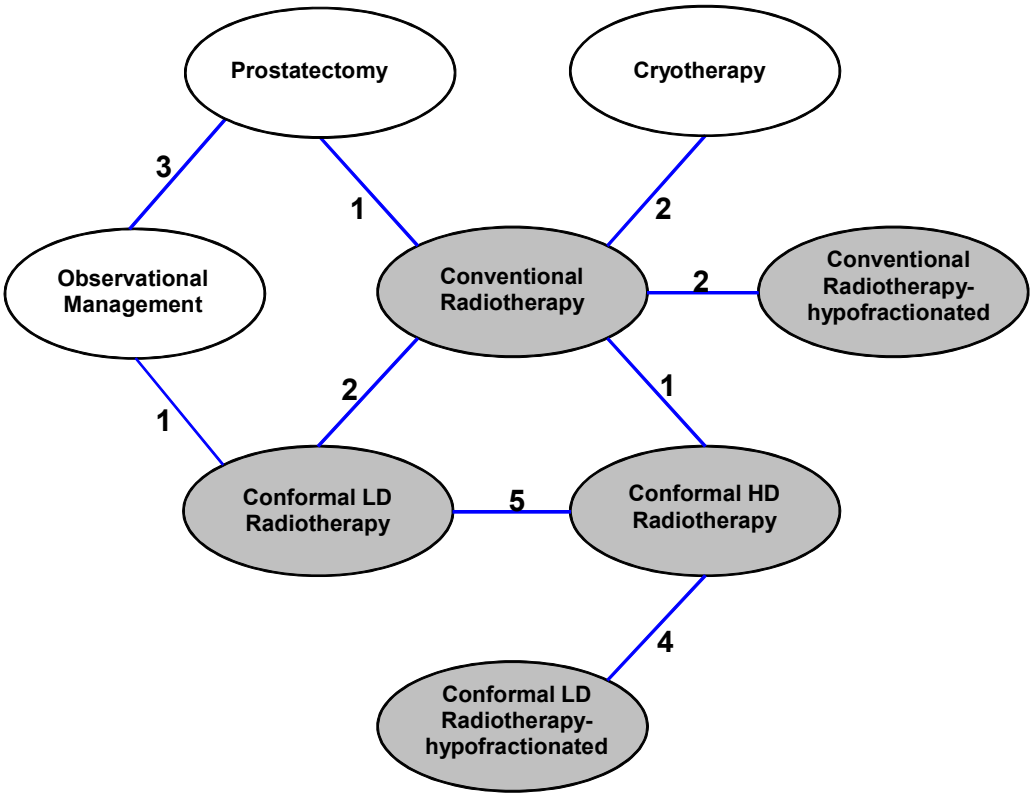


Figure 3. Network of comparisons of treatments for localized prostate cancer showing numbers of trials in which each pairwise comparison had been made



Abbreviations: LD: low dose; HD: high dose.
Grey-shaded ovals indicate external radiotherapy modalities.

Table 1. All-cause mortality: odds ratios (with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.79 (0.61,1.02)	0.84 (0.48,1.57)	0.72 (0.37,1.49)	0.73 (0.44,1.26)	0.70 (0.40,1.28)	0.53 (0.10,2.88)	0.76 (0.28,1.98)
Prostatectomy	[3] 0.80 (0.61,1.06)		1.06 (0.60,2.02)	0.91 (0.46,1.90)	0.92 (0.54,1.64)	0.88 (0.49,1.66)	0.67 (0.12,3.65)	0.96 (0.36,2.56)
Conventional radiotherapy	-	[1] 1.34 (0.55,3.24)		0.85 (0.59,1.24)	0.86 (0.55,1.35)	0.82 (0.51,1.35)	0.62 (0.11,3.21)	0.90 (0.41,1.89)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.85 (0.59,1.24)		1.01 (0.56,1.80)	0.97 (0.53,1.78)	0.73 (0.13,3.86)	1.05 (0.44,2.42)
Conformal LD radiotherapy	[1] 0.66 (0.35,1.21)	-	[1] 0.92 (0.50,1.72)	-		0.96 (0.72,1.29)	0.72 (0.14,3.51)	1.04 (0.42,2.49)
Conformal HD radiotherapy	-	-	[1] 0.87 (0.39,1.92)	-	[4] 0.95 (0.70,1.31)		0.74 (0.14,3.61)	1.09 (0.43,2.64)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.78 (0.13,4.25)		1.47 (0.22,9.40)
Cryotherapy	-	-	[2] 0.90 (0.41,2.02)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.08).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.07).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 2. Ranking of interventions with respect to all-cause and cancer-related mortality, adverse gastrointestinal and genitourinary events: SUCRA (Surface Under the Cumulative RAnking curve) values and median ranks (with 95% intervals).†

Intervention	All-cause mortality		Cancer-related mortality		Adverse gastrointestinal events		Adverse genitourinary events	
	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)
Observational management	18%	7 (2, 8)	30%	6 (3, 8)	-	-	-	-
Prostatectomy	49%	5 (1, 7)	64%	4 (1, 7)	-	-	-	-
Conventional radiotherapy	35%	6 (2, 8)	16%	7 (4, 8)	43%	4 (2, 6)	51%	3 (1, 6)
Conventional radiotherapy-hypofractionated	58%	4 (1, 8)	44%	5 (1, 8)	42%	4 (1, 6)	50%	3 (1, 6)
Conformal LD radiotherapy	57%	4 (1, 7)	61%	4 (2, 7)	67%	2 (2, 4)	66%	3 (1, 5)
Conformal HD radiotherapy	63%	3 (1, 7)	75%	2 (1, 6)	19%	5 (3, 6)	30%	5 (2, 6)
Conformal LD radiotherapy-hypofractionated	69%	1 (1, 8)	85%	1 (1, 8)	30%	5 (2, 6)	26%	5 (1, 6)
Cryotherapy	50%	4 (1, 8)	24%	7 (2, 8)	99%	1 (1, 2)	77%	1 (1, 6)

† The surface under the cumulative ranking curve (SUCRA) value is a numerical summary of the estimated probabilities that each treatment is the best, second best, third best (and so on) for that particular outcome. Higher values indicate higher rankings compared with other treatments. For example, for cryotherapy, the high SUCRA value of 99% and median rank of 1 for adverse gastrointestinal events shows that cryotherapy is expected to be superior with respect to this outcome.

LD: low dose; HD: high dose.

Table 3. Prostate cancer-caused mortality: odds ratios (with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.63 (0.40,1.02)	1.39 (0.49,4.16)	0.90 (0.24,3.42)	0.63 (0.29,1.31)	0.52 (0.22,1.19)	0.13 (0.00*,3.59)	1.37 (0.28,6.89)
Prostatectomy	[2] 0.60 (0.37,0.98)		2.20 (0.82,6.37)	1.42 (0.39,5.19)	0.99 (0.42,2.26)	0.83 (0.32,2.00)	0.20 (0.00*,6.07)	2.16 (0.46,10.9)
Conventional radiotherapy	-	[1] 1.65 (0.53,5.44)		0.64 (0.29,1.41)	0.45 (0.14,1.30)	0.38 (0.12,1.06)	0.09 (0.00*,3.08)	0.98 (0.28,3.35)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.65 (0.28,1.43)		0.70 (0.18,2.65)	0.59 (0.15,2.16)	0.14 (0.00*,5.08)	1.51 (0.36,6.54)
Conformal LD radiotherapy	[1] 0.70 (0.31,1.57)	-	-	-		0.84 (0.52,1.30)	0.20 (0.00*,5.73)	2.20 (0.44,11.4)
Conformal HD radiotherapy	-	-	[1] 0.21 (0.03,0.97)	-	[5] 0.86 (0.53,1.37)		0.25 (0.00*,6.79)	2.61 (0.53,14.1)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.22 (0.00*,6.85)		11.2 (0.24,5542)
Cryotherapy	-	-	[2] 0.96 (0.27,3.46)	-	-	-	-	

LD: low dose; HD: high dose.

* Odds ratio was less than 0.005.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.31).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.29).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 4. Adverse gastrointestinal events: odds ratios (with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 0.84 (0.33,1.88)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.01 (0.19,5.29)	0.72 (0.29,1.59)	1.42 (0.57,3.39)	1.26 (0.35,4.30)	0.17 (0.04,0.51)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.00 (0.22,4.56)		0.70 (0.11,4.37)	1.40 (0.21,9.02)	1.24 (0.15,9.76)	0.17 (0.02,1.19)
Conformal LD radiotherapy	-	-	[2] 0.46 (0.17,1.16)	-		1.98 (1.18,3.59)	1.77 (0.63,5.11)	0.24 (0.05,0.96)
Conformal HD radiotherapy	-	-	[1] 2.66 (0.85,8.62)	-	[5] 1.73 (1.07,2.97)		0.89 (0.36,2.15)	0.12 (0.02,0.48)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[3] 0.89 (0.39,1.96)		0.14 (0.02,0.70)
Cryotherapy	-	-	[2] 0.18 (0.05,0.50)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.14 (95% interval 0.01 to 0.97).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.24 (95% interval 0.02 to 1.23).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 5. Adverse genitourinary events: odds ratios (with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 2.27 (1.34,3.90)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.00 (0.34,2.90)	0.91 (0.54,1.51)	1.19 (0.69,2.11)	1.41 (0.49,4.07)	0.66 (0.22,2.00)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.01 (0.34,3.00)		0.90 (0.27,2.97)	1.19 (0.36,4.04)	1.41 (0.31,6.44)	0.66 (0.14,3.04)
Conformal LD radiotherapy	-	-	[2] 0.80 (0.43,1.51)	-		1.32 (0.97,1.86)	1.56 (0.61,4.09)	0.73 (0.21,2.52)
Conformal HD radiotherapy	-	-	[1] 1.53 (0.62,3.82)	-	[5] 1.28 (0.93,1.86)		1.18 (0.48,2.92)	0.55 (0.16,1.91)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 1.17 (0.48,2.91)		0.47 (0.10,2.15)
Cryotherapy	-	-	[2] 0.68 (0.22,2.03)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.003 to 0.29).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.002 to 0.26).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

DISCUSSION

Our study is mainly a methodological contribution to an area of modern medicine with sparse randomised controlled evidence. We highlight the potential for network meta-analysis to be used for evidence synthesis in this research area, particularly after the forthcoming advent of further randomised controlled trial data. The present state of the evidence is that considering data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.

Our analyses have several strengths. Using network meta-analysis, we were able to combine simultaneously all relevant evidence on treating patients with localized prostate cancer, even in the absence of direct comparative evidence for some treatment pairs, encompassing four efficacy and safety outcomes. Assumptions of consistency between direct and indirect evidence were tested; however, these tests had little power due to the relatively small number of trials available in most direct comparisons. Informative priors based on external evidence were used for heterogeneity variances, to increase precision for heterogeneity variances and improve estimation of treatment differences. To our knowledge, this is the first application of network meta-analysis incorporating data-based informative priors for heterogeneity. We had no data on the use of adjuvant hormonal therapy combined with radiotherapy.

Our findings have implications for research funding prioritisation and study design; and for clinical practice. The study identified particular ‘weak links’ in the network of comparative treatment options, which should be prioritized for future investment in randomized controlled trials. This is particularly applicable for studies comparing HIFU (which currently is bereft of any comparative evidence) and brachytherapy against all other treatment options, and also for trials examining the comparative efficacy and safety of prostatecotmy versus conformal

radiotherapy modalities. For clinicians, and for men diagnosed with prostate cancer, our findings highlight that the optimal treatment options may be different in respect of different outcomes: patients need to be given appropriate information about the uncertainty surrounding treatment choice currently, and be allowed to opt for 'trade-offs' between efficacy and safety outcomes as they judge appropriately.[95] It is also important to note that observational studies have consistently shown that radical prostatectomy has better cause-specific mortality outcomes compared with radiotherapy.[96-99]

In conclusion, clinically important information from high quality randomized trials is still needed to inform decision making regarding primary treatment options for men with localized prostate cancer. The upcoming results of the ProtecT study,[13] which is evaluating effectiveness of multiple therapies in men with PSA-detected localized prostate cancer, together with other treatment studies in progress, will hopefully contribute to the evidence base. It is however unlikely that evidential uncertainty about all relevant and important outcomes will be resolved by these trials, and an updated network meta-analysis incorporating new evidence may be useful to synthesize the new with the existing evidence. We demonstrate a high degree of uncertainty about treatment superiority in the management of localized prostate cancer. Clinicians and patients need to grapple with this uncertainty in the context of shared-decision making.

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Appendix 1. Full search strategy for Medline made on 12 Sep 2012

1	"watchful wait$".ti,ab	1408
2	(watch$ adj2 wait$).ti,ab	1795
3	"observation".ti,ab	201605
4	"watchful surveillance".ti,ab	3
5	"watchful monitoring".ti,ab	14
6	"active surveillance".ti,ab	2609
7	"active monitoring".ti,ab	177
8	"expectant manag$".ti,ab	1501
9	"expectant monitoring".ti,ab	18
10	"expectant surveillance".ti,ab	3
11	"deferred treatment$".ti,ab	174
12	"deferred therap$".ti,ab	53
13	"delayed treatment$".ti,ab	1752
14	"delayed therap$".ti,ab	264
15	"conservative monitoring".ti,ab	10
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	209461
17	exp PROSTATIC NEOPLASMS/	83203
18	PROSTATIC INTRAEPITHELIAL NEOPLASIA/	1124
19	pin.ti,ab	9241
20	((prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR intraepithelial$ OR adeno$))).ti,ab	85456
21	17 OR 18 OR 19 OR 20	109867
22	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	82900
23	RANDOMIZED CONTROLLED TRIAL/	336590
24	RANDOM ALLOCATION/	75700
25	DOUBLE BLIND METHOD/	116906
26	SINGLE BLIND METHOD/	16674
27	CLINICAL TRIAL/	473817
28	"clinical trial, phase i".pt	12527
29	"clinical trial, phase ii".pt	20003
30	"clinical trial, phase iii".pt	7335
31	"clinical trial, phase iv".pt	739
32	"controlled clinical trial".pt	85134
33	"randomized controlled trial".pt	336590
34	"multicenter study".pt	149366
35	"clinical trial".pt	473817
36	exp CLINICAL TRIALS AS TOPIC/	260613
37	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36	933873
38	(clinical ADJ trial$).ti,ab	185348
39	((singl$ OR doubl$ OR treb$ OR tripl$) AND (blind$3 OR mask$3)).ti,ab	129000
40	PLACEBOS/	31302
41	placebo$.ti,ab	144213
42	"randomly allocated".ti,ab	14778
43	(allocated adj2 random$).ti,ab	17183
44	38 OR 39 OR 40 OR 41 OR 42 OR 43	383691
45	37 OR 44	1064978
46	(case AND report).ti,ab	372325
47	LETTER/	776512

48	HISTORICAL ARTICLE/	286394
49	46 OR 47 OR 48	1422877
50	45 NOT 49	1033939
51	CRYOTHERAPY/	3337
52	CRYOSURGERY/	10459
53	HYPOTHERMIA, INDUCED/	15628
54	cryoablat$.ti,ab	1810
55	(cryo$ ADJ ablat$).ti,ab	351
56	cryotreatment$.ti,ab	65
57	cryotherap$.ti,ab	4776
58	cryotherm$.ti,ab	212
59	(cryo$ ADJ surgery).ti,ab	149
60	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	31372
61	((cryo$ OR hypotherm$ OR freez$) adj5 prostat$).ti,ab	709
62	60 AND 21	916
63	61 OR 62	1089
64	PROSTATECTOMY/	19443
65	prostatectom$.ti,ab	18653
66	resection.ti,ab	170070
67	64 OR 65 OR 66	192628
68	(radical OR complete$ OR total OR "en bloc").ti,ab	2057017
69	67 AND 68	69466
70	(LRP OR TLRP OR RALRP OR RAP OR RRP OR RPP OR EERP).ti,ab	7847
71	"heilbronn technique".ti,ab	8
72	70 OR 71	7853
73	69 OR 72	76420
74	exp RADIOTHERAPY/	125988
75	"radiation therap$".ti,ab	46061
76	"radiation treatment$".ti,ab	6068
77	radiotherap$.ti,ab	103759
78	exp RADIOTHERAPY PLANNING/	11242
79	irradiation.ti,ab	133551
80	RADIOTHERAPY, ADJUVANT/	15412
81	74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80	307483
82	META-ANALYSIS AS TOPIC/	12419
83	"meta analy$".ti,ab	45804
84	metaanaly$.ti,ab	1171
85	META-ANALYSIS/	36142
86	(systematic ADJ review$1).ti,ab	37644
87	(systematic ADJ overview$1).ti,ab	489
88	exp REVIEW LITERATURE AS TOPIC/	6486
89	82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88	93039
90	cochrane.ab	22743
91	embase.ab	20328
92	(psychlit OR psyclit).ab	865
93	(psychinfo OR psycinfo).ab	7698
94	(cinahl OR cinhal).ab	7537
95	"science citation index".ab	1633
96	bids.ab	331
97	cancerlit.ab	560
98	90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97	37065
99	"reference list$".ab	7905

100	bibliograph$.ab	10314
101	hand-search$.ab	3303
102	"relevant journals".ab	586
103	"manual search$".ab	1920
104	99 OR 100 OR 101 OR 102 OR 103	21486
105	"selection criteria".ab	16935
106	"data extraction".ab	8148
107	105 OR 106	23737
108	REVIEW/	1733836
109	107 AND 108	15770
110	COMMENT/	517077
111	LETTER/	776512
112	EDITORIAL/	317040
113	ANIMAL/	5040870
114	HUMAN/	12536636
115	113 NOT (113 AND 114)	3686418
116	110 OR 111 OR 112 OR 115	4846136
117	89 OR 98 OR 104 OR 109	118824
118	117 NOT 116	110572
119	ULTRASOUND, HIGH-INTENSITY FOCUSED, TRANSRECTAL/	306
120	((high intensity adj2 ultraso$)).ti,ab	2103
121	HIFU.ti,ab	1012
122	((high intensity focused ultrasound)).ti,ab	1381
123	"focal therapy".ti,ab	295
124	119 OR 120 OR 121 OR 122 OR 123	2619
125	21 AND 50 AND 124	**99**
126	16 AND 21 AND 50 AND 63 [Limit to: Publication Year 2005-Current]	**10**
127	16 AND 21 AND 50 AND 73 [Limit to: Publication Year 2005-Current]	**94**
128	16 AND 21 AND 50 AND 81 [Limit to: Publication Year 2005-Current]	**82**
129	50 AND 63 AND 81 [Limit to: Publication Year 2005-Current]	**27**
130	50 AND 63 AND 73 [Limit to: Publication Year 2005-Current]	**14**
131	21 AND 50 AND 73 AND 81 [Limit to: Publication Year 2005-Current]	**267**
132	(21 AND 50 AND 81) NOT (128 OR 131) [Limit to: Publication Year 2005-Current]	**947**
133	16 AND 21 AND 63 AND 118 [Limit to: Publication Year 2005-Current]	**5**
134	16 AND 21 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**25**
135	16 AND 21 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**27**
136	63 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**14**
137	63 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**12**
138	21 AND 73 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**56**
139	(21 AND 81 AND 118) NOT (135 OR 138) [Limit to: Publication Year 2005-Current]	**61**

Appendix 2. Characteristics of included studies

Comparison	Trial title	Author, year	Country	Population	No.of men	Interventions and Comparisons	Outcomes	Follow up
Observational management v Prostatectomy (3 trials)	Graversen 1990 (1 paper)	Graversen 1990	USA	Dates of enrolment to study: Between May 1967 and March 1975; Setting: Multi-centre (15 participating hospitals); Age: All age; Disease status: stage I or II (T0 – T2).	142	1. Watchful waiting (74 men) 2. Prostatectomy (68 men)	Overall survival.	15 years.
	PIVOT trial (1 paper)	Wilt 2012	USA	Dates of enrolment to study: Nov 1994 to Jan 2002; Setting: multicentre; Mean age: 67yr; Disease status: T1-T2NxM0.	731	1. Observation (367 men) 2. Prostatectomy (364 men)	All cause mortality; Cancer caused mortality; Bone metastases; Urinary incontinence; Bowel dysfunction; Erectile dysfunction.	10 years.
	Scandinavian Prostate Cancer Group Study No 4 (SPCG-4) (6 papers)	Bill-Axelson 2005, 2008, 2011; Johansson 2009, 2011 Steineck 2002;	Sweden, Finland, Iceland	Dates of enrolment to study: Oct 1989 to Feb 1999; Setting: Multi-centre (14 participating hospitals); Age: Mean age 64.7; Disease status: T0d, T1, T2.	695	1. Watchful waiting (348 men) 2. Prostatectomy (347 men)	Death due to prostate cancer; All-caused mortality; Distance metastasis; Local progression; overall distress from all bowel symptoms, overall distress from all urinary symptoms.	8.2 - 12.8 years.
Observational management v Conformal LD radiotherapy (1 trial)	Widmark 2011 (1 paper)	Widmark 2011	Sweden, Denmark and Norway	Dates of enrolment to study: Apr 1986 to Jan 1997; Setting: unknown; Age: up to 75; Disease status: T1b-T2, pN0, G1-G2, M0.	214	1. Watchful waiting (107 men) 2. 3D conformal radiotherapy, either 64 Gy in 32 fractions with 2cm margin, or 64-68 Gy with 1.5cm margin (107 men)	All-cause mortality, Prostate cancer mortality, Distant progression, Recurrence free survival, Clinical progression, Biochemical progression, Local progression.	20 years.

Prostatectomy v Conventional radiotherapy (2 trials)	Akakura 2006(1 paper)	Akakura 2006	Japan	Dates of enrolment to study: 1989 to 1993; Setting: Multi-centre; Age: Mean 68.1, SD 7.0 in surgery group; mean 68.7, SD 6.6 in radiation group; Disease status: T2b-3N0M0, no evidence of lymph node metastasis.	95	1. Prostatectomy (46 men).2. Conventional radiotherapy (49 men): Irradiation by linear accelerator with a 40-50 Gy beam to the whole pelvis followed by a 20 Gy boost to the prostatic area for 6-7 weeks fractionated five times per week. All men received an initial treatment with 8 weeks of neoadjuvant endocrine therapy.	Biochemical progression-free survival at 10 years; Clinical progression-free survival at 10 years; Cause-specific survival at 10 years; Overall survival at 10 years; Adverse effects.	Median follow-up was 102 months.
Cryotherapy v Conventional radiotherapy (2 trials)	Canada trial (3 papers)	Donnelly 2007, 2010; Robinson 2009	Canada	Dates of enrolment to study: Dec 1997 to Feb 2003; Setting: Tom Baker Cancer Center, Calgary, Canada; Age: Median 69.4, range 52.8-81.4 in CT group; median 68.6, range 53.2-78.6 in EBRT group; Disease status: T2 - T3.	244	1. Cryotherapy (122 men). 2. Conventional EBRT (122 men): dose of 68 Gy given in 2 Gy fractions daily, 5 days per week, later increased to 70 Gy and later 73.5 Gy.	Treatment Failure; 5 year overall survival; Biopsy rate at 36 months; Disease-specific survival at 5 years; Genitourinary and gastrointestinal adverse effects; Quality of life.	Median follow-up was 82 months.
	Chin 2008 (1 paper)	Chin 2008	Canada	Setting: London Health Sciences Centre, University of Western Ontario; Age: Median age 70 in each group; Disease status: T2 - T3.	64	1. Cryotherapy (33 men). 2. Conventional EBRT (31 men): 66 Gy in 33 fractions.	Biochemical disease-free survival at 4 years; Overall survival at 4 years; Disease specific survival at 4 years; Positive biopsy rate; Gastrointestinal toxicity; Genitourinary toxicity; Hormonal adverse effects.	Mean follow-up 37 months.

Conventional radiotherapy v Conventional radiotherapy-hypofractionated (2 trials)	Yeoh trial (4 papers)	Yeoh 2003, 2006, 2009, 2011	Australia	Dates of enrolment to study: July 1996 to Aug 2003; Setting: Department of Radiation Oncology and Gastroenterology, Royal Adelaide Hospital; Age: Median age 69 (44 ~ 82 yrs); Disease status: T1, T2, N0 M0.	217	1. Conventional EBRT: 64 Gy in 32 fractions within 6.5 weeks (109 men). 2. Hypofractionated EBRT: 55 Gy in 20 fractions within 4 weeks (108 men).	Gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival rate; biochemical ±clinical relapse; biochemical ±clinical relapse-free survival; cancer-related mortality.	5 years.
	Lukka 2005 (1 paper)	Lukka 2005	Canada	Dates of enrolment to study: March 1995 – December 1998; Setting: 8 Ontario regional cancer centres and 8 additional Canadian centres; Age: Mean 70.3, range 53-84 in group 1; mean 70.0, range 53-84 in group 2; Disease status: T1, T2.	936	1. Conventional EBRT (470 men): 66 Gy in 33 fractions over 45 days. 2. Hypofractionated EBRT (466 men): 52.5 Gy in 20 fractions over 28 days.	Composite of biochemical or clinical failure (BCF); local persistence of tumour on biopsy of the prostate at 2 years; overall survival; acute and late radiation-induced toxicity; prostate cancer-related mortality.	Median follow-up was 5.7 years.
Conventional radiotherapy v Conformal LD radiotherapy (2 trials)	Koper trial (2 papers)	Koper 1999, 2004	Nether-lands	Dates of enrolment to study: June 1994 to March 1996; Setting: Erasmus Medical Center/Daniel den Hoed Cancer Center; Mean age: group1: 70 (6.4); group 2: 69.5 (6.1); Disease status: T1-T4 N0M0.	266	1. Conventional radiotherapy (134 men); 2. Conformal radiotherapy (129 men). All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure.	Gastrointestinal (GI) and genitourinary (GU) toxicity.	2 years.
	Royal Marsden and Institute of Cancer Research study (2 papers)	Dearnaley 1999; Tait 1997	UK	Dates of enrolment to study: 1988 to 1995; Setting: Tertiary care, single centre; Median age (range): 69 (51-80) in group 1, 68 (50-83) in group 2; Disease status: T1-T4 N0M0.	225	1. Conventional radiotherapy (111 men): 60 to 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy (114 men): 60 to 64 Gy in 2 Gy fractions.	Overall survival; Biochemical progression free survival; Late GI toxicity; Late GU toxicity.	2 - 5 years.

Conformal LD radiotherapy v Conformal HD radiotherapy (5 trials)	Dutch trial (7 papers)	Al-Mamgani 2008, 2011; Heemsbergen 2007; Peeters 2005, 2006a,b; van der Wielen 2008	Netherlands	Dates of enrolment to study: between June 1997 and February 2003; Setting: multicenter; Age: mean 68.6 and 68.8, range 50.3-82.9 and 48.7-83.6; Disease status: T1-T4.	669	1. 3D conformal radiotherapy 68 Gy (331 men). 2. 3D conformal radiotherapy 78 Gy (333 men).	freedom from failure; biochemical progression free survival; clinical progression free survival; overall survival; late GI toxicity; late GU toxicity; prostete cancer related deaths.	2 - 7 years.
	MRC RT01 pilot trial (1 paper)	Dearnaley 2005	UK	Dates of enrolment to study: between Jul 1995 and Dec 1997; Setting: Royal Marsden NHS Trust and Institute of Cancer Research; Age: median 66 and 69; Disease status: T1b-T3b N0 M0.	127	1. Conformal radiotherapy, standard dose (64 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (63 men): 74 Gy in 2 Gy fractions.	Biochemical (PSA) failure; Local or metastatic failure; Hormone therapy restarted; acute GU toxicity; acute GI toxicity; late GU toxicity; late GI toxicity; prostate cancer caused deaths.	5 years.
	MRC RT01 (3 papers)	Dearnaley 2007a,b; Syndikus 2010.	UK	Dates of enrolment to study: Jan 1998 to Dec 2002; Setting: multi-centre; Age: median 67 (IQR 63-71); Disease status: T1b-T3a N0 M0.	843	1. Conformal radiotherapy, standard dose (421 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (422 men): 74 Gy in 2 Gy fractions.	Biochemical-progression-free survival; 5-year overall survival; Progression-free survival; Freedom from local progression; Freedom from salvage androgen suppression; Metastases-free survival; Bowel dysfunction; Urinary or bladder dysfunction; Sexual dysfunction; prostate cancer mortality.	5 years.
	GETUG 06 Tial (2 papers)	Beckendorf 2004, 2011	France	Dates of enrolment to study: Sep 1999 to Feb 2002; Setting: Multicentre; Age: mean 67; Disease status: T1b-T3a, N0M0.	306	1. Conformal radiotherapy, standard dose (153 men): 70 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (153 men): 80 Gy in 2 Gy fractions.	Biochemical relapse alone; PSA and clinical relapse; Free from relapse; All cause death; Cancer cause death; RTOG rectal and urinary toxicity grade 2 and worse.	61 months.
	Zietman trial (2 papers)	Zietman AL, 2005, 2010	USA	Dates of enrolment to study: between Jan 1996 and Dec 1999; Setting: 2 US academic institutions; Age: 67 (45~91) in 70.2 Gy arm, 66 (47~78) in 79.2 Gy arm; Disease status: T1-T2, N0, Nx.	393	1. External beam radiation 70.2 Gy (197 men); 2. External beam radiation 79.2 Gy (195 men).	Freedom from biochemical failure 5 yrs after treatment (measured by PSA level); Acute and late GU and GI morbidity, overall survival, prostate cancer-related mortality.	5.5 - 8.9 years.

Conformal HD radiotherapy v Conformal LD radiotherapy-hypofractionated (4 trials)	Arcangeli 2010 (2 papers)	Arcangeli 2010, 2011	Italy	Dates of enrolment to study: Jan 2003 to Dec 2007; Setting: single centre; Mean age: 75 years; Disease status: no evidence of distant metastases.	168	1. hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week): 83 men. 2. conventional fractionation radiotherapy (80 Gy/40 fractions/8 weeks): 85 men.	Acute and late GU and GI toxicity; biochemical failure; freedom from biochemical failure; distant metastasis rates; all cause mortality; cancer related mortality.	4 years.
	Marzi 2009 (1 paper)	Marzi 2009	Italy	Dates of enrolment to study: March 2003 to June 2008; Setting: single centre; Age: all; Disease status: T1-T4.	162	1. Conformal radiotherapy hypofractionated: 62 Gy in 20 fractions over 5 weeks (57 men); 2. Conformal radiotherapy: 80 Gy in 40 fractions over 8 weeks (57 men).	Late rectal toxicity.	Median followup was 30 months.
	Norkus 2009 (2 papers)	Norkus 2009 a,b	Lithuania	Dates of enrolment to study: 2004; Setting: single centre; Age: median 63 (range 53-75) in group 1, median 65 (range 50-78) in group 2; Disease status: T1-T3.	91	1. Hypofractionated external beam radiotherapy: 57 Gy given as 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy (47 men). 2. Conventionally fractionated external beam radiotherapy: 74 Gy given in 37 fractions of 2 Gy (44 men).	Biochemical (PSA) response; acute gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival; prostate cancer-related mortality.	3 - 12 months.
	CHHiP trial (1 paper)	Dearnaley 2012	UK	Dates of enrolment to study: Oct 2002 to Aug 2006; Setting: multicentre; Age: median 67 - 68 (range 44-82); Disease status: T1b – T3a N0M0.	457	1. Conventional fractionation: 74 Gy in 37 fractions at 2 Gy per fraction (153 men). 2. Hypofractionation: 60 Gy in 20 fractions at 3 Gy per fraction (153 men). 3. Hypofractionation: 57 Gy in 19 fractions at 3 Gy per fraction (151 men).	Acute bowel toxicity; Acute bladder toxicity; Late bowel toxicity; Late bladder toxicity; Sexual dysfunction.	50.5 months.
Conventional radiotherapy v Conformal HD radiotherapy (1 trial)	M. D. Anderson randomized dose-escalation trial (4 papers)	Kuban 2008, 2011; Pollack 2002; Storey 2000.	USA	Dates of enrolment to study: 1993 to 1998; Setting: M. D. Anderson Cancer Center, University of Texas; Median age 69 for each arm; Disease status: T1-T3 N0M0.	305	1. Conventional radiotherapy (150 men): 70 Gy, given in daily 2 Gy fractions. 2. 3D conformal radiotherapy (151 men): 78 Gy, given in daily 2 Gy fractions.	freedom from biochemical or clinical failure; freedom from distant metastasis; overall survival; disease-specific survival; late GI toxicity; late GU toxicity; prostate cancer-related mortality.	Median follow-up of 5 - 8 years.

LD: low dose; HD: high dose.

Appendix 3. Assessment of risk of bias for included randomized trials (please refer to www.cochrane-handbook.org for instructions on how to complete the tables).

Outcomes measured:
a - all cause mortality.
b - cancer related mortality.
c - gastrointestinal and genitourinary toxicity.

Study ID: CHHiP trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random permuted blocks were used
Allocation concealment	Low risk	Independent randomisation was via telephone to the ICR-CTSU.
Blinding of participants and personnel	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Blinding of outcome assessment	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Incomplete outcome data	Low risk	Losses to follow-up are disclosed
Selective reporting	Low risk	Pre-planned analyses.
Other bias	Low risk	No other sources of bias identified.

Study ID: PIVOT trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome	Low risk	After randomization, a central pathologist reviewed the biopsy and radical-prostatectomy specimens, and a

assessment		central laboratory measured PSA.
Incomplete outcome data	Low risk	Losses to follow-up described and were low
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Toxicity outcomes are patient-reported and therefore at high risk of bias.
Incomplete outcome data	High risk	Moderate losses to follow-up, 23% in each group.
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified

Study ID: GETUG 06 Tial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Study ID: Widmark 2011

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No details available.
Allocation concealment	Unclear	No details available.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Unclear	No details available.
Selective reporting	Unclear	No details available.
Other bias	Unclear	No details available.

Study ID: Yeoh trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Low risk	Blocked computer-generated random numbers (Yeoh EE 2003)
Allocation concealment	Unclear risk	Not clear
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Incomplete outcome data	Low risk	Report Kaplan Meier estimates, log-rank test results.
Selective reporting	Low risk	Pre-specified
Other bias	Low risk	Not identified

Study ID: Royal Marsden trial

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".
Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".

Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	High risk	Some cut-off values reporting.
Other bias	Low risk	No other sources of bias identified.

Study ID: Zietman trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	unclear	No clear
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and	High risk	Lack of blinding is likely to poses conceptual risks to

personnel		toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	Unclear	No clear
Other bias	Low	Not identified

Study ID: SPCG-4

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Stratification according to tumor grade and randomization center. The randomization list was computer generated, and the block size was unknown to the investigators
Allocation concealment	Unclear	Not stated
Blinding of participants and personnel	Low	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low	"Blinding to analyst". The pathologists were blinded to patient outcome and assignment. Only the results from the central review are used. Members of the endpoint committee were blinded to patients' group assignment and treatment received." Or, "Blinded evaluation (2005)".
Incomplete outcome data	Low	Losses of follow-up disclose
Selective reporting	Low	Outcomes pre-specified
Other bias	Low	Not other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	The randomization list was computer generated (Bill-Axelson,2002)
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	Outcome assessment was obtained by asking patients to return questionnaire after intervention, from which the blinding of assessor is impossible.

Incomplete outcome data	Low risk	88% and 87% of participants return questionnaires from prostatectomy and watchful waiting, respectively.
Selective reporting	Unclear risk	Study report doesn't make clear if this outcom were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Graversen1990

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	More elderly patients in placebo group
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	High risk	Outcome data incomplete.
Selective reporting	Unclear risk	Not stated
Other bias	High risk	31 stage I and 20 stage II patients were assigned to placebo; 31 stage I and 30 stage II patients were assigned to prostatectomy.

Study ID: Canada trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival, biopsy rate, disease-specific survival.
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival,

		biopsy rate, disease-specific survival.
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk (need further discussion)	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk (need further discussion)	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: MRC RT01

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Incomplete outcome data	Unclear risk	Losses to follow-up are disclosed and appear balanced across groups for other outcomes reported, but we can't adjust for losses to follow-up for overall survival since this outcome isn't formally reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol

Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Adjustment made for losses to follow-up in calculation of the hazard ratios and cumulative proportions reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol
Other bias	Low risk	No other sources of bias identified.

Study ID: Chin 2008

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		

	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.

Study ID: MRC RT01 pilot trial

Risk of bias table for outcome b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design
Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Blinding of outcome assessment	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design

Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified

Study ID: Akakura 2006

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No details given, but may be reported in the earlier design paper
Allocation concealment	Unclear risk	No details given, but may be reported in the earlier design paper
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: Arcangeli 2010

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information

Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risk to the toxicity assessment.
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified
Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information
Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Blinding of outcome assessment	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified

Study ID: Kopper trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low	Follow-up completed in (Kopper 2004)

Selective reporting	Unclear	Not clear which outcomes were pre-specified.
Other bias	Low	No other sources of bias identified

Study ID: Lukka 2005

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect measurement of overall survival.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.

Other bias	Low risk	No other sources of bias identified.

Study ID: Marzi 2009

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	High risk	Losses to follow-up are fairly high and no information is given about the patients lost to follow-up.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Norkus 2009

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	Methods not stated
Allocation concealment	Unclear	Methods not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Incomplete outcome data	Low risk	Low losses to follow-up
Selective reporting	Low risk	The two 2009 papers list the planned endpoints and report the early 12-month findings. It's unlikely that other pre-specified outcomes would be omitted at this stage of the trial.
Other bias	Low risk	No other bias identified

Study ID: Dutch trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	Low risk	Not clear but low risk for mortality
Blinding of outcome assessment	Low risk	Not clear but low risk for mortality
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for the rest outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: M. D. Anderson trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Cut-points may have been chosen based on significance.
Other bias	Low risk	No other sources of bias identified.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 – 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 – 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 – 7 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8 – 10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7 – 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9 – 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12 – 14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 – 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12 – 21
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Comparative Efficacy and Safety of Treatments for Localized Prostate Cancer: An Application of Network Meta-Analysis.

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COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR LOCALIZED PROSTATE CANCER: AN APPLICATION OF NETWORK META-ANALYSIS

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Word count: 2925

Key words: *Prostate cancer; Treatment; Randomised trials; Systematic review; Meta-analysis.*

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ABSTRACT

Context: There is ongoing uncertainty about the optimal management of patients with localized prostate cancer.

Objective: To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Design: Systematic review with Bayesian network meta-analysis to estimate comparative odds ratios, and a score (0-100%) that, for a given outcome, reflects average rank order of superiority of each treatment compared against all others, using the surface under the cumulative ranking curve (SUCRA) statistic.

Data sources: Electronic searches of Medline without language restriction.

Study selection: Randomized trials comparing the efficacy and safety of different primary treatments (48 papers from 21 randomized trials included 7,350 men).

Data extraction: Two reviewers independently extracted data and assessed risk of bias.

Results: Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU). There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality after 5 years. Cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiotherapy (SUCRA: 99% and 77% for gastrointestinal and genitourinary toxicity, respectively).

Conclusions: The limited available evidence suggests that different treatments may be optimal for different efficacy and safety outcomes. These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes. More trial evidence is required to reduce uncertainty. Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

ARTICLE SUMMARY

Article focus

- To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Key messages

- Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU).
- There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Different treatments may be optimal for different efficacy and safety outcomes.
- Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

Strengths and limitations of this study

- Network meta-analysis enabled us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).
- This network meta-analysis only included randomised controlled trials and the risk of bias in each included study had been comprehensively assessed by using the Cochrane Collaboration's Risk of Bias tool, which strengthens the robustness of evidence synthesis.
- The number of available randomized controlled trials was small which could be a limitation of the study.

BACKGROUND

Prostate cancer is a worldwide major public health issue.[1] Nearly 75% of diagnosed cases, however, occur in developed countries,[2] where it is typically the most common cancer in men.[3-4] In the UK, about 40,000 men are diagnosed with prostate cancer and 10,000 men die from it every year.[3] In the US, there are 240,000 new diagnoses of prostate cancer, with 34,000 associated deaths every year.[5] Most patients with prostate cancers are diagnosed at an early stage,[6-7] and many diagnoses are made in asymptomatic men.[8-10]

The main treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy and observational management (that is, regular testing of clinical, biochemical or radiological markers or as prompted by occurrence of symptoms).[8] Because some of these treatments are associated with substantial risk of side effects, it is important to try to resolve the current uncertainty about the optimal treatment options.

Some randomized trials have compared the efficacy and safety of two or three treatments. For example, the SPCG-4 trial in Europe and the PIVOT study in the US compared radical prostatectomy with observational management.[11-12] The UK Prostate Testing for Cancer and Treatment (ProtecT) trial is evaluating treatment effectiveness of active monitoring, radical prostatectomy and external beam radiotherapy for clinically localized prostate cancer in men aged 50-69 years identified through population-based PSA testing.[13] The recruitment phase for the ProtecT trial, which began in 1999, has been completed, but outcomes will not be available until a minimum follow-up period has been accrued.

It is unlikely that any single trial will compare all available treatment options. We therefore performed a network meta-analysis based on a systematic review of completed randomized trials comparing different interventions for patients with localized prostate cancer. The network meta-analysis allowed us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).[14-16] Our objective was to apply the established methodology used in network meta-analysis to an area of clinical practice where no such previous studies existed. In doing so, our aims were to summarise existing evidence; 'map out' current gaps in comparative evidence to help motivate the design and conduct of future comparative studies; and develop an approach 'primed' for subsequent updating and incorporation of future trial evidence.

METHODS

Eligibility criteria

We sought completed randomized trials in men with localized prostate cancer that had compared two or more of the following interventions (as primary treatment, with or without the same adjuvant therapy in all arms): prostatectomy; radiotherapy including brachytherapy; cryotherapy; high-intensity focused ultrasound (HIFU) and observational management. Observational management is characterized by testing of clinical, biochemical or radiological markers of disease progression at regular intervals (typically every 6 months) or as prompted by the occurrence of new symptoms, possibly leading to either radical or palliative treatment. We opted to use the term 'observational management' in preference to active surveillance or active monitoring because the latter terms typically aim to keep men in a window of curability so that only those who require it undergo radical treatment.

Eligible trials had to have reported any of the following efficacy and safety outcomes: all-cause mortality, prostate cancer mortality and gastrointestinal or genitourinary toxicity. Studies comparing treatment combinations or sequences (e.g. per protocol management by surgery with subsequent radiotherapy) were excluded.

Identification of studies

We adopted the search strategy of a systematic review that supported the development of clinical guidelines on the diagnosis and treatment of prostate cancer by the UK's National Institute for Health and Clinical Excellence (NICE) in 2008.[8] Studies had been identified by searching Medline (in 2006) and scanning reference list of papers. We retrieved all relevant randomized trials identified in the NICE guideline and implemented the same search strategies to update the collection of trials. We restricted the search to the period from January 2005 to September 2012.

No language limits were placed on the searches (see Appendix 1 for full search strategies).

Data extraction

Two reviewers (TX and RT) independently screened all the titles and abstracts of the studies retrieved by the searches for potentially eligible trials, and then independently assessed the full articles of these trials to confirm whether they met the eligibility criteria. The results were checked and discussed by TX and RT to agree upon a final list of included studies. Using a structured and piloted data collection form, all relevant data in each included paper were extracted by two reviewers independently (TX and RT/YW). The data extracted were cross-checked and unresolved discrepancies were referred to a third reviewer; where necessary, problems were discussed in a panel meeting (TX, RT, YW, JH and GL) whilst DN acted as a clinical expert advisor.

For each included study, we extracted characteristics of participants and interventions, outcomes reported and collected, sample size (randomized and analysed) in each arm, numerical results, losses to follow-up and details of patients excluded from the analyses.[17] To inform the appropriateness of including studies in the meta-analysis and facilitate assessment of the strength of the evidence we assessed the risk of bias in each included study using The Cochrane Collaboration's Risk of Bias tool.[18] Two reviewers (TX and either RT or YW) completed this independently and agreed on final assessments. The tool assesses risk of bias arising from inadequacies in processes of generation of the random allocation sequence, concealment of the allocation sequence and blinding, and from incomplete outcome data and selective outcome reporting.

Outcomes

We analysed all-cause mortality and cancer-related mortality at 5 years, late gastrointestinal and late genitourinary toxicity at 3 years. The choice of these follow-up times was pragmatic, as they were the ones most frequently reported in the included trials. Once these time points had been chosen, we extracted the outcome data from the time nearest to these targeted measurement times. Late gastrointestinal and late genitourinary toxicity were defined as scores ≥ 2 measured by the Radiation Therapy Oncology Group (RTOG) questionnaire scale by 3 years follow-up.[19] We have not encompassed biochemical or clinical failure as operational definitions of either of those outcomes tend to be specific to different radical treatment modalities.[20]

Statistical analyses

Initially, we compared each pair of treatments using direct evidence alone, for each outcome. Separate meta-analyses were performed for each pair-wise comparison of interventions: a random-effects model was fitted within each comparison,[21] with a common between-study heterogeneity variance assumed across comparisons to allow for heterogeneity even when only a single study was available. Results are reported as odds ratios with 95% confidence intervals, for every comparison evaluated directly in one or more studies.

Next, we fitted a network meta-analysis model for each outcome separately,[22] combining direct evidence for each comparison (e.g. from studies comparing interventions A with B) with indirect evidence (e.g. from studies comparing A with C and studies comparing B with C), for all pair-wise comparisons simultaneously. The model accounts explicitly for the binary nature of each outcome using a binomial likelihood function; allows for heterogeneity of treatment effects between trials of the

same comparison (assuming the same amount of heterogeneity for each comparison, irrespective of how many trials address it); and enforces an underlying relationship between direct and indirect evidence for a particular comparison, assuming these are consistent between the two sources. For each 'loop' of treatment comparisons from three or more independent sources and for each outcome, we computed the difference between estimates from direct and indirect evidence on the log odds ratio scale.[100] This provides a measure of inconsistency between the different sources. We did not implement more sophisticated methods for testing or adjusting for inconsistency, due to the small number of loops in the network.

Results are reported as odds ratios with 95% credible intervals, for all pair-wise comparisons of interventions. All analyses were performed within a Bayesian framework, using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[23] Informative prior distributions were used for the heterogeneity variance, from a published set of distributions for heterogeneity expected in meta-analyses examining particular intervention and outcome types,[24] since heterogeneity is imprecisely estimated when the number of studies is small. For all-cause mortality, a log-normal (-3.93, 1.51^2) distribution was used. For gastrointestinal and genitourinary toxicity, a log-normal (-2.01, 1.64^2) distribution was used. For cancer-related mortality, a log-normal (-2.89, 1.91^2) distribution was used. Vague N (0, 10^4) priors were used for all other model parameters. Results were based on 100,000 iterations, following a burn-in of 20,000 iterations.

For each outcome, we estimated the probability that each intervention is superior to all others, the second best, the third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain. These ranking probabilities were used to calculate a summary numerical value: the SUCRA (surface under the cumulative ranking curve).[25] SUCRA values are expressed as percentages; if an

intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%. If all interventions are equivalent, we would expect all SUCRA values to be near 50%. We also report the median ranks and 95% credible intervals for each intervention.

RESULTS

Included studies and interventions

The NICE systematic review[8] had identified 20 reports relating to 14 randomized trials.[26-45] Our updated searches retrieved 1,740 studies and identified 39 reports of relevant randomized trials, of which 30 had not been included in the NICE review (Figure 1).[46-75] One of these reports was the sole report of a trial providing data only on acute toxicity,[40] one paper reported only clinical failure,[38] and one paper reported biochemical failure, biochemical disease-free survival and quality of life;[56] these 3 studies were then excluded since they did not report the outcomes of interest to us. In addition to the remaining 47 full papers from peer-reviewed journals, we identified and included in the analysis data from a conference abstract, describing a randomized trial comparing external beam radiotherapy versus watchful waiting,[76] and reporting data on long term mortality not previously reported in full-text related publications.[77-78]

Our searches also identified 16 relevant systematic reviews.[79-94] We scrutinized the reference lists of all these as well as any further systematic reviews identified by the NICE review, and found no further relevant randomized trials.

The 48 identified reports described 21 randomized trials comparing the effectiveness of different treatments for localized prostate cancer.[26-37, 39, 41-55, 57-76] Seventeen trials reported all-cause mortality, 16 trials reported cancer-related mortality, 16 trials reported gastrointestinal (GI) toxicity, 15 trials reported genitourinary (GU) toxicity. The characteristics of included studies are summarized in Appendix 2.

The risk of bias assessments for the included trials are illustrated in Figure 2. Most of the evidence was of moderate to good quality. About half of the studies did not report

adequate information about allocation sequence generation and allocation sequence concealment. Unblinded designs were used in all trials included; we judged this unlikely to cause bias for objectively-measured outcomes such as mortality, but generate bias in the reporting and assessment of patient-reported toxicity outcomes. The small number of studies precluded the investigation of potential reporting biases across studies (for example using funnel plots). Our searches were appropriate, but the possibility of publication bias cannot be excluded. It is unclear, however, whether reporting biases would tend to favour any particular treatment (see Appendix 3 for details of bias assessments for included trials).

We categorized the interventions into the following eight categories: observational management; prostatectomy; conventional radiotherapy (refers to two dimensional external beam radiation therapy); conventional radiotherapy- hypofractionated (refers to less than 20 fractions); conformal low dose (LD) radiotherapy (refers to less than 68 Gy); conformal high dose (HD) radiotherapy (refers to more than 74 Gy); conformal LD radiotherapy-hypofractionated; and cryotherapy. Twenty trials had two intervention arms. One trial compared three interventions;[54] since two of the three interventions were very similar and both met our definition of conformal LD radiotherapy-hypofractionated, we combined the data from these two arms and regarded the trial as a two-treatment comparison (conformal LD radiotherapy-hypofractionated versus conformal HD radiotherapy). None of the reviewed studied assessed brachytherapy and HIFU. Figure 3 illustrates the full network of comparisons. There were two closed loops of comparisons, one connecting prostatectomy, observational management and radiotherapy modalities; and the other connecting different radiotherapy modalities.[100] No inconsistency was detected in our estimates of the difference between direct and indirect evidence; however, precision was very low. Cryotherapy only had a single link to the network.

All-cause mortality

All-cause mortality was reported in 17 trials, covering all the eight interventions of interest. There is no evidence of superiority of any treatment for all-cause mortality. For each pairwise comparison of interventions, the 95% intervals for odds ratios were wide and included 1. The lower-left triangle of results in Table 1 presents odds ratios estimated from direct evidence alone, while the upper-right triangle of results presents odds ratios estimated from the network meta-analysis. The intervals are slightly narrower when based on indirect as well as direct evidence rather than direct evidence alone. The SUCRA values presented in Table 2 summarize the ranking information for all interventions. With respect to all-cause mortality, the highest SUCRA values are 69% for conformal LD radiotehrapy-hypofractionated and 63% for conformal HD radiotherapy, indicating that these are most likely to be among the best treatments for this outcome. However, there is very high uncertainty in the rankings of the interventions, as indicated by wide 95% credible intervals.

Cancer-related mortality

Cancer-related mortality was reported in 16 trials, covering eight of the interventions. This was a rare outcome in most treatment groups, as expected for patients with localized prostate cancer with a 5 year end point. Odds ratio estimates had wide 95% credible intervals, particularly in comparisons for which only indirect evidence was available, and there was no evidence of superiority for any of the comparator treatments (Table 3). Based on direct comparisons alone, conformal HD radiotherapy was superior to conventional radiotherapy [odds ratio 0.21 (95% interval 0.03, 0.97)] and prostatectomy was superior to observational management [odds ratio 0.60 (95% interval 0.37, 0.98)].

Gastrointestinal and genitourinary toxicity

Late gastrointestinal toxicity was reported in 16 trials and late genitourinary toxicity was reported in 15 trials. There was evidence that cryotherapy resulted in fewer adverse gastrointestinal events than radiotherapy treatments (estimated odds ratios comparing cryotherapy against the five radiotherapy options ranged from 0.12 to 0.24, whilst all but one of the respective 95% credible intervals excluded 1). The SUCRA value of 99% for cryotherapy and the median rank of 1 (95% interval 1, 2) suggest that cryotherapy is almost certainly superior among the six treatments included in the network meta-analysis in relation to adverse gastrointestinal events (Table 2 and 4). There was also evidence that gastrointestinal toxicity was more likely with conformal HD radiotherapy than with conformal LD radiotherapy. Interpretation of such findings for toxicity should be more cautious than for the other outcomes, due to a concern that lack of blinding could have led to a risk of detection bias. For genitourinary toxicity, there was no evidence favouring one intervention over another (Table 5), although cryotherapy tended to receive better rankings than the five radiotherapy treatments (Table 2), and the odds ratio estimates favour cryotherapy, but the 95% intervals all included 1.

Table 1. All-cause mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.79 (0.61,1.02)	0.84 (0.48,1.57)	0.72 (0.37,1.49)	0.73 (0.44,1.26)	0.70 (0.40,1.28)	0.53 (0.10,2.88)	0.76 (0.28,1.98)
Prostatectomy	[3] 0.80 (0.61,1.06)		1.06 (0.60,2.02)	0.91 (0.46,1.90)	0.92 (0.54,1.64)	0.88 (0.49,1.66)	0.67 (0.12,3.65)	0.96 (0.36,2.56)
Conventional radiotherapy	-	[1] 1.34 (0.55,3.24)		0.85 (0.59,1.24)	0.86 (0.55,1.35)	0.82 (0.51,1.35)	0.62 (0.11,3.21)	0.90 (0.41,1.89)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.85 (0.59,1.24)		1.01 (0.56,1.80)	0.97 (0.53,1.78)	0.73 (0.13,3.86)	1.05 (0.44,2.42)
Conformal LD radiotherapy	[1] 0.66 (0.35,1.21)	-	[1] 0.92 (0.50,1.72)	-		0.96 (0.72,1.29)	0.72 (0.14,3.51)	1.04 (0.42,2.49)
Conformal HD radiotherapy	-	-	[1] 0.87 (0.39,1.92)	-	[4] 0.95 (0.70,1.31)		0.74 (0.14,3.61)	1.09 (0.43,2.64)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.78 (0.13,4.25)		1.47 (0.22,9.40)
Cryotherapy	-	-	[2] 0.90 (0.41,2.02)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.08).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.07).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 2. Ranking of interventions with respect to all-cause and cancer-related mortality, adverse gastrointestinal and genitourinary events: SUCRA (Surface Under the Cumulative RAnking curve) values and median ranks (with 95% intervals).†

Intervention	All-cause mortality		Cancer-related mortality		Adverse gastrointestinal events		Adverse genitourinary events	
	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)
Observational management	18%	7 (2, 8)	30%	6 (3, 8)	-	-	-	-
Prostatectomy	49%	5 (1, 7)	64%	4 (1, 7)	-	-	-	-
Conventional radiotherapy	35%	6 (2, 8)	16%	7 (4, 8)	43%	4 (2, 6)	51%	3 (1, 6)
Conventional radiotherapy-hypofractionated	58%	4 (1, 8)	44%	5 (1, 8)	42%	4 (1, 6)	50%	3 (1, 6)
Conformal LD radiotherapy	57%	4 (1, 7)	61%	4 (2, 7)	67%	2 (2, 4)	66%	3 (1, 5)
Conformal HD radiotherapy	63%	3 (1, 7)	75%	2 (1, 6)	19%	5 (3, 6)	30%	5 (2, 6)
Conformal LD radiotherapy-hypofractionated	69%	1 (1, 8)	85%	1 (1, 8)	30%	5 (2, 6)	26%	5 (1, 6)
Cryotherapy	50%	4 (1, 8)	24%	7 (2, 8)	99%	1 (1, 2)	77%	1 (1, 6)

† The surface under the cumulative ranking curve (SUCRA) value is a numerical summary of the estimated probabilities that each treatment is the best, second best, third best (and so on) for that particular outcome. Higher values indicate higher rankings compared with other treatments. For example, for cryotherapy, the high SUCRA value of 99% and median rank of 1 for adverse gastrointestinal events shows that cryotherapy is expected to be superior with respect to this outcome.

LD: low dose; HD: high dose.

Table 3. Prostate cancer-caused mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.63 (0.40,1.02)	1.39 (0.49,4.16)	0.90 (0.24,3.42)	0.63 (0.29,1.31)	0.52 (0.22,1.19)	0.13 (0.00*,3.59)	1.37 (0.28,6.89)
Prostatectomy	[2] 0.60 (0.37,0.98)		2.20 (0.82,6.37)	1.42 (0.39,5.19)	0.99 (0.42,2.26)	0.83 (0.32,2.00)	0.20 (0.00*,6.07)	2.16 (0.46,10.9)
Conventional radiotherapy	-	[1] 1.65 (0.53,5.44)		0.64 (0.29,1.41)	0.45 (0.14,1.30)	0.38 (0.12,1.06)	0.09 (0.00*,3.08)	0.98 (0.28,3.35)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.65 (0.28,1.43)		0.70 (0.18,2.65)	0.59 (0.15,2.16)	0.14 (0.00*,5.08)	1.51 (0.36,6.54)
Conformal LD radiotherapy	[1] 0.70 (0.31,1.57)	-	-	-		0.84 (0.52,1.30)	0.20 (0.00*,5.73)	2.20 (0.44,11.4)
Conformal HD radiotherapy	-	-	[1] 0.21 (0.03,0.97)	-	[5] 0.86 (0.53,1.37)		0.25 (0.00*,6.79)	2.61 (0.53,14.1)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.22 (0.00*,6.85)		11.2 (0.24,5542)
Cryotherapy	-	-	[2] 0.96 (0.27,3.46)	-	-	-	-	

LD: low dose; HD: high dose.

* Odds ratio was less than 0.005.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.31).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.29).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 4. Adverse gastrointestinal events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 0.84 (0.33,1.88)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.01 (0.19,5.29)	0.72 (0.29,1.59)	1.42 (0.57,3.39)	1.26 (0.35,4.30)	0.17 (0.04,0.51)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.00 (0.22,4.56)		0.70 (0.11,4.37)	1.40 (0.21,9.02)	1.24 (0.15,9.76)	0.17 (0.02,1.19)
Conformal LD radiotherapy	-	-	[2] 0.46 (0.17,1.16)	-		1.98 (1.18,3.59)	1.77 (0.63,5.11)	0.24 (0.05,0.96)
Conformal HD radiotherapy	-	-	[1] 2.66 (0.85,8.62)	-	[5] 1.73 (1.07,2.97)		0.89 (0.36,2.15)	0.12 (0.02,0.48)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[3] 0.89 (0.39,1.96)		0.14 (0.02,0.70)
Cryotherapy	-	-	[2] 0.18 (0.05,0.50)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.14 (95% interval 0.01 to 0.97).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.24 (95% interval 0.02 to 1.23).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 5. Adverse genitourinary events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 2.27 (1.34,3.90)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.00 (0.34,2.90)	0.91 (0.54,1.51)	1.19 (0.69,2.11)	1.41 (0.49,4.07)	0.66 (0.22,2.00)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.01 (0.34,3.00)		0.90 (0.27,2.97)	1.19 (0.36,4.04)	1.41 (0.31,6.44)	0.66 (0.14,3.04)
Conformal LD radiotherapy	-	-	[2] 0.80 (0.43,1.51)	-		1.32 (0.97,1.86)	1.56 (0.61,4.09)	0.73 (0.21,2.52)
Conformal HD radiotherapy	-	-	[1] 1.53 (0.62,3.82)	-	[5] 1.28 (0.93,1.86)		1.18 (0.48,2.92)	0.55 (0.16,1.91)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 1.17 (0.48,2.91)		0.47 (0.10,2.15)
Cryotherapy	-	-	[2] 0.68 (0.22,2.03)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.003 to 0.29).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.002 to 0.26).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

DISCUSSION

Using network meta-analysis, we were able to combine simultaneously all relevant evidence on treating patients with localized prostate cancer, even in the absence of direct comparative evidence for some treatment pairs, encompassing four efficacy and safety outcomes. Based on data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes for localized prostate cancer, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.

Assumptions of consistency between direct and indirect evidence were tested to justify the joint synthesis of all studies; however, these tests had little power due to the relatively small number of trials available in most direct comparisons. Instead we must rely on judgements about the similarity of studies included in the analysis in aspects such as patient groups, outcome measures and study methodology. Although we defined the population of interest as patients with localized prostate cancer, there was heterogeneity between individual study populations in terms of the severity of disease. Some of the trials were conducted several decades ago, when surgery and radiology techniques may have been different, and we observed that stage migration has occurred in men diagnosed with prostate cancer, due to emerging bio-marker and image technologies. Furthermore, some of the trials used adjuvant therapy, although this was applied in all the arms within the trial.

Two further limitations warrant mention. Literature searches were completed in September of 2012. However, the results of one of the most important randomized trials – ProtecT study[13] – has not been published so far, and to our knowledge there are no other new relevant RCTs have been reported after this systematic review. Our choices of measurements may have favoured some treatments over others: for example the RTOG scale had been used to define the late gastrointestinal and late genitourinary toxicity in the included studies, but it

does not measure incontinence which could be the most common adverse event post-prostatectomy.[102]

Methodologically, we used informative prior distributions based on external evidence for heterogeneity variances, to increase precision in their estimation and improve estimation of treatment differences. Data-based informative priors have previously been considered by Lu & Ades,[101] who used them for the between-study correlation structure. To our knowledge, our paper is the first application of network meta-analysis incorporating data-based informative priors for between-study heterogeneity.

Our findings have implications for research funding prioritisation and study design; and for clinical practice. The study identified particular 'weak links' in the network of comparative treatment options, which might be prioritized for future investment in randomized controlled trials. This is particularly the case for studies comparing HIFU (which currently is bereft of any comparative evidence) or brachytherapy against other treatment options, and also for trials examining the comparative efficacy and safety of prostatecotmy versus conformal radiotherapy modalities. For clinicians, and for men diagnosed with prostate cancer, our findings highlight that the optimal treatment options may be different in respect of different outcomes: patients need to be given appropriate information about the uncertainty surrounding treatment choice currently, and be allowed to opt for 'trade-offs' between efficacy and safety outcomes as they judge appropriately.[95] Observational studies have consistently shown that radical prostatectomy has better cause-specific mortality outcomes compared with radiotherapy.[96-99,103]

In conclusion, clinically important information from high quality randomized trials is still needed to inform decision making regarding primary treatment options for men with localized prostate cancer. The findings of this study highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs

between multiple outcomes. The upcoming results of the ProtecT study,[13] which is evaluating effectiveness of multiple therapies in men with PSA-detected localized prostate cancer, together with other treatment studies in progress, will hopefully contribute to the evidence base. It is however unlikely that evidential uncertainty about all relevant and important outcomes will be resolved by these trials, and an updated network meta-analysis incorporating new evidence may be useful to synthesize the new with the existing evidence. We demonstrate a high degree of uncertainty about treatment superiority in the management of localized prostate cancer. Clinicians and patients need to grapple with this uncertainty in the context of shared-decision making.

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Figure Legends

Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis

Figure 2. Risk of bias assessments for the included randomized trials

Figure 3. Network of comparisons of treatments for localized prostate cancer showing numbers of trials in which each pairwise comparison had been made

COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR LOCALIZED PROSTATE CANCER: AN APPLICATION OF NETWORK META-ANALYSIS

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ABSTRACT

Context: There is ongoing uncertainty about the optimal management of patients with localized prostate cancer.

Objective: To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Design: Systematic review with Bayesian network meta-analysis to estimate comparative odds ratios, and a score (0-100%) that, for a given outcome, reflects average rank order of superiority of each treatment compared against all others, using the surface under the cumulative ranking curve (SUCRA) statistic.

Data sources: Electronic searches of Medline without language restriction.

Study selection: Randomized trials comparing the efficacy and safety of different primary treatments (48 papers from 21 randomized trials included 7,350 men).

Data extraction: Two reviewers independently extracted data and assessed risk of bias.

Results: Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU). There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality after 5 years. Cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiotherapy (SUCRA: 99% and 77% for gastrointestinal and genitourinary toxicity, respectively).

Conclusions: The limited available evidence suggests that different treatments may be optimal for different efficacy and safety outcomes. These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes. More trial evidence is required to reduce uncertainty. Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

ARTICLE SUMMARY

Article focus

- To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Key messages

- Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU).
- There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Different treatments may be optimal for different efficacy and safety outcomes.
- Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

Strengths and limitations of this study

- Network meta-analysis enabled us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).
- This network meta-analysis only included randomised controlled trials and the risk of bias in each included study had been comprehensively assessed by using the Cochrane Collaboration's Risk of Bias tool, which strengthens the robustness of evidence synthesis.
- The number of available randomized controlled trials was small which could be a limitation of the study.

BACKGROUND

Prostate cancer is a worldwide major public health issue.[1] Nearly 75% of diagnosed cases, however, occur in developed countries,[2] where it is typically the most common cancer in men.[3-4] In the UK, about 40,000 men are diagnosed with prostate cancer and 10,000 men die from it every year.[3] In the US, there are 240,000 new diagnoses of prostate cancer, with 34,000 associated deaths every year.[5] Most patients with prostate cancers are diagnosed at an early stage,[6-7] and many diagnoses are made in asymptomatic men.[8-10]

The main treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy and observational management (that is, regular testing of clinical, biochemical or radiological markers or as prompted by occurrence of symptoms).[8] Because some of these treatments are associated with substantial risk of side effects, it is important to try to resolve the current uncertainty about the optimal treatment options.

Some randomized trials have compared the efficacy and safety of two or three treatments. For example, the SPCG-4 trial in Europe and the PIVOT study in the US compared radical prostatectomy with observational management.[11-12] The UK Prostate Testing for Cancer and Treatment (ProtecT) trial is evaluating treatment effectiveness of active monitoring, radical prostatectomy and external beam radiotherapy for clinically localized prostate cancer in men aged 50-69 years identified through population-based PSA testing.[13] The recruitment phase for the ProtecT trial, which began in 1999, has been completed, but outcomes will not be available until a minimum follow-up period has been accrued.

It is unlikely that any single trial will compare all available treatment options. We therefore performed a network meta-analysis based on a systematic review of completed randomized trials comparing different interventions for patients with localized prostate cancer. The network meta-analysis allowed us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).[14-16] Our objective was to apply the established methodology used in network meta-analysis to an area of clinical practice where no such previous studies existed. In doing so, our aims were to summarise existing evidence; 'map out' current gaps in comparative evidence to help motivate the design and conduct of future comparative studies; and develop an approach 'primed' for subsequent updating and incorporation of future trial evidence.

METHODS

Eligibility criteria

We sought completed randomized trials in men with localized prostate cancer that had compared two or more of the following interventions (as primary treatment, with or without the same adjuvant therapy in all arms): prostatectomy; radiotherapy including brachytherapy; cryotherapy; high-intensity focused ultrasound (HIFU) and observational management. Observational management is characterized by testing of clinical, biochemical or radiological markers of disease progression at regular intervals (typically every 6 months) or as prompted by the occurrence of new symptoms, possibly leading to either radical or palliative treatment. We opted to use the term 'observational management' in preference to active surveillance or active monitoring because the latter terms typically aim to keep men in a window of curability so that only those who require it undergo radical treatment.

Eligible trials had to have reported any of the following efficacy and safety outcomes: all-cause mortality, prostate cancer mortality and gastrointestinal or genitourinary toxicity. Studies comparing treatment combinations or sequences (e.g. per protocol management by surgery with subsequent radiotherapy) were excluded.

Identification of studies

We adopted the search strategy of a systematic review that supported the development of clinical guidelines on the diagnosis and treatment of prostate cancer by the UK's National Institute for Health and Clinical Excellence (NICE) in 2008.[8] Studies had been identified by searching Medline (in 2006) and scanning reference list of papers. We retrieved all relevant randomized trials identified in the NICE guideline and implemented the same search strategies to update the collection of trials. We restricted the search to the period from January 2005 to September 2012.

No language limits were placed on the searches (see Appendix 1 for full search strategies).

Data extraction

Two reviewers (TX and RT) independently screened all the titles and abstracts of the studies retrieved by the searches for potentially eligible trials, and then independently assessed the full articles of these trials to confirm whether they met the eligibility criteria. The results were checked and discussed by TX and RT to agree upon a final list of included studies. Using a structured and piloted data collection form, all relevant data in each included paper were extracted by two reviewers independently (TX and RT/YW). The data extracted were cross-checked and unresolved discrepancies were referred to a third reviewer; where necessary, problems were discussed in a panel meeting (TX, RT, YW, JH and GL) whilst DN acted as a clinical expert advisor.

For each included study, we extracted characteristics of participants and interventions, outcomes reported and collected, sample size (randomized and analysed) in each arm, numerical results, losses to follow-up and details of patients excluded from the analyses.[17] To inform the appropriateness of including studies in the meta-analysis and facilitate assessment of the strength of the evidence we assessed the risk of bias in each included study using The Cochrane Collaboration's Risk of Bias tool.[18] Two reviewers (TX and either RT or YW) completed this independently and agreed on final assessments. The tool assesses risk of bias arising from inadequacies in processes of generation of the random allocation sequence, concealment of the allocation sequence and blinding, and from incomplete outcome data and selective outcome reporting.

Outcomes

We analysed all-cause mortality and cancer-related mortality at 5 years, late gastrointestinal and late genitourinary toxicity at 3 years. The choice of these follow-up times was pragmatic, as they were the ones most frequently reported in the included trials. Once these time points had been chosen, we extracted the outcome data from the time nearest to these targeted measurement times. Late gastrointestinal and late genitourinary toxicity were defined as scores ≥ 2 measured by the Radiation Therapy Oncology Group (RTOG) questionnaire scale by 3 years follow-up.[19] We have not encompassed biochemical or clinical failure as operational definitions of either of those outcomes tend to be specific to different radical treatment modalities.[20]

Statistical analyses

Initially, we compared each pair of treatments using direct evidence alone, for each outcome. Separate meta-analyses were performed for each pair-wise comparison of interventions: a random-effects model was fitted within each comparison,[21] with a common between-study heterogeneity variance assumed across comparisons to allow for heterogeneity even when only a single study was available. Results are reported as odds ratios with 95% confidence intervals, for every comparison evaluated directly in one or more studies.

Next, we fitted a network meta-analysis model for each outcome separately,[22] combining direct evidence for each comparison (e.g. from studies comparing interventions A with B) with indirect evidence (e.g. from studies comparing A with C and studies comparing B with C), for all pair-wise comparisons simultaneously. The model accounts explicitly for the binary nature of each outcome using a binomial likelihood function; allows for heterogeneity of treatment effects between trials of the

same comparison (assuming the same amount of heterogeneity for each comparison, irrespective of how many trials address it); and enforces an underlying relationship between direct and indirect evidence for a particular comparison, assuming these are consistent between the two sources. For each 'loop' of treatment comparisons from three or more independent sources and for each outcome, we computed the difference between estimates from direct and indirect evidence on the log odds ratio scale.[100] This provides a measure of inconsistency between the different sources. We did not implement more sophisticated methods for testing or adjusting for inconsistency, due to the small number of loops in the network.

Results are reported as odds ratios with 95% credible intervals, for all pair-wise comparisons of interventions. All analyses were performed within a Bayesian framework, using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[23] Informative prior distributions were used for the heterogeneity variance, from a published set of distributions for heterogeneity expected in meta-analyses examining particular intervention and outcome types,[24] since heterogeneity is imprecisely estimated when the number of studies is small. For all-cause mortality, a log-normal (-3.93, 1.51^2) distribution was used. For gastrointestinal and genitourinary toxicity, a log-normal (-2.01, 1.64^2) distribution was used. For cancer-related mortality, a log-normal (-2.89, 1.91^2) distribution was used. Vague N (0, 10^4) priors were used for all other model parameters. Results were based on 100,000 iterations, following a burn-in of 20,000 iterations.

For each outcome, we estimated the probability that each intervention is superior to all others, the second best, the third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain. These ranking probabilities were used to calculate a summary numerical value: the SUCRA (surface under the cumulative ranking curve).[25] SUCRA values are expressed as percentages; if an

intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%. If all interventions are equivalent, we would expect all SUCRA values to be near 50%. We also report the median ranks and 95% credible intervals for each intervention.

RESULTS

Included studies and interventions

The NICE systematic review[8] had identified 20 reports relating to 14 randomized trials.[26-45] Our updated searches retrieved 1,740 studies and identified 39 reports of relevant randomized trials, of which 30 had not been included in the NICE review (Figure 1).[46-75] One of these reports was the sole report of a trial providing data only on acute toxicity,[40] one paper reported only clinical failure,[38] and one paper reported biochemical failure, biochemical disease-free survival and quality of life;[56] these 3 studies were then excluded since they did not report the outcomes of interest to us. In addition to the remaining 47 full papers from peer-reviewed journals, we identified and included in the analysis data from a conference abstract, describing a randomized trial comparing external beam radiotherapy versus watchful waiting,[76] and reporting data on long term mortality not previously reported in full-text related publications.[77-78]

Our searches also identified 16 relevant systematic reviews.[79-94] We scrutinized the reference lists of all these as well as any further systematic reviews identified by the NICE review, and found no further relevant randomized trials.

The 48 identified reports described 21 randomized trials comparing the effectiveness of different treatments for localized prostate cancer.[26-37, 39, 41-55, 57-76] Seventeen trials reported all-cause mortality, 16 trials reported cancer-related mortality, 16 trials reported gastrointestinal (GI) toxicity, 15 trials reported genitourinary (GU) toxicity. The characteristics of included studies are summarized in Appendix 2.

The risk of bias assessments for the included trials are illustrated in Figure 2. Most of the evidence was of moderate to good quality. About half of the studies did not report

adequate information about allocation sequence generation and allocation sequence concealment. Unblinded designs were used in all trials included; we judged this unlikely to cause bias for objectively-measured outcomes such as mortality, but generate bias in the reporting and assessment of patient-reported toxicity outcomes. The small number of studies precluded the investigation of potential reporting biases across studies (for example using funnel plots). Our searches were appropriate, but the possibility of publication bias cannot be excluded. It is unclear, however, whether reporting biases would tend to favour any particular treatment (see Appendix 3 for details of bias assessments for included trials).

We categorized the interventions into the following eight categories: observational management; prostatectomy; conventional radiotherapy (refers to two dimensional external beam radiation therapy); conventional radiotherapy- hypofractionated (refers to less than 20 fractions); conformal low dose (LD) radiotherapy (refers to less than 68 Gy); conformal high dose (HD) radiotherapy (refers to more than 74 Gy); conformal LD radiotherapy-hypofractionated; and cryotherapy. Twenty trials had two intervention arms. One trial compared three interventions;[54] since two of the three interventions were very similar and both met our definition of conformal LD radiotherapy-hypofractionated, we combined the data from these two arms and regarded the trial as a two-treatment comparison (conformal LD radiotherapy-hypofractionated versus conformal HD radiotherapy). None of the reviewed studied assessed brachytherapy and HIFU. Figure 3 illustrates the full network of comparisons. There were two closed loops of comparisons, one connecting prostatectomy, observational management and radiotherapy modalities; and the other connecting different radiotherapy modalities.[100] No inconsistency was detected in our estimates of the difference between direct and indirect evidence; however, precision was very low. Cryotherapy only had a single link to the network.

All-cause mortality

All-cause mortality was reported in 17 trials, covering all the eight interventions of interest. There is no evidence of superiority of any treatment for all-cause mortality. For each pairwise comparison of interventions, the 95% intervals for odds ratios were wide and included 1. The lower-left triangle of results in Table 1 presents odds ratios estimated from direct evidence alone, while the upper-right triangle of results presents odds ratios estimated from the network meta-analysis. The intervals are slightly narrower when based on indirect as well as direct evidence rather than direct evidence alone. The SUCRA values presented in Table 2 summarize the ranking information for all interventions. With respect to all-cause mortality, the highest SUCRA values are 69% for conformal LD radiotehrapy-hypofractionated and 63% for conformal HD radiotherapy, indicating that these are most likely to be among the best treatments for this outcome. However, there is very high uncertainty in the rankings of the interventions, as indicated by wide 95% credible intervals.

Cancer-related mortality

Cancer-related mortality was reported in 16 trials, covering eight of the interventions. This was a rare outcome in most treatment groups, as expected for patients with localized prostate cancer with a 5 year end point. Odds ratio estimates had wide 95% credible intervals, particularly in comparisons for which only indirect evidence was available, and there was no evidence of superiority for any of the comparator treatments (Table 3). Based on direct comparisons alone, conformal HD radiotherapy was superior to conventional radiotherapy [odds ratio 0.21 (95% interval 0.03, 0.97)] and prostatectomy was superior to observational management [odds ratio 0.60 (95% interval 0.37, 0.98)].

Gastrointestinal and genitourinary toxicity

Late gastrointestinal toxicity was reported in 16 trials and late genitourinary toxicity was reported in 15 trials. There was evidence that cryotherapy resulted in fewer adverse gastrointestinal events than radiotherapy treatments (estimated odds ratios comparing cryotherapy against the five radiotherapy options ranged from 0.12 to 0.24, whilst all but one of the respective 95% credible intervals excluded 1). The SUCRA value of 99% for cryotherapy and the median rank of 1 (95% interval 1, 2) suggest that cryotherapy is almost certainly superior among the six treatments included in the network meta-analysis in relation to adverse gastrointestinal events (Table 2 and 4). There was also evidence that gastrointestinal toxicity was more likely with conformal HD radiotherapy than with conformal LD radiotherapy. Interpretation of such findings for toxicity should be more cautious than for the other outcomes, due to a concern that lack of blinding could have led to a risk of detection bias. For genitourinary toxicity, there was no evidence favouring one intervention over another (Table 5), although cryotherapy tended to receive better rankings than the five radiotherapy treatments (Table 2), and the odds ratio estimates favour cryotherapy, but the 95% intervals all included 1.

Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis

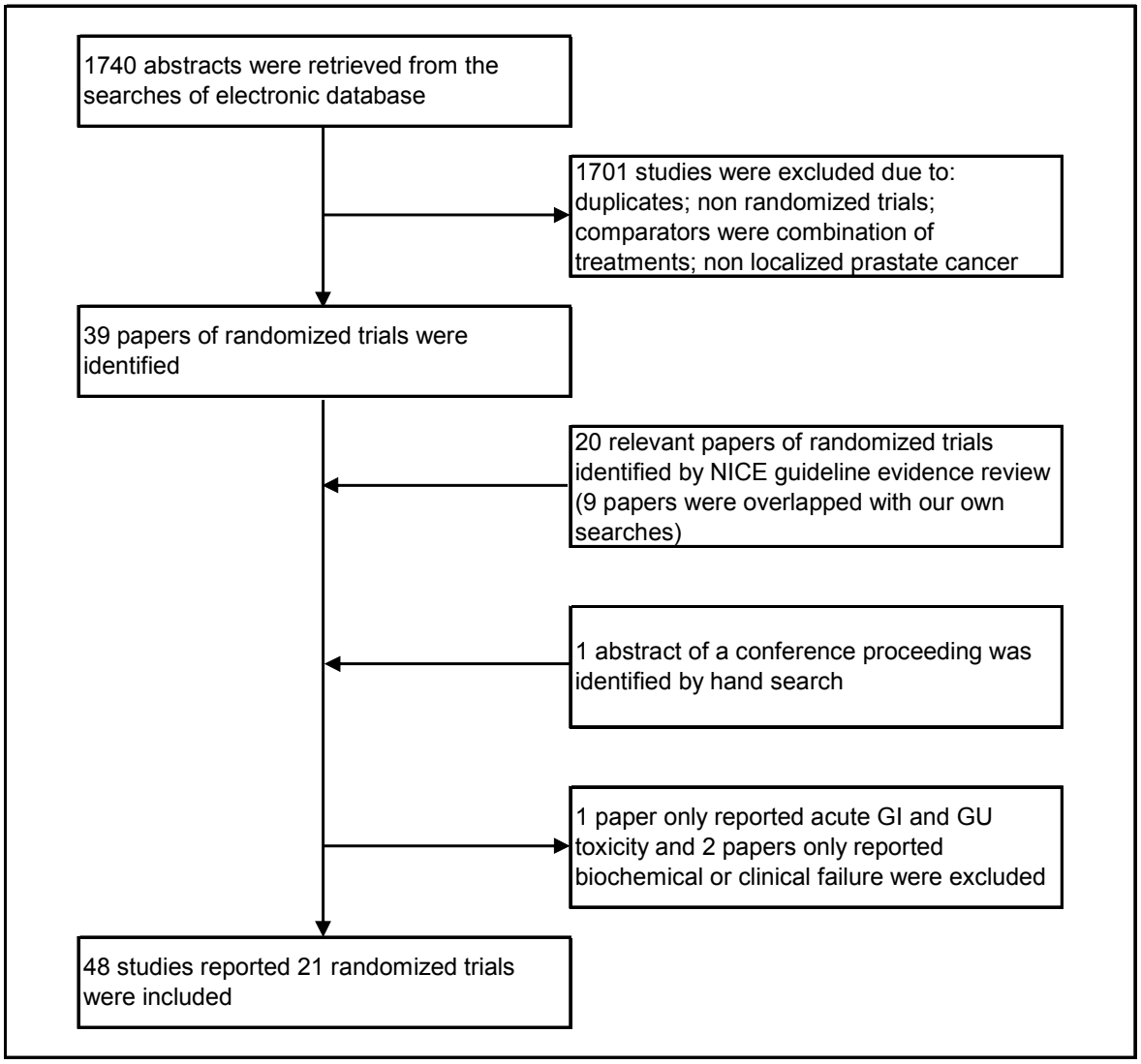


Figure 2. Risk of bias assessments for the included randomized trials

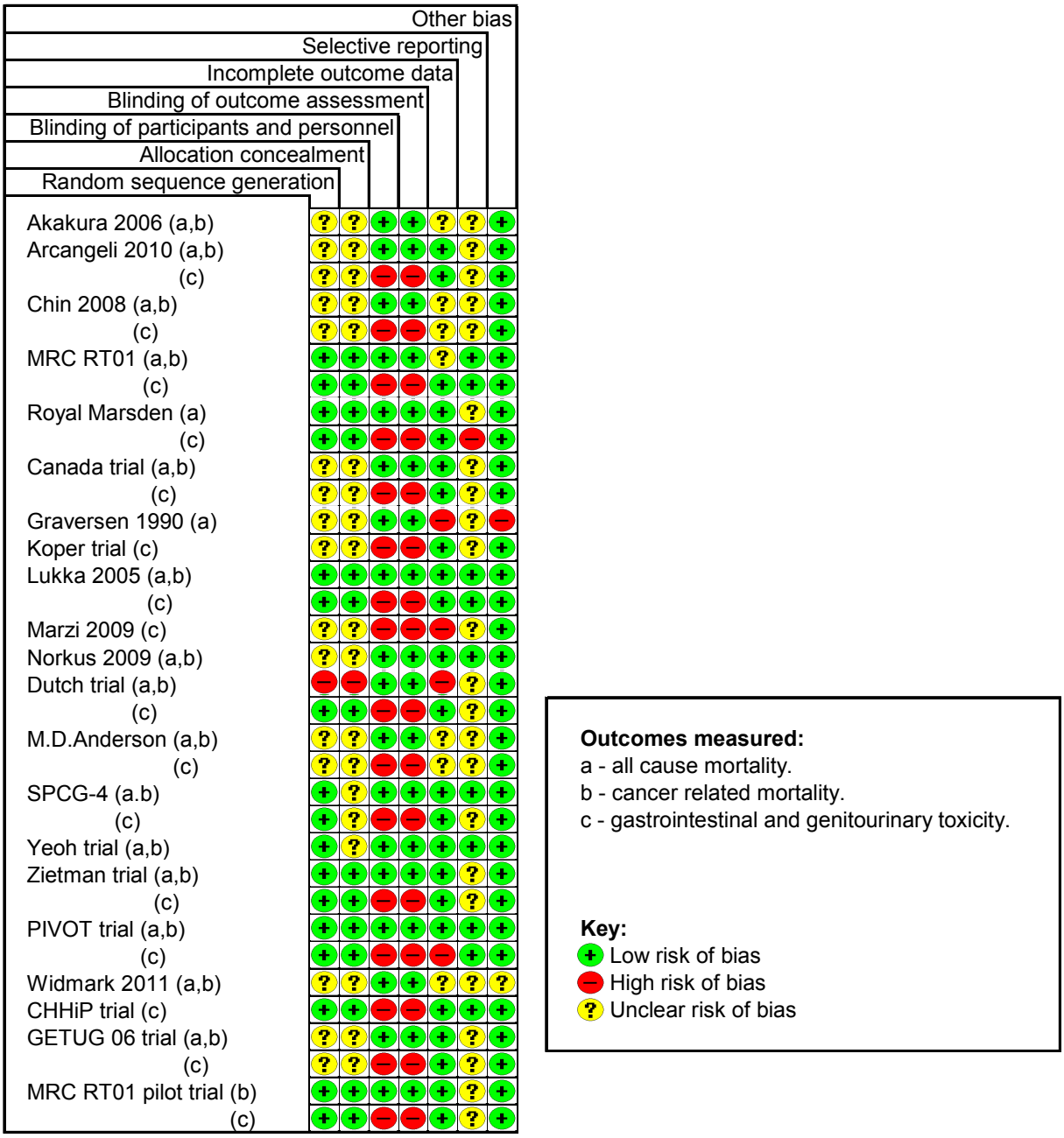
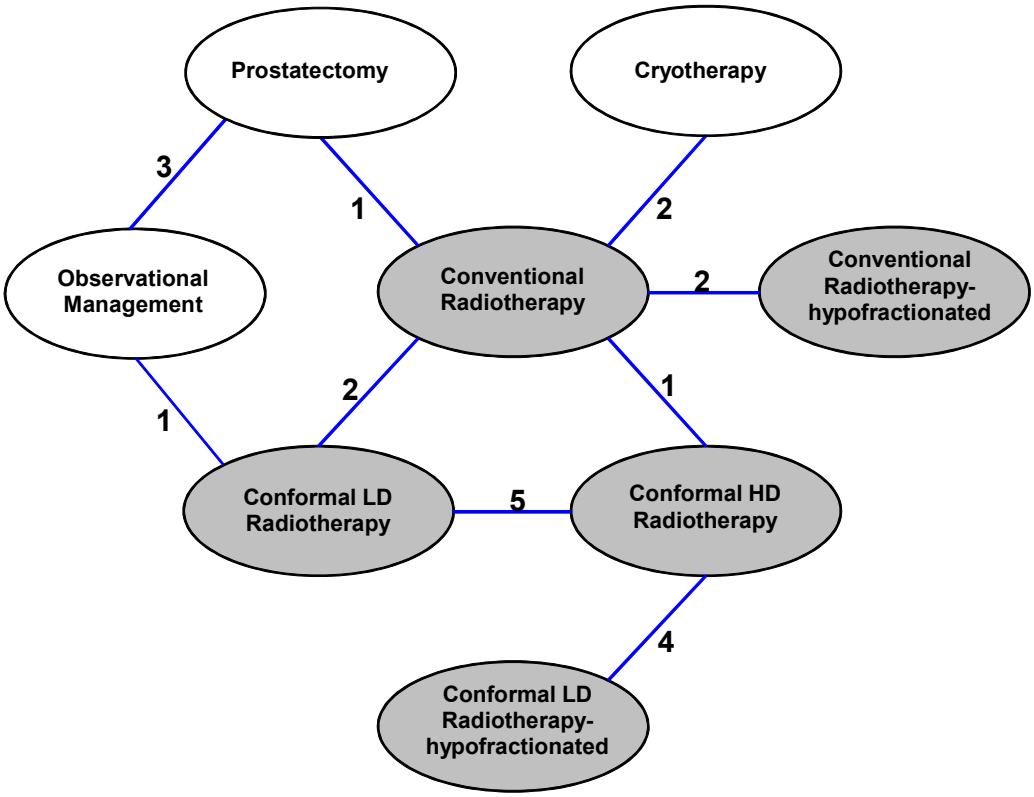


Figure 3. Network of comparisons of treatments for localized prostate cancer showing numbers of trials in which each pairwise comparison had been made



Abbreviations: LD: low dose; HD: high dose.
Grey-shaded ovals indicate external radiotherapy modalities.

Table 1. All-cause mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.79 (0.61,1.02)	0.84 (0.48,1.57)	0.72 (0.37,1.49)	0.73 (0.44,1.26)	0.70 (0.40,1.28)	0.53 (0.10,2.88)	0.76 (0.28,1.98)
Prostatectomy	[3] 0.80 (0.61,1.06)		1.06 (0.60,2.02)	0.91 (0.46,1.90)	0.92 (0.54,1.64)	0.88 (0.49,1.66)	0.67 (0.12,3.65)	0.96 (0.36,2.56)
Conventional radiotherapy	-	[1] 1.34 (0.55,3.24)		0.85 (0.59,1.24)	0.86 (0.55,1.35)	0.82 (0.51,1.35)	0.62 (0.11,3.21)	0.90 (0.41,1.89)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.85 (0.59,1.24)		1.01 (0.56,1.80)	0.97 (0.53,1.78)	0.73 (0.13,3.86)	1.05 (0.44,2.42)
Conformal LD radiotherapy	[1] 0.66 (0.35,1.21)	-	[1] 0.92 (0.50,1.72)	-		0.96 (0.72,1.29)	0.72 (0.14,3.51)	1.04 (0.42,2.49)
Conformal HD radiotherapy	-	-	[1] 0.87 (0.39,1.92)	-	[4] 0.95 (0.70,1.31)		0.74 (0.14,3.61)	1.09 (0.43,2.64)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.78 (0.13,4.25)		1.47 (0.22,9.40)
Cryotherapy	-	-	[2] 0.90 (0.41,2.02)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.08).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.07).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 2. Ranking of interventions with respect to all-cause and cancer-related mortality, adverse gastrointestinal and genitourinary events: SUCRA (Surface Under the Cumulative RAnking curve) values and median ranks (with 95% intervals).†

Intervention	All-cause mortality		Cancer-related mortality		Adverse gastrointestinal events		Adverse genitourinary events	
	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)
Observational management	18%	7 (2, 8)	30%	6 (3, 8)	-	-	-	-
Prostatectomy	49%	5 (1, 7)	64%	4 (1, 7)	-	-	-	-
Conventional radiotherapy	35%	6 (2, 8)	16%	7 (4, 8)	43%	4 (2, 6)	51%	3 (1, 6)
Conventional radiotherapy-hypofractionated	58%	4 (1, 8)	44%	5 (1, 8)	42%	4 (1, 6)	50%	3 (1, 6)
Conformal LD radiotherapy	57%	4 (1, 7)	61%	4 (2, 7)	67%	2 (2, 4)	66%	3 (1, 5)
Conformal HD radiotherapy	63%	3 (1, 7)	75%	2 (1, 6)	19%	5 (3, 6)	30%	5 (2, 6)
Conformal LD radiotherapy-hypofractionated	69%	1 (1, 8)	85%	1 (1, 8)	30%	5 (2, 6)	26%	5 (1, 6)
Cryotherapy	50%	4 (1, 8)	24%	7 (2, 8)	99%	1 (1, 2)	77%	1 (1, 6)

† The surface under the cumulative ranking curve (SUCRA) value is a numerical summary of the estimated probabilities that each treatment is the best, second best, third best (and so on) for that particular outcome. Higher values indicate higher rankings compared with other treatments. For example, for cryotherapy, the high SUCRA value of 99% and median rank of 1 for adverse gastrointestinal events shows that cryotherapy is expected to be superior with respect to this outcome.

LD: low dose; HD: high dose.

Table 3. Prostate cancer-caused mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.63 (0.40,1.02)	1.39 (0.49,4.16)	0.90 (0.24,3.42)	0.63 (0.29,1.31)	0.52 (0.22,1.19)	0.13 (0.00*,3.59)	1.37 (0.28,6.89)
Prostatectomy	[2] 0.60 (0.37,0.98)		2.20 (0.82,6.37)	1.42 (0.39,5.19)	0.99 (0.42,2.26)	0.83 (0.32,2.00)	0.20 (0.00*,6.07)	2.16 (0.46,10.9)
Conventional radiotherapy	-	[1] 1.65 (0.53,5.44)		0.64 (0.29,1.41)	0.45 (0.14,1.30)	0.38 (0.12,1.06)	0.09 (0.00*,3.08)	0.98 (0.28,3.35)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.65 (0.28,1.43)		0.70 (0.18,2.65)	0.59 (0.15,2.16)	0.14 (0.00*,5.08)	1.51 (0.36,6.54)
Conformal LD radiotherapy	[1] 0.70 (0.31,1.57)	-	-	-		0.84 (0.52,1.30)	0.20 (0.00*,5.73)	2.20 (0.44,11.4)
Conformal HD radiotherapy	-	-	[1] 0.21 (0.03,0.97)	-	[5] 0.86 (0.53,1.37)		0.25 (0.00*,6.79)	2.61 (0.53,14.1)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.22 (0.00*,6.85)		11.2 (0.24,5542)
Cryotherapy	-	-	[2] 0.96 (0.27,3.46)	-	-	-	-	

LD: low dose; HD: high dose.

* Odds ratio was less than 0.005.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.31).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.29).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 4. Adverse gastrointestinal events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 0.84 (0.33,1.88)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.01 (0.19,5.29)	0.72 (0.29,1.59)	1.42 (0.57,3.39)	1.26 (0.35,4.30)	0.17 (0.04,0.51)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.00 (0.22,4.56)		0.70 (0.11,4.37)	1.40 (0.21,9.02)	1.24 (0.15,9.76)	0.17 (0.02,1.19)
Conformal LD radiotherapy	-	-	[2] 0.46 (0.17,1.16)	-		1.98 (1.18,3.59)	1.77 (0.63,5.11)	0.24 (0.05,0.96)
Conformal HD radiotherapy	-	-	[1] 2.66 (0.85,8.62)	-	[5] 1.73 (1.07,2.97)		0.89 (0.36,2.15)	0.12 (0.02,0.48)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[3] 0.89 (0.39,1.96)		0.14 (0.02,0.70)
Cryotherapy	-	-	[2] 0.18 (0.05,0.50)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.14 (95% interval 0.01 to 0.97).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.24 (95% interval 0.02 to 1.23).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 5. Adverse genitourinary events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 2.27 (1.34,3.90)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.00 (0.34,2.90)	0.91 (0.54,1.51)	1.19 (0.69,2.11)	1.41 (0.49,4.07)	0.66 (0.22,2.00)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.01 (0.34,3.00)		0.90 (0.27,2.97)	1.19 (0.36,4.04)	1.41 (0.31,6.44)	0.66 (0.14,3.04)
Conformal LD radiotherapy	-	-	[2] 0.80 (0.43,1.51)	-		1.32 (0.97,1.86)	1.56 (0.61,4.09)	0.73 (0.21,2.52)
Conformal HD radiotherapy	-	-	[1] 1.53 (0.62,3.82)	-	[5] 1.28 (0.93,1.86)		1.18 (0.48,2.92)	0.55 (0.16,1.91)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 1.17 (0.48,2.91)		0.47 (0.10,2.15)
Cryotherapy	-	-	[2] 0.68 (0.22,2.03)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.003 to 0.29).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.002 to 0.26).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

DISCUSSION

~~Our study is mainly a methodological contribution to an area of modern medicine with sparse randomised controlled evidence. We highlight the potential for network meta-analysis to be used for evidence synthesis in this research area, particularly after the forthcoming advent of further randomised controlled trial data. The present state of the evidence is that considering data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.~~

~~Our analyses have several strengths.~~ Using network meta-analysis, we were able to combine simultaneously all relevant evidence on treating patients with localized prostate cancer, even in the absence of direct comparative evidence for some treatment pairs, encompassing four efficacy and safety outcomes. Based on data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes for localized prostate cancer, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.

Assumptions of consistency between direct and indirect evidence were tested to justify the joint synthesis of all studies; however, these tests had little power due to the relatively small number of trials available in most direct comparisons. Instead we must rely on judgements about the similarity of studies included in the analysis in aspects such as patient groups, outcome measures and study methodology. Although we defined the population of interest as patients with localized prostate cancer, there was heterogeneity between individual study populations in terms of the severity of disease. Some of the trials were conducted several decades ago, when surgery and radiology techniques may have been different, and we observed that stage migration has occurred in men diagnosed with prostate cancer, due to

emerging bio-marker and image technologies. Furthermore, some of the trials used adjuvant therapy, although this was applied in all the arms within the trial.

Two further limitations warrant mention. Literature searches were completed in September of 2012. However, the results of one of the most important randomized trials – ProtecT study[13] – has not been published so far, and to our knowledge there are no other new relevant RCTs have been reported after this systematic review. Our choices of measurements may have favoured some treatments over others: for example the RTOG scale had been used to define the late gastrointestinal and late genitourinary toxicity in the included studies, but it does not measure incontinence which could be the most common adverse event post-prostatectomy.[102]

Methodologically, we used informative prior distributions based on external evidence for heterogeneity variances, to increase precision in their estimation and improve estimation of treatment differences. Data-based informative priors have previously been considered by Lu & Ades,[101] who used them for the between-study correlation structure. To our knowledge, our paper is the first application of network meta-analysis incorporating data-based informative priors for between-study heterogeneity.

Our findings have implications for research funding prioritisation and study design; and for clinical practice. The study identified particular 'weak links' in the network of comparative treatment options, which might be prioritized for future investment in randomized controlled trials. This is particularly the case for studies comparing HIFU (which currently is bereft of any comparative evidence) or brachytherapy against other treatment options, and also for trials examining the comparative efficacy and safety of prostatecotmy versus conformal radiotherapy modalities. For clinicians, and for men diagnosed with prostate cancer, our findings highlight that the optimal treatment options may be different in respect of different outcomes: patients need to be given appropriate information about the uncertainty

surrounding treatment choice currently, and be allowed to opt for 'trade-offs' between efficacy and safety outcomes as they judge appropriately.[95] Observational studies have consistently shown that radical prostatectomy has better cause-specific mortality outcomes compared with radiotherapy.[96-99,103]

In conclusion, clinically important information from high quality randomized trials is still needed to inform decision making regarding primary treatment options for men with localized prostate cancer. The findings of this study highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between multiple outcomes. The upcoming results of the ProtecT study,[13] which is evaluating effectiveness of multiple therapies in men with PSA-detected localized prostate cancer, together with other treatment studies in progress, will hopefully contribute to the evidence base. It is however unlikely that evidential uncertainty about all relevant and important outcomes will be resolved by these trials, and an updated network meta-analysis incorporating new evidence may be useful to synthesize the new with the existing evidence. We demonstrate a high degree of uncertainty about treatment superiority in the management of localized prostate cancer. Clinicians and patients need to grapple with this uncertainty in the context of shared-decision making.

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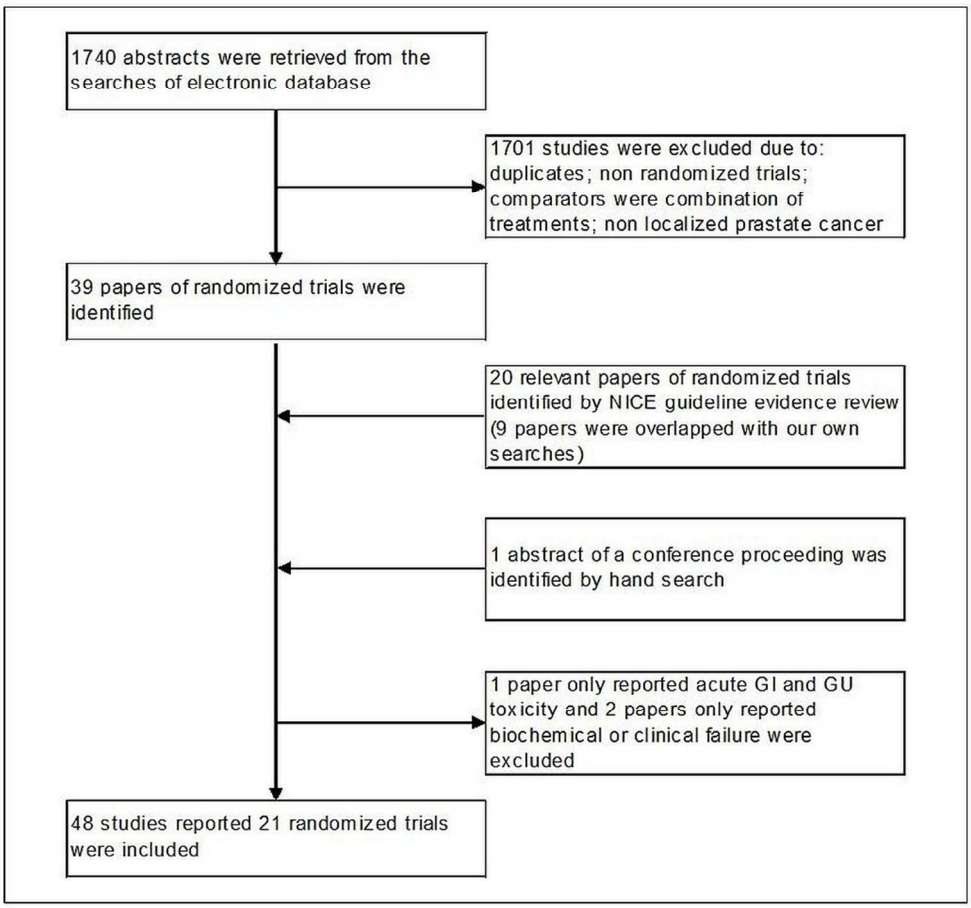

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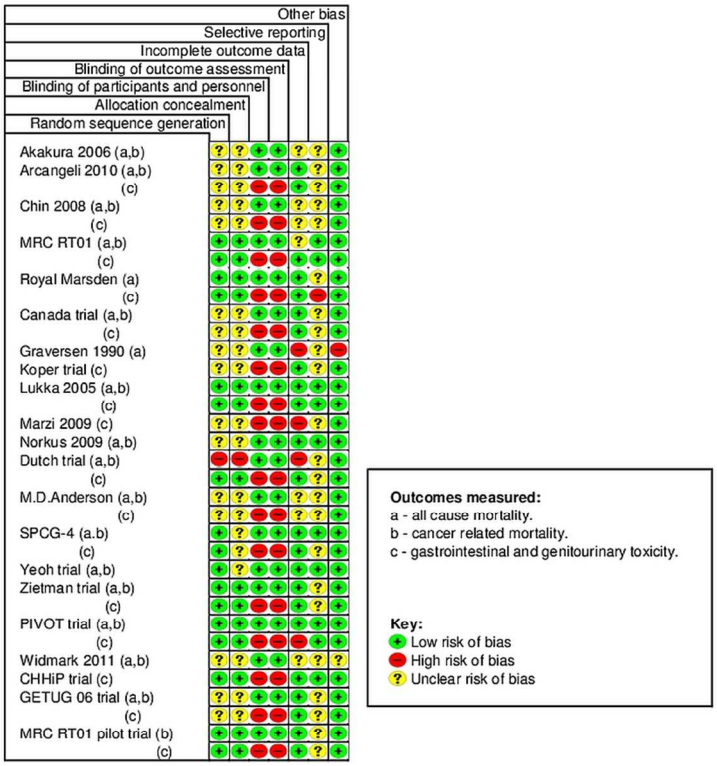
Figure 2. Risk of bias assessments for the included randomized trials



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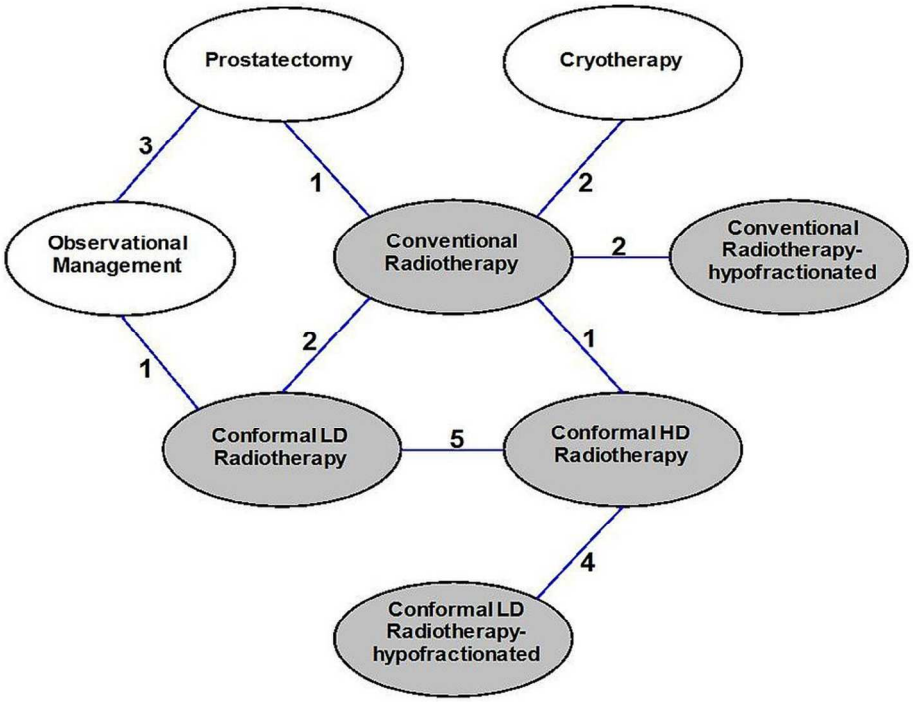

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Appendix 1. Full search strategy for Medline made on 12 Sep 2012

1	"watchful wait$".ti,ab	1408
2	(watch$ adj2 wait$).ti,ab	1795
3	"observation".ti,ab	201605
4	"watchful surveillance".ti,ab	3
5	"watchful monitoring".ti,ab	14
6	"active surveillance".ti,ab	2609
7	"active monitoring".ti,ab	177
8	"expectant manag$".ti,ab	1501
9	"expectant monitoring".ti,ab	18
10	"expectant surveillance".ti,ab	3
11	"deferred treatment$".ti,ab	174
12	"deferred therap$".ti,ab	53
13	"delayed treatment$".ti,ab	1752
14	"delayed therap$".ti,ab	264
15	"conservative monitoring".ti,ab	10
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	209461
17	exp PROSTATIC NEOPLASMS/	83203
18	PROSTATIC INTRAEPITHELIAL NEOPLASIA/	1124
19	pin.ti,ab	9241
20	((prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR intraepithelial$ OR adeno$))).ti,ab	85456
21	17 OR 18 OR 19 OR 20	109867
22	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	82900
23	RANDOMIZED CONTROLLED TRIAL/	336590
24	RANDOM ALLOCATION/	75700
25	DOUBLE BLIND METHOD/	116906
26	SINGLE BLIND METHOD/	16674
27	CLINICAL TRIAL/	473817
28	"clinical trial, phase i".pt	12527
29	"clinical trial, phase ii".pt	20003
30	"clinical trial, phase iii".pt	7335
31	"clinical trial, phase iv".pt	739
32	"controlled clinical trial".pt	85134
33	"randomized controlled trial".pt	336590
34	"multicenter study".pt	149366
35	"clinical trial".pt	473817
36	exp CLINICAL TRIALS AS TOPIC/	260613
37	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36	933873
38	(clinical ADJ trial$).ti,ab	185348
39	((singl$ OR doubl$ OR treb$ OR tripl$) AND (blind$3 OR mask$3)).ti,ab	129000
40	PLACEBOS/	31302
41	placebo$.ti,ab	144213
42	"randomly allocated".ti,ab	14778
43	(allocated adj2 random$).ti,ab	17183
44	38 OR 39 OR 40 OR 41 OR 42 OR 43	383691
45	37 OR 44	1064978
46	(case AND report).ti,ab	372325
47	LETTER/	776512

48	HISTORICAL ARTICLE/	286394
49	46 OR 47 OR 48	1422877
50	45 NOT 49	1033939
51	CRYOTHERAPY/	3337
52	CRYOSURGERY/	10459
53	HYPOTHERMIA, INDUCED/	15628
54	cryoablat$.ti,ab	1810
55	(cryo$ ADJ ablat$).ti,ab	351
56	cryotreatment$.ti,ab	65
57	cryotherap$.ti,ab	4776
58	cryotherm$.ti,ab	212
59	(cryo$ ADJ surgery).ti,ab	149
60	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	31372
61	((cryo$ OR hypotherm$ OR freez$) adj5 prostat$).ti,ab	709
62	60 AND 21	916
63	61 OR 62	1089
64	PROSTATECTOMY/	19443
65	prostatectom$.ti,ab	18653
66	resection.ti,ab	170070
67	64 OR 65 OR 66	192628
68	(radical OR complete$ OR total OR "en bloc").ti,ab	2057017
69	67 AND 68	69466
70	(LRP OR TLRP OR RALRP OR RAP OR RRP OR RPP OR EERP).ti,ab	7847
71	"heilbronn technique".ti,ab	8
72	70 OR 71	7853
73	69 OR 72	76420
74	exp RADIOTHERAPY/	125988
75	"radiation therap$".ti,ab	46061
76	"radiation treatment$".ti,ab	6068
77	radiotherap$.ti,ab	103759
78	exp RADIOTHERAPY PLANNING/	11242
79	irradiation.ti,ab	133551
80	RADIOTHERAPY, ADJUVANT/	15412
81	74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80	307483
82	META-ANALYSIS AS TOPIC/	12419
83	"meta analy$".ti,ab	45804
84	metaanaly$.ti,ab	1171
85	META-ANALYSIS/	36142
86	(systematic ADJ review$1).ti,ab	37644
87	(systematic ADJ overview$1).ti,ab	489
88	exp REVIEW LITERATURE AS TOPIC/	6486
89	82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88	93039
90	cochrane.ab	22743
91	embase.ab	20328
92	(psychlit OR psyclit).ab	865
93	(psychinfo OR psycinfo).ab	7698
94	(cinahl OR cinhal).ab	7537
95	"science citation index".ab	1633
96	bids.ab	331
97	cancerlit.ab	560
98	90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97	37065
99	"reference list$".ab	7905

100	bibliograph$.ab	10314
101	hand-search$.ab	3303
102	"relevant journals".ab	586
103	"manual search$".ab	1920
104	99 OR 100 OR 101 OR 102 OR 103	21486
105	"selection criteria".ab	16935
106	"data extraction".ab	8148
107	105 OR 106	23737
108	REVIEW/	1733836
109	107 AND 108	15770
110	COMMENT/	517077
111	LETTER/	776512
112	EDITORIAL/	317040
113	ANIMAL/	5040870
114	HUMAN/	12536636
115	113 NOT (113 AND 114)	3686418
116	110 OR 111 OR 112 OR 115	4846136
117	89 OR 98 OR 104 OR 109	118824
118	117 NOT 116	110572
119	ULTRASOUND, HIGH-INTENSITY FOCUSED, TRANSRECTAL/	306
120	((high intensity adj2 ultraso$)).ti,ab	2103
121	HIFU.ti,ab	1012
122	((high intensity focused ultrasound)).ti,ab	1381
123	"focal therapy".ti,ab	295
124	119 OR 120 OR 121 OR 122 OR 123	2619
125	21 AND 50 AND 124	**99**
126	16 AND 21 AND 50 AND 63 [Limit to: Publication Year 2005-Current]	**10**
127	16 AND 21 AND 50 AND 73 [Limit to: Publication Year 2005-Current]	**94**
128	16 AND 21 AND 50 AND 81 [Limit to: Publication Year 2005-Current]	**82**
129	50 AND 63 AND 81 [Limit to: Publication Year 2005-Current]	**27**
130	50 AND 63 AND 73 [Limit to: Publication Year 2005-Current]	**14**
131	21 AND 50 AND 73 AND 81 [Limit to: Publication Year 2005-Current]	**267**
132	(21 AND 50 AND 81) NOT (128 OR 131) [Limit to: Publication Year 2005-Current]	**947**
133	16 AND 21 AND 63 AND 118 [Limit to: Publication Year 2005-Current]	**5**
134	16 AND 21 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**25**
135	16 AND 21 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**27**
136	63 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**14**
137	63 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**12**
138	21 AND 73 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**56**
139	(21 AND 81 AND 118) NOT (135 OR 138) [Limit to: Publication Year 2005-Current]	**61**

Appendix 2. Characteristics of included studies

Comparison	Trial title	Author, year	Country	Population	No.of men	Interventions and Comparisons	Outcomes	Follow up
Observational management v Prostatectomy (3 trials)	Graversen 1990 (1 paper)	Graversen 1990	USA	Dates of enrolment to study: Between May 1967 and March 1975; Setting: Multi-centre (15 participating hospitals); Age: All age; Disease status: stage I or II (T0 – T2).	142	1. Watchful waiting (74 men) 2. Prostatectomy (68 men)	Overall survival.	15 years.
	PIVOT trial (1 paper)	Wilt 2012	USA	Dates of enrolment to study: Nov 1994 to Jan 2002; Setting: multicentre; Mean age: 67yr; Disease status: T1-T2NxM0.	731	1. Observation (367 men) 2. Prostatectomy (364 men)	All cause mortality; Cancer caused mortality; Bone metastases; Urinary incontinence; Bowel dysfunction; Erectile dysfunction.	10 years.
	Scandinavian Prostate Cancer Group Study No 4 (SPCG-4) (6 papers)	Bill-Axelson 2005, 2008, 2011; Johansson 2009, 2011 Steineck 2002;	Sweden, Finland, Iceland	Dates of enrolment to study: Oct 1989 to Feb 1999; Setting: Multi-centre (14 participating hospitals); Age: Mean age 64.7; Disease status: T0d, T1, T2.	695	1. Watchful waiting (348 men) 2. Prostatectomy (347 men)	Death due to prostate cancer; All-caused mortality; Distance metastasis; Local progression; overall distress from all bowel symptoms, overall distress from all urinary symptoms.	8.2 - 12.8 years.
Observational management v Conformal LD radiotherapy (1 trial)	Widmark 2011 (1 paper)	Widmark 2011	Sweden, Denmark and Norway	Dates of enrolment to study: Apr 1986 to Jan 1997; Setting: unknown; Age: up to 75; Disease status: T1b-T2, pN0, G1-G2, M0.	214	1. Watchful waiting (107 men) 2. 3D conformal radiotherapy, either 64 Gy in 32 fractions with 2cm margin, or 64-68 Gy with 1.5cm margin (107 men)	All-cause mortality, Prostate cancer mortality, Distant progression, Recurrence free survival, Clinical progression, Biochemical progression, Local progression.	20 years.

Prostatectomy v Conventional radiotherapy (2 trials)	Akakura 2006(1 paper)	Akakura 2006	Japan	Dates of enrolment to study: 1989 to 1993; Setting: Multi-centre; Age: Mean 68.1, SD 7.0 in surgery group; mean 68.7, SD 6.6 in radiation group; Disease status: T2b-3N0M0, no evidence of lymph node metastasis.	95	1. Prostatectomy (46 men).2. Conventional radiotherapy (49 men): Irradiation by linear accelerator with a 40-50 Gy beam to the whole pelvis followed by a 20 Gy boost to the prostatic area for 6-7 weeks fractionated five times per week. All men received an initial treatment with 8 weeks of neoadjuvant endocrine therapy.	Biochemical progression-free survival at 10 years; Clinical progression-free survival at 10 years; Cause-specific survival at 10 years; Overall survival at 10 years; Adverse effects.	Median follow-up was 102 months.
Cryotherapy v Conventional radiotherapy (2 trials)	Canada trial (3 papers)	Donnelly 2007, 2010; Robinson 2009	Canada	Dates of enrolment to study: Dec 1997 to Feb 2003; Setting: Tom Baker Cancer Center, Calgary, Canada; Age: Median 69.4, range 52.8-81.4 in CT group; median 68.6, range 53.2-78.6 in EBRT group; Disease status: T2 - T3.	244	1. Cryotherapy (122 men). 2. Conventional EBRT (122 men): dose of 68 Gy given in 2 Gy fractions daily, 5 days per week, later increased to 70 Gy and later 73.5 Gy.	Treatment Failure; 5 year overall survival; Biopsy rate at 36 months; Disease-specific survival at 5 years; Genitourinary and gastrointestinal adverse effects; Quality of life.	Median follow-up was 82 months.
	Chin 2008 (1 paper)	Chin 2008	Canada	Setting: London Health Sciences Centre, University of Western Ontario; Age: Median age 70 in each group; Disease status: T2 - T3.	64	1. Cryotherapy (33 men). 2. Conventional EBRT (31 men): 66 Gy in 33 fractions.	Biochemical disease-free survival at 4 years; Overall survival at 4 years; Disease specific survival at 4 years; Positive biopsy rate; Gastrointestinal toxicity; Genitourinary toxicity; Hormonal adverse effects.	Mean follow-up 37 months.

Conventional radiotherapy v Conventional radiotherapy-hypofractionated (2 trials)	Yeoh trial (4 papers)	Yeoh 2003, 2006, 2009, 2011	Australia	Dates of enrolment to study: July 1996 to Aug 2003; Setting: Department of Radiation Oncology and Gastroenterology, Royal Adelaide Hospital; Age: Median age 69 (44 ~ 82 yrs); Disease status: T1, T2, N0 M0.	217	1. Conventional EBRT: 64 Gy in 32 fractions within 6.5 weeks (109 men). 2. Hypofractionated EBRT: 55 Gy in 20 fractions within 4 weeks (108 men).	Gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival rate; biochemical ±clinical relapse; biochemical ±clinical relapse-free survival; cancer-related mortality.	5 years.
	Lukka 2005 (1 paper)	Lukka 2005	Canada	Dates of enrolment to study: March 1995 – December 1998; Setting: 8 Ontario regional cancer centres and 8 additional Canadian centres; Age: Mean 70.3, range 53-84 in group 1; mean 70.0, range 53-84 in group 2; Disease status: T1, T2.	936	1. Conventional EBRT (470 men): 66 Gy in 33 fractions over 45 days. 2. Hypofractionated EBRT (466 men): 52.5 Gy in 20 fractions over 28 days.	Composite of biochemical or clinical failure (BCF); local persistence of tumour on biopsy of the prostate at 2 years; overall survival; acute and late radiation-induced toxicity; prostate cancer-related mortality.	Median follow-up was 5.7 years.
Conventional radiotherapy v Conformal LD radiotherapy (2 trials)	Koper trial (2 papers)	Koper 1999, 2004	Nether-lands	Dates of enrolment to study: June 1994 to March 1996; Setting: Erasmus Medical Center/Daniel den Hoed Cancer Center; Mean age: group1: 70 (6.4); group 2: 69.5 (6.1); Disease status: T1-T4 N0M0.	266	1. Conventional radiotherapy (134 men); 2. Conformal radiotherapy (129 men). All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure.	Gastrointestinal (GI) and genitourinary (GU) toxicity.	2 years.
	Royal Marsden and Institute of Cancer Research study (2 papers)	Dearnaley 1999; Tait 1997	UK	Dates of enrolment to study: 1988 to 1995; Setting: Tertiary care, single centre; Median age (range): 69 (51-80) in group 1, 68 (50-83) in group 2; Disease status: T1-T4 N0M0.	225	1. Conventional radiotherapy (111 men): 60 to 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy (114 men): 60 to 64 Gy in 2 Gy fractions.	Overall survival; Biochemical progression free survival; Late GI toxicity; Late GU toxicity.	2 - 5 years.

Conformal LD radiotherapy v Conformal HD radiotherapy (5 trials)	Dutch trial (7 papers)	Al-Mamgani 2008, 2011; Heemsbergen 2007; Peeters 2005, 2006a,b; van der Wielen 2008	Netherlands	Dates of enrolment to study: between June 1997 and February 2003; Setting: multicenter; Age: mean 68.6 and 68.8, range 50.3-82.9 and 48.7-83.6; Disease status: T1-T4.	669	1. 3D conformal radiotherapy 68 Gy (331 men). 2. 3D conformal radiotherapy 78 Gy (333 men).	freedom from failure; biochemical progression free survival; clinical progression free survival; overall survival; late GI toxicity; late GU toxicity; prostete cancer related deaths.	2 - 7 years.
	MRC RT01 pilot trial (1 paper)	Dearnaley 2005	UK	Dates of enrolment to study: between Jul 1995 and Dec 1997; Setting: Royal Marsden NHS Trust and Institute of Cancer Research; Age: median 66 and 69; Disease status: T1b-T3b N0 M0.	127	1. Conformal radiotherapy, standard dose (64 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (63 men): 74 Gy in 2 Gy fractions.	Biochemical (PSA) failure; Local or metastatic failure; Hormone therapy restarted; acute GU toxicity; acute GI toxicity; late GU toxicity; late GI toxicity; prostate cancer caused deaths.	5 years.
	MRC RT01 (3 papers)	Dearnaley 2007a,b; Syndikus 2010.	UK	Dates of enrolment to study: Jan 1998 to Dec 2002; Setting: multi-centre; Age: median 67 (IQR 63-71); Disease status: T1b-T3a N0 M0.	843	1. Conformal radiotherapy, standard dose (421 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (422 men): 74 Gy in 2 Gy fractions.	Biochemical-progression-free survival; 5-year overall survival; Progression-free survival; Freedom from local progression; Freedom from salvage androgen suppression; Metastases-free survival; Bowel dysfunction; Urinary or bladder dysfunction; Sexual dysfunction; prostate cancer mortality.	5 years.
	GETUG 06 Tial (2 papers)	Beckendorf 2004, 2011	France	Dates of enrolment to study: Sep 1999 to Feb 2002; Setting: Multicentre; Age: mean 67; Disease status: T1b-T3a, N0M0.	306	1. Conformal radiotherapy, standard dose (153 men): 70 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (153 men): 80 Gy in 2 Gy fractions.	Biochemical relapse alone; PSA and clinical relapse; Free from relapse; All cause death; Cancer cause death; RTOG rectal and urinary toxicity grade 2 and worse.	61 months.
	Zietman trial (2 papers)	Zietman AL, 2005, 2010	USA	Dates of enrolment to study: between Jan 1996 and Dec 1999; Setting: 2 US academic institutions; Age: 67 (45~91) in 70.2 Gy arm, 66 (47~78) in 79.2 Gy arm; Disease status: T1-T2, N0, Nx.	393	1. External beam radiation 70.2 Gy (197 men); 2. External beam radiation 79.2 Gy (195 men).	Freedom from biochemical failure 5 yrs after treatment (measured by PSA level); Acute and late GU and GI morbidity, overall survival, prostate cancer-related mortality.	5.5 - 8.9 years.

Conformal HD radiotherapy v Conformal LD radiotherapy-hypofractionated (4 trials)	Arcangeli 2010 (2 papers)	Arcangeli 2010, 2011	Italy	Dates of enrolment to study: Jan 2003 to Dec 2007; Setting: single centre; Mean age: 75 years; Disease status: no evidence of distant metastases.	168	1. hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week): 83 men. 2. conventional fractionation radiotherapy (80 Gy/40 fractions/8 weeks): 85 men.	Acute and late GU and GI toxicity; biochemical failure; freedom from biochemical failure; distant metastasis rates; all cause mortality; cancer related mortality.	4 years.
	Marzi 2009 (1 paper)	Marzi 2009	Italy	Dates of enrolment to study: March 2003 to June 2008; Setting: single centre; Age: all; Disease status: T1-T4.	162	1. Conformal radiotherapy hypofractionated: 62 Gy in 20 fractions over 5 weeks (57 men); 2. Conformal radiotherapy: 80 Gy in 40 fractions over 8 weeks (57 men).	Late rectal toxicity.	Median followup was 30 months.
	Norkus 2009 (2 papers)	Norkus 2009 a,b	Lithuania	Dates of enrolment to study: 2004; Setting: single centre; Age: median 63 (range 53-75) in group 1, median 65 (range 50-78) in group 2; Disease status: T1-T3.	91	1. Hypofractionated external beam radiotherapy: 57 Gy given as 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy (47 men). 2. Conventionally fractionated external beam radiotherapy: 74 Gy given in 37 fractions of 2 Gy (44 men).	Biochemical (PSA) response; acute gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival; prostate cancer-related mortality.	3 - 12 months.
	CHHiP trial (1 paper)	Dearnaley 2012	UK	Dates of enrolment to study: Oct 2002 to Aug 2006; Setting: multicentre; Age: median 67 - 68 (range 44-82); Disease status: T1b – T3a N0M0.	457	1. Conventional fractionation: 74 Gy in 37 fractions at 2 Gy per fraction (153 men). 2. Hypofractionation: 60 Gy in 20 fractions at 3 Gy per fraction (153 men). 3. Hypofractionation: 57 Gy in 19 fractions at 3 Gy per fraction (151 men).	Acute bowel toxicity; Acute bladder toxicity; Late bowel toxicity; Late bladder toxicity; Sexual dysfunction.	50.5 months.
Conventional radiotherapy v Conformal HD radiotherapy (1 trial)	M. D. Anderson randomized dose-escalation trial (4 papers)	Kuban 2008, 2011; Pollack 2002; Storey 2000.	USA	Dates of enrolment to study: 1993 to 1998; Setting: M. D. Anderson Cancer Center, University of Texas; Median age 69 for each arm; Disease status: T1-T3 N0M0.	305	1. Conventional radiotherapy (150 men): 70 Gy, given in daily 2 Gy fractions. 2. 3D conformal radiotherapy (151 men): 78 Gy, given in daily 2 Gy fractions.	freedom from biochemical or clinical failure; freedom from distant metastasis; overall survival; disease-specific survival; late GI toxicity; late GU toxicity; prostate cancer-related mortality.	Median follow-up of 5 - 8 years.

LD: low dose; HD: high dose.

Appendix 3. Assessment of risk of bias for included randomized trials (please refer to www.cochrane-handbook.org for instructions on how to complete the tables).

Outcomes measured:
a - all cause mortality.
b - cancer related mortality.
c - gastrointestinal and genitourinary toxicity.

Study ID: CHHiP trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random permuted blocks were used
Allocation concealment	Low risk	Independent randomisation was via telephone to the ICR-CTSU.
Blinding of participants and personnel	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Blinding of outcome assessment	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Incomplete outcome data	Low risk	Losses to follow-up are disclosed
Selective reporting	Low risk	Pre-planned analyses.
Other bias	Low risk	No other sources of bias identified.

Study ID: PIVOT trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome	Low risk	After randomization, a central pathologist reviewed the biopsy and radical-prostatectomy specimens, and a

assessment		central laboratory measured PSA.
Incomplete outcome data	Low risk	Losses to follow-up described and were low
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Toxicity outcomes are patient-reported and therefore at high risk of bias.
Incomplete outcome data	High risk	Moderate losses to follow-up, 23% in each group.
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified

Study ID: GETUG 06 Tial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Study ID: Widmark 2011

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No details available.
Allocation concealment	Unclear	No details available.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Unclear	No details available.
Selective reporting	Unclear	No details available.
Other bias	Unclear	No details available.

Study ID: Yeoh trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Low risk	Blocked computer-generated random numbers (Yeoh EE 2003)
Allocation concealment	Unclear risk	Not clear
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Incomplete outcome data	Low risk	Report Kaplan Meier estimates, log-rank test results.
Selective reporting	Low risk	Pre-specified
Other bias	Low risk	Not identified

Study ID: Royal Marsden trial

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".
Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".

Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	High risk	Some cut-off values reporting.
Other bias	Low risk	No other sources of bias identified.

Study ID: Zietman trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	unclear	No clear
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and	High risk	Lack of blinding is likely to poses conceptual risks to

personnel		toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	Unclear	No clear
Other bias	Low	Not identified

Study ID: SPCG-4

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Stratification according to tumor grade and randomization center. The randomization list was computer generated, and the block size was unknown to the investigators
Allocation concealment	Unclear	Not stated
Blinding of participants and personnel	Low	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low	"Blinding to analyst". The pathologists were blinded to patient outcome and assignment. Only the results from the central review are used. Members of the endpoint committee were blinded to patients' group assignment and treatment received." Or, "Blinded evaluation (2005)".
Incomplete outcome data	Low	Losses of follow-up disclose
Selective reporting	Low	Outcomes pre-specified
Other bias	Low	Not other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	The randomization list was computer generated (Bill-Axelson,2002)
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	Outcome assessment was obtained by asking patients to return questionnaire after intervention, from which the blinding of assessor is impossible.

Incomplete outcome data	Low risk	88% and 87% of participants return questionnaires from prostatectomy and watchful waiting, respectively.
Selective reporting	Unclear risk	Study report doesn't make clear if this outcom were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Graversen1990

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	More elderly patients in placebo group
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	High risk	Outcome data incomplete.
Selective reporting	Unclear risk	Not stated
Other bias	High risk	31 stage I and 20 stage II patients were assigned to placebo; 31 stage I and 30 stage II patients were assigned to prostatectomy.

Study ID: Canada trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival, biopsy rate, disease-specific survival.
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival,

		biopsy rate, disease-specific survival.
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk (need further discussion)	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk (need further discussion)	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: MRC RT01

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Incomplete outcome data	Unclear risk	Losses to follow-up are disclosed and appear balanced across groups for other outcomes reported, but we can't adjust for losses to follow-up for overall survival since this outcome isn't formally reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol

Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Adjustment made for losses to follow-up in calculation of the hazard ratios and cumulative proportions reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol
Other bias	Low risk	No other sources of bias identified.

Study ID: Chin 2008

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		

	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.

Study ID: MRC RT01 pilot trial

Risk of bias table for outcome b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design
Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Blinding of outcome assessment	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design

Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified

Study ID: Akakura 2006

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No details given, but may be reported in the earlier design paper
Allocation concealment	Unclear risk	No details given, but may be reported in the earlier design paper
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: Arcangeli 2010

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information

Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risk to the toxicity assessment.
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified
Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information
Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Blinding of outcome assessment	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified

Study ID: Kopper trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low	Follow-up completed in (Kopper 2004)

Selective reporting	Unclear	Not clear which outcomes were pre-specified.
Other bias	Low	No other sources of bias identified

Study ID: Lukka 2005

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect measurement of overall survival.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.

Other bias	Low risk	No other sources of bias identified.

Study ID: Marzi 2009

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	High risk	Losses to follow-up are fairly high and no information is given about the patients lost to follow-up.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Norkus 2009

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	Methods not stated
Allocation concealment	Unclear	Methods not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Incomplete outcome data	Low risk	Low losses to follow-up
Selective reporting	Low risk	The two 2009 papers list the planned endpoints and report the early 12-month findings. It's unlikely that other pre-specified outcomes would be omitted at this stage of the trial.
Other bias	Low risk	No other bias identified

Study ID: Dutch trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	Low risk	Not clear but low risk for mortality
Blinding of outcome assessment	Low risk	Not clear but low risk for mortality
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for the rest outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: M. D. Anderson trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Cut-points may have been chosen based on significance.
Other bias	Low risk	No other sources of bias identified.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 – 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 – 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 – 7 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8 – 10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7 – 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9 – 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12 – 14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 – 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12 – 21
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Comparative Efficacy and Safety of Treatments for Localized Prostate Cancer: An Application of Network Meta-Analysis.

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COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR LOCALIZED PROSTATE CANCER: AN APPLICATION OF NETWORK META-ANALYSIS

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Word count: 2925

Key words: *Prostate cancer; Treatment; Randomised trials; Systematic review; Meta-analysis.*

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ABSTRACT

Context: There is ongoing uncertainty about the optimal management of patients with localized prostate cancer.

Objective: To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Design: Systematic review with Bayesian network meta-analysis to estimate comparative odds ratios, and a score (0-100%) that, for a given outcome, reflects average rank order of superiority of each treatment compared against all others, using the surface under the cumulative ranking curve (SUCRA) statistic.

Data sources: Electronic searches of Medline without language restriction.

Study selection: Randomized trials comparing the efficacy and safety of different primary treatments (48 papers from 21 randomized trials included 7,350 men).

Data extraction: Two reviewers independently extracted data and assessed risk of bias.

Results: Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU). There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality after 5 years. Cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiotherapy (SUCRA: 99% and 77% for gastrointestinal and genitourinary toxicity, respectively).

Conclusions: The limited available evidence suggests that different treatments may be optimal for different efficacy and safety outcomes. These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes. More trial evidence is required to reduce uncertainty. Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

ARTICLE SUMMARY

Article focus

- To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Key messages

- Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU).
- There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Different treatments may be optimal for different efficacy and safety outcomes.
- Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

Strengths and limitations of this study

- Network meta-analysis enabled us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).
- This network meta-analysis only included randomised controlled trials and the risk of bias in each included study had been comprehensively assessed by using the Cochrane Collaboration's Risk of Bias tool, which strengthens the robustness of evidence synthesis.
- The number of available randomized controlled trials was small which could be a limitation of the study.

BACKGROUND

Prostate cancer is a worldwide major public health issue.[1] Nearly 75% of diagnosed cases, however, occur in developed countries,[2] where it is typically the most common cancer in men.[3-4] In the UK, about 40,000 men are diagnosed with prostate cancer and 10,000 men die from it every year.[3] In the US, there are 240,000 new diagnoses of prostate cancer, with 34,000 associated deaths every year.[5] Most patients with prostate cancers are diagnosed at an early stage,[6-7] and many diagnoses are made in asymptomatic men.[8-10]

The main treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy and observational management (that is, regular testing of clinical, biochemical or radiological markers or as prompted by occurrence of symptoms).[8] Because some of these treatments are associated with substantial risk of side effects, it is important to try to resolve the current uncertainty about the optimal treatment options.

Some randomized trials have compared the efficacy and safety of two or three treatments. For example, the SPCG-4 trial in Europe and the PIVOT study in the US compared radical prostatectomy with observational management.[11-12] The UK Prostate Testing for Cancer and Treatment (ProtecT) trial is evaluating treatment effectiveness of active monitoring, radical prostatectomy and external beam radiotherapy for clinically localized prostate cancer in men aged 50-69 years identified through population-based PSA testing.[13] The recruitment phase for the ProtecT trial, which began in 1999, has been completed, but outcomes will not be available until a minimum follow-up period has been accrued.

It is unlikely that any single trial will compare all available treatment options. We therefore performed a network meta-analysis based on a systematic review of completed randomized trials comparing different interventions for patients with localized prostate cancer. The network meta-analysis allowed us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).[14-16] Our objective was to apply the established methodology used in network meta-analysis to an area of clinical practice where no such previous studies existed. In doing so, our aims were to summarise existing evidence; 'map out' current gaps in comparative evidence to help motivate the design and conduct of future comparative studies; and develop an approach 'primed' for subsequent updating and incorporation of future trial evidence.

METHODS

Eligibility criteria

We sought completed randomized trials in men with localized prostate cancer that had compared two or more of the following interventions (as primary treatment, with or without the same adjuvant therapy in all arms): prostatectomy; radiotherapy including brachytherapy; cryotherapy; high-intensity focused ultrasound (HIFU) and observational management. Observational management is characterized by testing of clinical, biochemical or radiological markers of disease progression at regular intervals (typically every 6 months) or as prompted by the occurrence of new symptoms, possibly leading to either radical or palliative treatment. We opted to use the term 'observational management' in preference to active surveillance or active monitoring because the latter terms typically aim to keep men in a window of curability so that only those who require it undergo radical treatment.

Eligible trials had to have reported any of the following efficacy and safety outcomes: all-cause mortality, prostate cancer mortality and gastrointestinal or genitourinary toxicity. Studies comparing treatment combinations or sequences (e.g. per protocol management by surgery with subsequent radiotherapy) were excluded.

Identification of studies

We adopted the search strategy of a systematic review that supported the development of clinical guidelines on the diagnosis and treatment of prostate cancer by the UK's National Institute for Health and Clinical Excellence (NICE) in 2008.[8] Studies had been identified by searching Medline (in 2006) and scanning reference list of papers. We retrieved all relevant randomized trials identified in the NICE guideline and implemented the same search strategies to update the collection of trials. We restricted the search to the period from January 2005 to September 2012.

No language limits were placed on the searches (see Appendix 1 for full search strategies).

Data extraction

Two reviewers (TX and RT) independently screened all the titles and abstracts of the studies retrieved by the searches for potentially eligible trials, and then independently assessed the full articles of these trials to confirm whether they met the eligibility criteria. The results were checked and discussed by TX and RT to agree upon a final list of included studies. Using a structured and piloted data collection form, all relevant data in each included paper were extracted by two reviewers independently (TX and RT/YW). The data extracted were cross-checked and unresolved discrepancies were referred to a third reviewer; where necessary, problems were discussed in a panel meeting (TX, RT, YW, JH and GL) whilst DN acted as a clinical expert advisor.

For each included study, we extracted characteristics of participants and interventions, outcomes reported and collected, sample size (randomized and analysed) in each arm, numerical results, losses to follow-up and details of patients excluded from the analyses.[17] To inform the appropriateness of including studies in the meta-analysis and facilitate assessment of the strength of the evidence we assessed the risk of bias in each included study using The Cochrane Collaboration's Risk of Bias tool.[18] Two reviewers (TX and either RT or YW) completed this independently and agreed on final assessments. The tool assesses risk of bias arising from inadequacies in processes of generation of the random allocation sequence, concealment of the allocation sequence and blinding, and from incomplete outcome data and selective outcome reporting.

Outcomes

We analysed all-cause mortality and cancer-related mortality at 5 years, late gastrointestinal and late genitourinary toxicity at 3 years. The choice of these follow-up times was pragmatic, as they were the ones most frequently reported in the included trials. Once these time points had been chosen, we extracted the outcome data from the time nearest to these targeted measurement times. Late gastrointestinal and late genitourinary toxicity were defined as scores ≥ 2 measured by the Radiation Therapy Oncology Group (RTOG) questionnaire scale by 3 years follow-up.[19] We have not encompassed biochemical or clinical failure as operational definitions of either of those outcomes tend to be specific to different radical treatment modalities.[20]

Statistical analyses

Initially, we compared each pair of treatments using direct evidence alone, for each outcome. Separate meta-analyses were performed for each pair-wise comparison of interventions: a random-effects model was fitted within each comparison,[21] with a common between-study heterogeneity variance assumed across comparisons to allow for heterogeneity even when only a single study was available. Results are reported as odds ratios with 95% confidence intervals, for every comparison evaluated directly in one or more studies.

Next, we fitted a network meta-analysis model for each outcome separately,[22] combining direct evidence for each comparison (e.g. from studies comparing interventions A with B) with indirect evidence (e.g. from studies comparing A with C and studies comparing B with C), for all pair-wise comparisons simultaneously. The model accounts explicitly for the binary nature of each outcome using a binomial likelihood function; allows for heterogeneity of treatment effects between trials of the

same comparison (assuming the same amount of heterogeneity for each comparison, irrespective of how many trials address it); and enforces an underlying relationship between direct and indirect evidence for a particular comparison, assuming these are consistent between the two sources. For each 'loop' of treatment comparisons from three or more independent sources and for each outcome, we computed the difference between estimates from direct and indirect evidence on the log odds ratio scale.[100] This provides a measure of inconsistency between the different sources. We did not implement more sophisticated methods for testing or adjusting for inconsistency, due to the small number of loops in the network.

Results are reported as odds ratios with 95% credible intervals, for all pair-wise comparisons of interventions. All analyses were performed within a Bayesian framework, using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[23] Informative prior distributions were used for the heterogeneity variance, from a published set of distributions for heterogeneity expected in meta-analyses examining particular intervention and outcome types,[24] since heterogeneity is imprecisely estimated when the number of studies is small. For all-cause mortality, a log-normal (-3.93, 1.51^2) distribution was used. For gastrointestinal and genitourinary toxicity, a log-normal (-2.01, 1.64^2) distribution was used. For cancer-related mortality, a log-normal (-2.89, 1.91^2) distribution was used. Vague N (0, 10^4) priors were used for all other model parameters. Results were based on 100,000 iterations, following a burn-in of 20,000 iterations.

For each outcome, we estimated the probability that each intervention is superior to all others, the second best, the third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain. These ranking probabilities were used to calculate a summary numerical value: the SUCRA (surface under the cumulative ranking curve).[25] SUCRA values are expressed as percentages; if an

intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%. If all interventions are equivalent, we would expect all SUCRA values to be near 50%. We also report the median ranks and 95% credible intervals for each intervention.

RESULTS

Included studies and interventions

The NICE systematic review[8] had identified 20 reports relating to 14 randomized trials.[26-45] Our updated searches retrieved 1,740 studies and identified 39 reports of relevant randomized trials, of which 30 had not been included in the NICE review (Figure 1).[46-75] One of these reports was the sole report of a trial providing data only on acute toxicity,[40] one paper reported only clinical failure,[38] and one paper reported biochemical failure, biochemical disease-free survival and quality of life;[56] these 3 studies were then excluded since they did not report the outcomes of interest to us. In addition to the remaining 47 full papers from peer-reviewed journals, we identified and included in the analysis data from a conference abstract, describing a randomized trial comparing external beam radiotherapy versus watchful waiting,[76] and reporting data on long term mortality not previously reported in full-text related publications.[77-78]

Our searches also identified 16 relevant systematic reviews.[79-94] We scrutinized the reference lists of all these as well as any further systematic reviews identified by the NICE review, and found no further relevant randomized trials.

The 48 identified reports described 21 randomized trials comparing the effectiveness of different treatments for localized prostate cancer.[26-37, 39, 41-55, 57-76] Seventeen trials reported all-cause mortality, 16 trials reported cancer-related mortality, 16 trials reported gastrointestinal (GI) toxicity, 15 trials reported genitourinary (GU) toxicity. The characteristics of included studies are summarized in Appendix 2.

The risk of bias assessments for the included trials are illustrated in Figure 2. Most of the evidence was of moderate to good quality. About half of the studies did not report

adequate information about allocation sequence generation and allocation sequence concealment. Unblinded designs were used in all trials included; we judged this unlikely to cause bias for objectively-measured outcomes such as mortality, but generate bias in the reporting and assessment of patient-reported toxicity outcomes. The small number of studies precluded the investigation of potential reporting biases across studies (for example using funnel plots). Our searches were appropriate, but the possibility of publication bias cannot be excluded. It is unclear, however, whether reporting biases would tend to favour any particular treatment (see Appendix 3 for details of bias assessments for included trials).

We categorized the interventions into the following eight categories: observational management; prostatectomy; conventional radiotherapy (refers to two dimensional external beam radiation therapy); conventional radiotherapy- hypofractionated (refers to less than 20 fractions); conformal low dose (LD) radiotherapy (refers to less than 68 Gy); conformal high dose (HD) radiotherapy (refers to more than 74 Gy); conformal LD radiotherapy-hypofractionated; and cryotherapy. Twenty trials had two intervention arms. One trial compared three interventions;[54] since two of the three interventions were very similar and both met our definition of conformal LD radiotherapy-hypofractionated, we combined the data from these two arms and regarded the trial as a two-treatment comparison (conformal LD radiotherapy-hypofractionated versus conformal HD radiotherapy). None of the reviewed studied assessed brachytherapy and HIFU. Figure 3 illustrates the full network of comparisons. There were two closed loops of comparisons, one connecting prostatectomy, observational management and radiotherapy modalities; and the other connecting different radiotherapy modalities.[100] No inconsistency was detected in our estimates of the difference between direct and indirect evidence; however, precision was very low. Cryotherapy only had a single link to the network.

All-cause mortality

All-cause mortality was reported in 17 trials, covering all the eight interventions of interest. There is no evidence of superiority of any treatment for all-cause mortality. For each pairwise comparison of interventions, the 95% intervals for odds ratios were wide and included 1. The lower-left triangle of results in Table 1 presents odds ratios estimated from direct evidence alone, while the upper-right triangle of results presents odds ratios estimated from the network meta-analysis. The intervals are slightly narrower when based on indirect as well as direct evidence rather than direct evidence alone. The SUCRA values presented in Table 2 summarize the ranking information for all interventions. With respect to all-cause mortality, the highest SUCRA values are 69% for conformal LD radiotehrapy-hypofractionated and 63% for conformal HD radiotherapy, indicating that these are most likely to be among the best treatments for this outcome. However, there is very high uncertainty in the rankings of the interventions, as indicated by wide 95% credible intervals.

Cancer-related mortality

Cancer-related mortality was reported in 16 trials, covering eight of the interventions. This was a rare outcome in most treatment groups, as expected for patients with localized prostate cancer with a 5 year end point. Odds ratio estimates had wide 95% credible intervals, particularly in comparisons for which only indirect evidence was available, and there was no evidence of superiority for any of the comparator treatments (Table 3). Based on direct comparisons alone, conformal HD radiotherapy was superior to conventional radiotherapy [odds ratio 0.21 (95% interval 0.03, 0.97)] and prostatectomy was superior to observational management [odds ratio 0.60 (95% interval 0.37, 0.98)].

Gastrointestinal and genitourinary toxicity

Late gastrointestinal toxicity was reported in 16 trials and late genitourinary toxicity was reported in 15 trials. There was evidence that cryotherapy resulted in fewer adverse gastrointestinal events than radiotherapy treatments (estimated odds ratios comparing cryotherapy against the five radiotherapy options ranged from 0.12 to 0.24, whilst all but one of the respective 95% credible intervals excluded 1). The SUCRA value of 99% for cryotherapy and the median rank of 1 (95% interval 1, 2) suggest that cryotherapy is almost certainly superior among the six treatments included in the network meta-analysis in relation to adverse gastrointestinal events (Table 2 and 4). There was also evidence that gastrointestinal toxicity was more likely with conformal HD radiotherapy than with conformal LD radiotherapy. Interpretation of such findings for toxicity should be more cautious than for the other outcomes, due to a concern that lack of blinding could have led to a risk of detection bias. For genitourinary toxicity, there was no evidence favouring one intervention over another (Table 5), although cryotherapy tended to receive better rankings than the five radiotherapy treatments (Table 2), and the odds ratio estimates favour cryotherapy, but the 95% intervals all included 1.

Table 1. All-cause mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.79 (0.61,1.02)	0.84 (0.48,1.57)	0.72 (0.37,1.49)	0.73 (0.44,1.26)	0.70 (0.40,1.28)	0.53 (0.10,2.88)	0.76 (0.28,1.98)
Prostatectomy	[3] 0.80 (0.61,1.06)		1.06 (0.60,2.02)	0.91 (0.46,1.90)	0.92 (0.54,1.64)	0.88 (0.49,1.66)	0.67 (0.12,3.65)	0.96 (0.36,2.56)
Conventional radiotherapy	-	[1] 1.34 (0.55,3.24)		0.85 (0.59,1.24)	0.86 (0.55,1.35)	0.82 (0.51,1.35)	0.62 (0.11,3.21)	0.90 (0.41,1.89)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.85 (0.59,1.24)		1.01 (0.56,1.80)	0.97 (0.53,1.78)	0.73 (0.13,3.86)	1.05 (0.44,2.42)
Conformal LD radiotherapy	[1] 0.66 (0.35,1.21)	-	[1] 0.92 (0.50,1.72)	-		0.96 (0.72,1.29)	0.72 (0.14,3.51)	1.04 (0.42,2.49)
Conformal HD radiotherapy	-	-	[1] 0.87 (0.39,1.92)	-	[4] 0.95 (0.70,1.31)		0.74 (0.14,3.61)	1.09 (0.43,2.64)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.78 (0.13,4.25)		1.47 (0.22,9.40)
Cryotherapy	-	-	[2] 0.90 (0.41,2.02)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.08).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.07).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 2. Ranking of interventions with respect to all-cause and cancer-related mortality, adverse gastrointestinal and genitourinary events: SUCRA (Surface Under the Cumulative RAnking curve) values and median ranks (with 95% intervals).†

Intervention	All-cause mortality		Cancer-related mortality		Adverse gastrointestinal events		Adverse genitourinary events	
	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)
Observational management	18%	7 (2, 8)	30%	6 (3, 8)	-	-	-	-
Prostatectomy	49%	5 (1, 7)	64%	4 (1, 7)	-	-	-	-
Conventional radiotherapy	35%	6 (2, 8)	16%	7 (4, 8)	43%	4 (2, 6)	51%	3 (1, 6)
Conventional radiotherapy-hypofractionated	58%	4 (1, 8)	44%	5 (1, 8)	42%	4 (1, 6)	50%	3 (1, 6)
Conformal LD radiotherapy	57%	4 (1, 7)	61%	4 (2, 7)	67%	2 (2, 4)	66%	3 (1, 5)
Conformal HD radiotherapy	63%	3 (1, 7)	75%	2 (1, 6)	19%	5 (3, 6)	30%	5 (2, 6)
Conformal LD radiotherapy-hypofractionated	69%	1 (1, 8)	85%	1 (1, 8)	30%	5 (2, 6)	26%	5 (1, 6)
Cryotherapy	50%	4 (1, 8)	24%	7 (2, 8)	99%	1 (1, 2)	77%	1 (1, 6)

† The surface under the cumulative ranking curve (SUCRA) value is a numerical summary of the estimated probabilities that each treatment is the best, second best, third best (and so on) for that particular outcome. Higher values indicate higher rankings compared with other treatments. For example, for cryotherapy, the high SUCRA value of 99% and median rank of 1 for adverse gastrointestinal events shows that cryotherapy is expected to be superior with respect to this outcome.

LD: low dose; HD: high dose.

Table 3. Prostate cancer-caused mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.63 (0.40,1.02)	1.39 (0.49,4.16)	0.90 (0.24,3.42)	0.63 (0.29,1.31)	0.52 (0.22,1.19)	0.13 (0.00*,3.59)	1.37 (0.28,6.89)
Prostatectomy	[2] 0.60 (0.37,0.98)		2.20 (0.82,6.37)	1.42 (0.39,5.19)	0.99 (0.42,2.26)	0.83 (0.32,2.00)	0.20 (0.00*,6.07)	2.16 (0.46,10.9)
Conventional radiotherapy	-	[1] 1.65 (0.53,5.44)		0.64 (0.29,1.41)	0.45 (0.14,1.30)	0.38 (0.12,1.06)	0.09 (0.00*,3.08)	0.98 (0.28,3.35)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.65 (0.28,1.43)		0.70 (0.18,2.65)	0.59 (0.15,2.16)	0.14 (0.00*,5.08)	1.51 (0.36,6.54)
Conformal LD radiotherapy	[1] 0.70 (0.31,1.57)	-	-	-		0.84 (0.52,1.30)	0.20 (0.00*,5.73)	2.20 (0.44,11.4)
Conformal HD radiotherapy	-	-	[1] 0.21 (0.03,0.97)	-	[5] 0.86 (0.53,1.37)		0.25 (0.00*,6.79)	2.61 (0.53,14.1)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.22 (0.00*,6.85)		11.2 (0.24,5542)
Cryotherapy	-	-	[2] 0.96 (0.27,3.46)	-	-	-	-	

LD: low dose; HD: high dose.

* Odds ratio was less than 0.005.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.31).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.29).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 4. Adverse gastrointestinal events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 0.84 (0.33,1.88)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.01 (0.19,5.29)	0.72 (0.29,1.59)	1.42 (0.57,3.39)	1.26 (0.35,4.30)	0.17 (0.04,0.51)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.00 (0.22,4.56)		0.70 (0.11,4.37)	1.40 (0.21,9.02)	1.24 (0.15,9.76)	0.17 (0.02,1.19)
Conformal LD radiotherapy	-	-	[2] 0.46 (0.17,1.16)	-		1.98 (1.18,3.59)	1.77 (0.63,5.11)	0.24 (0.05,0.96)
Conformal HD radiotherapy	-	-	[1] 2.66 (0.85,8.62)	-	[5] 1.73 (1.07,2.97)		0.89 (0.36,2.15)	0.12 (0.02,0.48)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[3] 0.89 (0.39,1.96)		0.14 (0.02,0.70)
Cryotherapy	-	-	[2] 0.18 (0.05,0.50)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.14 (95% interval 0.01 to 0.97).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.24 (95% interval 0.02 to 1.23).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 5. Adverse genitourinary events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 2.27 (1.34,3.90)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.00 (0.34,2.90)	0.91 (0.54,1.51)	1.19 (0.69,2.11)	1.41 (0.49,4.07)	0.66 (0.22,2.00)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.01 (0.34,3.00)		0.90 (0.27,2.97)	1.19 (0.36,4.04)	1.41 (0.31,6.44)	0.66 (0.14,3.04)
Conformal LD radiotherapy	-	-	[2] 0.80 (0.43,1.51)	-		1.32 (0.97,1.86)	1.56 (0.61,4.09)	0.73 (0.21,2.52)
Conformal HD radiotherapy	-	-	[1] 1.53 (0.62,3.82)	-	[5] 1.28 (0.93,1.86)		1.18 (0.48,2.92)	0.55 (0.16,1.91)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 1.17 (0.48,2.91)		0.47 (0.10,2.15)
Cryotherapy	-	-	[2] 0.68 (0.22,2.03)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.003 to 0.29).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.002 to 0.26).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

DISCUSSION

Using network meta-analysis, we were able to combine simultaneously all relevant evidence on treating patients with localized prostate cancer, even in the absence of direct comparative evidence for some treatment pairs, encompassing four efficacy and safety outcomes. Based on data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes for localized prostate cancer, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.

Assumptions of consistency between direct and indirect evidence were tested to justify the joint synthesis of all studies; however, these tests had little power due to the relatively small number of trials available in most direct comparisons. Instead we must rely on judgements about the similarity of studies included in the analysis in aspects such as patient groups, outcome measures and study methodology. Although we defined the population of interest as patients with localized prostate cancer, there was heterogeneity between individual study populations in terms of the severity of disease. Some of the trials were conducted several decades ago, when surgery and radiology techniques may have been different, and we observed that stage migration has occurred in men diagnosed with prostate cancer, due to emerging bio-marker and image technologies. Furthermore, some of the trials used adjuvant therapy, although this was applied in all the arms within the trial.

Two further limitations warrant mention. Literature searches were completed in September of 2012. However, the results of one of the most important randomized trials – ProtecT study[13] – has not been published so far, and to our knowledge there are no other new relevant RCTs have been reported after this systematic review. Our choices of measurements may have favoured some treatments over others: for example the RTOG scale had been used to define the late gastrointestinal and late genitourinary toxicity in the included studies, but it

does not measure incontinence which could be the most common adverse event post-prostatectomy.[102]

Methodologically, we used informative prior distributions based on external evidence for heterogeneity variances, to increase precision in their estimation and improve estimation of treatment differences. Data-based informative priors have previously been considered by Lu & Ades,[101] who used them for the between-study correlation structure. To our knowledge, our paper is the first application of network meta-analysis incorporating data-based informative priors for between-study heterogeneity.

Our findings have implications for research funding prioritisation and study design; and for clinical practice. The study identified particular 'weak links' in the network of comparative treatment options, which might be prioritized for future investment in randomized controlled trials. This is particularly the case for studies comparing HIFU (which currently is bereft of any comparative evidence) or brachytherapy against other treatment options, and also for trials examining the comparative efficacy and safety of prostatecotmy versus conformal radiotherapy modalities. For clinicians, and for men diagnosed with prostate cancer, our findings highlight that the optimal treatment options may be different in respect of different outcomes: patients need to be given appropriate information about the uncertainty surrounding treatment choice currently, and be allowed to opt for 'trade-offs' between efficacy and safety outcomes as they judge appropriately.[95] Observational studies have consistently shown that radical prostatectomy has better cause-specific mortality outcomes compared with radiotherapy.[96-99,103]

In conclusion, clinically important information from high quality randomized trials is still needed to inform decision making regarding primary treatment options for men with localized prostate cancer. The findings of this study highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs

between multiple outcomes. The upcoming results of the ProtecT study,[13] which is evaluating effectiveness of multiple therapies in men with PSA-detected localized prostate cancer, together with other treatment studies in progress, will hopefully contribute to the evidence base. It is however unlikely that evidential uncertainty about all relevant and important outcomes will be resolved by these trials, and an updated network meta-analysis incorporating new evidence may be useful to synthesize the new with the existing evidence. We demonstrate a high degree of uncertainty about treatment superiority in the management of localized prostate cancer. Clinicians and patients need to grapple with this uncertainty in the context of shared-decision making.

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Figure Legends

Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis

Figure 2. Risk of bias assessments for the included randomized trials

Figure 3. Network of comparisons of treatments for localized prostate cancer showing numbers of trials in which each pairwise comparison had been made

COMPARATIVE EFFICACY AND SAFETY OF TREATMENTS FOR LOCALIZED PROSTATE CANCER: AN APPLICATION OF NETWORK META-ANALYSIS

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ABSTRACT

Context: There is ongoing uncertainty about the optimal management of patients with localized prostate cancer.

Objective: To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Design: Systematic review with Bayesian network meta-analysis to estimate comparative odds ratios, and a score (0-100%) that, for a given outcome, reflects average rank order of superiority of each treatment compared against all others, using the surface under the cumulative ranking curve (SUCRA) statistic.

Data sources: Electronic searches of Medline without language restriction.

Study selection: Randomized trials comparing the efficacy and safety of different primary treatments (48 papers from 21 randomized trials included 7,350 men).

Data extraction: Two reviewers independently extracted data and assessed risk of bias.

Results: Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU). There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality after 5 years. Cryotherapy was associated with less gastrointestinal and genitourinary toxicity than radiotherapy (SUCRA: 99% and 77% for gastrointestinal and genitourinary toxicity, respectively).

Conclusions: The limited available evidence suggests that different treatments may be optimal for different efficacy and safety outcomes. These findings highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs between different outcomes. More trial evidence is required to reduce uncertainty. Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

ARTICLE SUMMARY

Article focus

- To evaluate the comparative efficacy and safety of different treatments for patients with localized prostate cancer.

Key messages

- Comparative efficacy and safety evidence was available for prostatectomy, external beam radiotherapy (different types and regimens), observational management and cryotherapy, but not high intensity focused ultrasound (HIFU).
- There was no evidence of superiority for any of the compared treatments in respect of all-cause mortality. Different treatments may be optimal for different efficacy and safety outcomes.
- Network meta-analysis may be useful to optimise the power of evidence synthesis studies once data from new randomised controlled studies in this field are published in the future.

Strengths and limitations of this study

- Network meta-analysis enabled us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).
- This network meta-analysis only included randomised controlled trials and the risk of bias in each included study had been comprehensively assessed by using the Cochrane Collaboration's Risk of Bias tool, which strengthens the robustness of evidence synthesis.
- The number of available randomized controlled trials was small which could be a limitation of the study.

BACKGROUND

Prostate cancer is a worldwide major public health issue.[1] Nearly 75% of diagnosed cases, however, occur in developed countries,[2] where it is typically the most common cancer in men.[3-4] In the UK, about 40,000 men are diagnosed with prostate cancer and 10,000 men die from it every year.[3] In the US, there are 240,000 new diagnoses of prostate cancer, with 34,000 associated deaths every year.[5] Most patients with prostate cancers are diagnosed at an early stage,[6-7] and many diagnoses are made in asymptomatic men.[8-10]

The main treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy and observational management (that is, regular testing of clinical, biochemical or radiological markers or as prompted by occurrence of symptoms).[8] Because some of these treatments are associated with substantial risk of side effects, it is important to try to resolve the current uncertainty about the optimal treatment options.

Some randomized trials have compared the efficacy and safety of two or three treatments. For example, the SPCG-4 trial in Europe and the PIVOT study in the US compared radical prostatectomy with observational management.[11-12] The UK Prostate Testing for Cancer and Treatment (ProtecT) trial is evaluating treatment effectiveness of active monitoring, radical prostatectomy and external beam radiotherapy for clinically localized prostate cancer in men aged 50-69 years identified through population-based PSA testing.[13] The recruitment phase for the ProtecT trial, which began in 1999, has been completed, but outcomes will not be available until a minimum follow-up period has been accrued.

It is unlikely that any single trial will compare all available treatment options. We therefore performed a network meta-analysis based on a systematic review of completed randomized trials comparing different interventions for patients with localized prostate cancer. The network meta-analysis allowed us to integrate evidence from both direct comparisons (treatments compared head-to-head within a randomized trial) and indirect comparisons (treatments compared by combining the results of randomized trials with common comparators).[14-16] Our objective was to apply the established methodology used in network meta-analysis to an area of clinical practice where no such previous studies existed. In doing so, our aims were to summarise existing evidence; 'map out' current gaps in comparative evidence to help motivate the design and conduct of future comparative studies; and develop an approach 'primed' for subsequent updating and incorporation of future trial evidence.

METHODS

Eligibility criteria

We sought completed randomized trials in men with localized prostate cancer that had compared two or more of the following interventions (as primary treatment, with or without the same adjuvant therapy in all arms): prostatectomy; radiotherapy including brachytherapy; cryotherapy; high-intensity focused ultrasound (HIFU) and observational management. Observational management is characterized by testing of clinical, biochemical or radiological markers of disease progression at regular intervals (typically every 6 months) or as prompted by the occurrence of new symptoms, possibly leading to either radical or palliative treatment. We opted to use the term 'observational management' in preference to active surveillance or active monitoring because the latter terms typically aim to keep men in a window of curability so that only those who require it undergo radical treatment.

Eligible trials had to have reported any of the following efficacy and safety outcomes: all-cause mortality, prostate cancer mortality and gastrointestinal or genitourinary toxicity. Studies comparing treatment combinations or sequences (e.g. per protocol management by surgery with subsequent radiotherapy) were excluded.

Identification of studies

We adopted the search strategy of a systematic review that supported the development of clinical guidelines on the diagnosis and treatment of prostate cancer by the UK's National Institute for Health and Clinical Excellence (NICE) in 2008.[8] Studies had been identified by searching Medline (in 2006) and scanning reference list of papers. We retrieved all relevant randomized trials identified in the NICE guideline and implemented the same search strategies to update the collection of trials. We restricted the search to the period from January 2005 to September 2012.

No language limits were placed on the searches (see Appendix 1 for full search strategies).

Data extraction

Two reviewers (TX and RT) independently screened all the titles and abstracts of the studies retrieved by the searches for potentially eligible trials, and then independently assessed the full articles of these trials to confirm whether they met the eligibility criteria. The results were checked and discussed by TX and RT to agree upon a final list of included studies. Using a structured and piloted data collection form, all relevant data in each included paper were extracted by two reviewers independently (TX and RT/YW). The data extracted were cross-checked and unresolved discrepancies were referred to a third reviewer; where necessary, problems were discussed in a panel meeting (TX, RT, YW, JH and GL) whilst DN acted as a clinical expert advisor.

For each included study, we extracted characteristics of participants and interventions, outcomes reported and collected, sample size (randomized and analysed) in each arm, numerical results, losses to follow-up and details of patients excluded from the analyses.[17] To inform the appropriateness of including studies in the meta-analysis and facilitate assessment of the strength of the evidence we assessed the risk of bias in each included study using The Cochrane Collaboration's Risk of Bias tool.[18] Two reviewers (TX and either RT or YW) completed this independently and agreed on final assessments. The tool assesses risk of bias arising from inadequacies in processes of generation of the random allocation sequence, concealment of the allocation sequence and blinding, and from incomplete outcome data and selective outcome reporting.

Outcomes

We analysed all-cause mortality and cancer-related mortality at 5 years, late gastrointestinal and late genitourinary toxicity at 3 years. The choice of these follow-up times was pragmatic, as they were the ones most frequently reported in the included trials. Once these time points had been chosen, we extracted the outcome data from the time nearest to these targeted measurement times. Late gastrointestinal and late genitourinary toxicity were defined as scores ≥ 2 measured by the Radiation Therapy Oncology Group (RTOG) questionnaire scale by 3 years follow-up.[19] We have not encompassed biochemical or clinical failure as operational definitions of either of those outcomes tend to be specific to different radical treatment modalities.[20]

Statistical analyses

Initially, we compared each pair of treatments using direct evidence alone, for each outcome. Separate meta-analyses were performed for each pair-wise comparison of interventions: a random-effects model was fitted within each comparison,[21] with a common between-study heterogeneity variance assumed across comparisons to allow for heterogeneity even when only a single study was available. Results are reported as odds ratios with 95% confidence intervals, for every comparison evaluated directly in one or more studies.

Next, we fitted a network meta-analysis model for each outcome separately,[22] combining direct evidence for each comparison (e.g. from studies comparing interventions A with B) with indirect evidence (e.g. from studies comparing A with C and studies comparing B with C), for all pair-wise comparisons simultaneously. The model accounts explicitly for the binary nature of each outcome using a binomial likelihood function; allows for heterogeneity of treatment effects between trials of the

same comparison (assuming the same amount of heterogeneity for each comparison, irrespective of how many trials address it); and enforces an underlying relationship between direct and indirect evidence for a particular comparison, assuming these are consistent between the two sources. For each 'loop' of treatment comparisons from three or more independent sources and for each outcome, we computed the difference between estimates from direct and indirect evidence on the log odds ratio scale.[100] This provides a measure of inconsistency between the different sources. We did not implement more sophisticated methods for testing or adjusting for inconsistency, due to the small number of loops in the network.

Results are reported as odds ratios with 95% credible intervals, for all pair-wise comparisons of interventions. All analyses were performed within a Bayesian framework, using Markov chain Monte Carlo methods in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[23] Informative prior distributions were used for the heterogeneity variance, from a published set of distributions for heterogeneity expected in meta-analyses examining particular intervention and outcome types,[24] since heterogeneity is imprecisely estimated when the number of studies is small. For all-cause mortality, a log-normal (-3.93, 1.51^2) distribution was used. For gastrointestinal and genitourinary toxicity, a log-normal (-2.01, 1.64^2) distribution was used. For cancer-related mortality, a log-normal (-2.89, 1.91^2) distribution was used. Vague N (0, 10^4) priors were used for all other model parameters. Results were based on 100,000 iterations, following a burn-in of 20,000 iterations.

For each outcome, we estimated the probability that each intervention is superior to all others, the second best, the third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain. These ranking probabilities were used to calculate a summary numerical value: the SUCRA (surface under the cumulative ranking curve).[25] SUCRA values are expressed as percentages; if an

intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%. If all interventions are equivalent, we would expect all SUCRA values to be near 50%. We also report the median ranks and 95% credible intervals for each intervention.

RESULTS

Included studies and interventions

The NICE systematic review[8] had identified 20 reports relating to 14 randomized trials.[26-45] Our updated searches retrieved 1,740 studies and identified 39 reports of relevant randomized trials, of which 30 had not been included in the NICE review (Figure 1).[46-75] One of these reports was the sole report of a trial providing data only on acute toxicity,[40] one paper reported only clinical failure,[38] and one paper reported biochemical failure, biochemical disease-free survival and quality of life;[56] these 3 studies were then excluded since they did not report the outcomes of interest to us. In addition to the remaining 47 full papers from peer-reviewed journals, we identified and included in the analysis data from a conference abstract, describing a randomized trial comparing external beam radiotherapy versus watchful waiting,[76] and reporting data on long term mortality not previously reported in full-text related publications.[77-78]

Our searches also identified 16 relevant systematic reviews.[79-94] We scrutinized the reference lists of all these as well as any further systematic reviews identified by the NICE review, and found no further relevant randomized trials.

The 48 identified reports described 21 randomized trials comparing the effectiveness of different treatments for localized prostate cancer.[26-37, 39, 41-55, 57-76] Seventeen trials reported all-cause mortality, 16 trials reported cancer-related mortality, 16 trials reported gastrointestinal (GI) toxicity, 15 trials reported genitourinary (GU) toxicity. The characteristics of included studies are summarized in Appendix 2.

The risk of bias assessments for the included trials are illustrated in Figure 2. Most of the evidence was of moderate to good quality. About half of the studies did not report

adequate information about allocation sequence generation and allocation sequence concealment. Unblinded designs were used in all trials included; we judged this unlikely to cause bias for objectively-measured outcomes such as mortality, but generate bias in the reporting and assessment of patient-reported toxicity outcomes. The small number of studies precluded the investigation of potential reporting biases across studies (for example using funnel plots). Our searches were appropriate, but the possibility of publication bias cannot be excluded. It is unclear, however, whether reporting biases would tend to favour any particular treatment (see Appendix 3 for details of bias assessments for included trials).

We categorized the interventions into the following eight categories: observational management; prostatectomy; conventional radiotherapy (refers to two dimensional external beam radiation therapy); conventional radiotherapy- hypofractionated (refers to less than 20 fractions); conformal low dose (LD) radiotherapy (refers to less than 68 Gy); conformal high dose (HD) radiotherapy (refers to more than 74 Gy); conformal LD radiotherapy-hypofractionated; and cryotherapy. Twenty trials had two intervention arms. One trial compared three interventions;[54] since two of the three interventions were very similar and both met our definition of conformal LD radiotherapy-hypofractionated, we combined the data from these two arms and regarded the trial as a two-treatment comparison (conformal LD radiotherapy-hypofractionated versus conformal HD radiotherapy). None of the reviewed studied assessed brachytherapy and HIFU. Figure 3 illustrates the full network of comparisons. There were two closed loops of comparisons, one connecting prostatectomy, observational management and radiotherapy modalities; and the other connecting different radiotherapy modalities.[100] No inconsistency was detected in our estimates of the difference between direct and indirect evidence; however, precision was very low. Cryotherapy only had a single link to the network.

All-cause mortality

All-cause mortality was reported in 17 trials, covering all the eight interventions of interest. There is no evidence of superiority of any treatment for all-cause mortality. For each pairwise comparison of interventions, the 95% intervals for odds ratios were wide and included 1. The lower-left triangle of results in Table 1 presents odds ratios estimated from direct evidence alone, while the upper-right triangle of results presents odds ratios estimated from the network meta-analysis. The intervals are slightly narrower when based on indirect as well as direct evidence rather than direct evidence alone. The SUCRA values presented in Table 2 summarize the ranking information for all interventions. With respect to all-cause mortality, the highest SUCRA values are 69% for conformal LD radiotehrapy-hypofractionated and 63% for conformal HD radiotherapy, indicating that these are most likely to be among the best treatments for this outcome. However, there is very high uncertainty in the rankings of the interventions, as indicated by wide 95% credible intervals.

Cancer-related mortality

Cancer-related mortality was reported in 16 trials, covering eight of the interventions. This was a rare outcome in most treatment groups, as expected for patients with localized prostate cancer with a 5 year end point. Odds ratio estimates had wide 95% credible intervals, particularly in comparisons for which only indirect evidence was available, and there was no evidence of superiority for any of the comparator treatments (Table 3). Based on direct comparisons alone, conformal HD radiotherapy was superior to conventional radiotherapy [odds ratio 0.21 (95% interval 0.03, 0.97)] and prostatectomy was superior to observational management [odds ratio 0.60 (95% interval 0.37, 0.98)].

Gastrointestinal and genitourinary toxicity

Late gastrointestinal toxicity was reported in 16 trials and late genitourinary toxicity was reported in 15 trials. There was evidence that cryotherapy resulted in fewer adverse gastrointestinal events than radiotherapy treatments (estimated odds ratios comparing cryotherapy against the five radiotherapy options ranged from 0.12 to 0.24, whilst all but one of the respective 95% credible intervals excluded 1). The SUCRA value of 99% for cryotherapy and the median rank of 1 (95% interval 1, 2) suggest that cryotherapy is almost certainly superior among the six treatments included in the network meta-analysis in relation to adverse gastrointestinal events (Table 2 and 4). There was also evidence that gastrointestinal toxicity was more likely with conformal HD radiotherapy than with conformal LD radiotherapy. Interpretation of such findings for toxicity should be more cautious than for the other outcomes, due to a concern that lack of blinding could have led to a risk of detection bias. For genitourinary toxicity, there was no evidence favouring one intervention over another (Table 5), although cryotherapy tended to receive better rankings than the five radiotherapy treatments (Table 2), and the odds ratio estimates favour cryotherapy, but the 95% intervals all included 1.

Table 1. All-cause mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.79 (0.61,1.02)	0.84 (0.48,1.57)	0.72 (0.37,1.49)	0.73 (0.44,1.26)	0.70 (0.40,1.28)	0.53 (0.10,2.88)	0.76 (0.28,1.98)
Prostatectomy	[3] 0.80 (0.61,1.06)		1.06 (0.60,2.02)	0.91 (0.46,1.90)	0.92 (0.54,1.64)	0.88 (0.49,1.66)	0.67 (0.12,3.65)	0.96 (0.36,2.56)
Conventional radiotherapy	-	[1] 1.34 (0.55,3.24)		0.85 (0.59,1.24)	0.86 (0.55,1.35)	0.82 (0.51,1.35)	0.62 (0.11,3.21)	0.90 (0.41,1.89)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.85 (0.59,1.24)		1.01 (0.56,1.80)	0.97 (0.53,1.78)	0.73 (0.13,3.86)	1.05 (0.44,2.42)
Conformal LD radiotherapy	[1] 0.66 (0.35,1.21)	-	[1] 0.92 (0.50,1.72)	-		0.96 (0.72,1.29)	0.72 (0.14,3.51)	1.04 (0.42,2.49)
Conformal HD radiotherapy	-	-	[1] 0.87 (0.39,1.92)	-	[4] 0.95 (0.70,1.31)		0.74 (0.14,3.61)	1.09 (0.43,2.64)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.78 (0.13,4.25)		1.47 (0.22,9.40)
Cryotherapy	-	-	[2] 0.90 (0.41,2.02)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.08).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.009 (95% interval 0.001 to 0.07).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 2. Ranking of interventions with respect to all-cause and cancer-related mortality, adverse gastrointestinal and genitourinary events: SUCRA (Surface Under the Cumulative RAnking curve) values and median ranks (with 95% intervals).†

Intervention	All-cause mortality		Cancer-related mortality		Adverse gastrointestinal events		Adverse genitourinary events	
	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)	SUCRA value	Median rank (95% interval)
Observational management	18%	7 (2, 8)	30%	6 (3, 8)	-	-	-	-
Prostatectomy	49%	5 (1, 7)	64%	4 (1, 7)	-	-	-	-
Conventional radiotherapy	35%	6 (2, 8)	16%	7 (4, 8)	43%	4 (2, 6)	51%	3 (1, 6)
Conventional radiotherapy-hypofractionated	58%	4 (1, 8)	44%	5 (1, 8)	42%	4 (1, 6)	50%	3 (1, 6)
Conformal LD radiotherapy	57%	4 (1, 7)	61%	4 (2, 7)	67%	2 (2, 4)	66%	3 (1, 5)
Conformal HD radiotherapy	63%	3 (1, 7)	75%	2 (1, 6)	19%	5 (3, 6)	30%	5 (2, 6)
Conformal LD radiotherapy-hypofractionated	69%	1 (1, 8)	85%	1 (1, 8)	30%	5 (2, 6)	26%	5 (1, 6)
Cryotherapy	50%	4 (1, 8)	24%	7 (2, 8)	99%	1 (1, 2)	77%	1 (1, 6)

† The surface under the cumulative ranking curve (SUCRA) value is a numerical summary of the estimated probabilities that each treatment is the best, second best, third best (and so on) for that particular outcome. Higher values indicate higher rankings compared with other treatments. For example, for cryotherapy, the high SUCRA value of 99% and median rank of 1 for adverse gastrointestinal events shows that cryotherapy is expected to be superior with respect to this outcome.

LD: low dose; HD: high dose.

Table 3. Prostate cancer-caused mortality: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		0.63 (0.40,1.02)	1.39 (0.49,4.16)	0.90 (0.24,3.42)	0.63 (0.29,1.31)	0.52 (0.22,1.19)	0.13 (0.00*,3.59)	1.37 (0.28,6.89)
Prostatectomy	[2] 0.60 (0.37,0.98)		2.20 (0.82,6.37)	1.42 (0.39,5.19)	0.99 (0.42,2.26)	0.83 (0.32,2.00)	0.20 (0.00*,6.07)	2.16 (0.46,10.9)
Conventional radiotherapy	-	[1] 1.65 (0.53,5.44)		0.64 (0.29,1.41)	0.45 (0.14,1.30)	0.38 (0.12,1.06)	0.09 (0.00*,3.08)	0.98 (0.28,3.35)
Conventional radiotherapy-hypofractionated	-	-	[2] 0.65 (0.28,1.43)		0.70 (0.18,2.65)	0.59 (0.15,2.16)	0.14 (0.00*,5.08)	1.51 (0.36,6.54)
Conformal LD radiotherapy	[1] 0.70 (0.31,1.57)	-	-	-		0.84 (0.52,1.30)	0.20 (0.00*,5.73)	2.20 (0.44,11.4)
Conformal HD radiotherapy	-	-	[1] 0.21 (0.03,0.97)	-	[5] 0.86 (0.53,1.37)		0.25 (0.00*,6.79)	2.61 (0.53,14.1)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 0.22 (0.00*,6.85)		11.2 (0.24,5542)
Cryotherapy	-	-	[2] 0.96 (0.27,3.46)	-	-	-	-	

LD: low dose; HD: high dose.

* Odds ratio was less than 0.005.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.31).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.02 (95% interval 0.001 to 0.29).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 4. Adverse gastrointestinal events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 0.84 (0.33,1.88)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.01 (0.19,5.29)	0.72 (0.29,1.59)	1.42 (0.57,3.39)	1.26 (0.35,4.30)	0.17 (0.04,0.51)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.00 (0.22,4.56)		0.70 (0.11,4.37)	1.40 (0.21,9.02)	1.24 (0.15,9.76)	0.17 (0.02,1.19)
Conformal LD radiotherapy	-	-	[2] 0.46 (0.17,1.16)	-		1.98 (1.18,3.59)	1.77 (0.63,5.11)	0.24 (0.05,0.96)
Conformal HD radiotherapy	-	-	[1] 2.66 (0.85,8.62)	-	[5] 1.73 (1.07,2.97)		0.89 (0.36,2.15)	0.12 (0.02,0.48)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[3] 0.89 (0.39,1.96)		0.14 (0.02,0.70)
Cryotherapy	-	-	[2] 0.18 (0.05,0.50)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.14 (95% interval 0.01 to 0.97).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.24 (95% interval 0.02 to 1.23).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

Table 5. Adverse genitourinary events: odds ratios (posterior mean with 95% intervals) for each pair-wise comparison of interventions, based on direct evidence alone (lower-left triangle) or direct and indirect evidence (upper-right triangle).

Intervention	Observational management	Prostatectomy	Conventional radiotherapy	Conventional radiotherapy-hypofractionated	Conformal LD radiotherapy	Conformal HD radiotherapy	Conformal LD radiotherapy-hypofractionated	Cryotherapy
Observational management		-	-	-	-	-	-	-
Prostatectomy	[2] 2.27 (1.34,3.90)		-	-	-	-	-	-
Conventional radiotherapy	-	-		1.00 (0.34,2.90)	0.91 (0.54,1.51)	1.19 (0.69,2.11)	1.41 (0.49,4.07)	0.66 (0.22,2.00)
Conventional radiotherapy-hypofractionated	-	-	[1] 1.01 (0.34,3.00)		0.90 (0.27,2.97)	1.19 (0.36,4.04)	1.41 (0.31,6.44)	0.66 (0.14,3.04)
Conformal LD radiotherapy	-	-	[2] 0.80 (0.43,1.51)	-		1.32 (0.97,1.86)	1.56 (0.61,4.09)	0.73 (0.21,2.52)
Conformal HD radiotherapy	-	-	[1] 1.53 (0.62,3.82)	-	[5] 1.28 (0.93,1.86)		1.18 (0.48,2.92)	0.55 (0.16,1.91)
Conformal LD radiotherapy-hypofractionated	-	-	-	-	-	[2] 1.17 (0.48,2.91)		0.47 (0.10,2.15)
Cryotherapy	-	-	[2] 0.68 (0.22,2.03)	-	-	-	-	

LD: low dose; HD: high dose.

Lower-left results compare row-defining interventions against column-defining interventions. Upper-right results compare column-defining interventions against row-defining interventions.

The comparison of prostatectomy with observational management was not linked to the rest of the network, so this evidence was included in the meta-analysis of direct comparisons only.

In the meta-analysis of direct comparisons (reported in lower-left triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.003 to 0.29).
In the network meta-analysis (reported in upper-right triangle), between-trial heterogeneity τ^2 was estimated as 0.04 (95% interval 0.002 to 0.26).

The small superscript numbers in the cells of lower-left triangle indicate the numbers of randomized trials which compared the two interventions directly.

DISCUSSION

Using network meta-analysis, we were able to combine simultaneously all relevant evidence on treating patients with localized prostate cancer, even in the absence of direct comparative evidence for some treatment pairs, encompassing four efficacy and safety outcomes. Based on data from 21 trials including 7,350 patients randomly assigned among eight different intervention regimes for localized prostate cancer, we found substantial uncertainty about the relative efficacy and safety of different interventions in respect of the studied outcomes.

Assumptions of consistency between direct and indirect evidence were tested to justify the joint synthesis of all studies; however, these tests had little power due to the relatively small number of trials available in most direct comparisons. Instead we must rely on judgements about the similarity of studies included in the analysis in aspects such as patient groups, outcome measures and study methodology. Although we defined the population of interest as patients with localized prostate cancer, there was heterogeneity between individual study populations in terms of the severity of disease. Some of the trials were conducted several decades ago, when surgery and radiology techniques may have been different, and we observed that stage migration has occurred in men diagnosed with prostate cancer, due to emerging bio-marker and image technologies. Furthermore, some of the trials used adjuvant therapy, although this was applied in all the arms within the trial.

Two further limitations warrant mention. Literature searches were completed in September of 2012. However, the results of one of the most important randomized trials – ProtecT study[13] – has not been published so far, and to our knowledge there are no other new relevant RCTs have been reported after this systematic review. Our choices of measurements may have favoured some treatments over others: for example the RTOG scale had been used to define the late gastrointestinal and late genitourinary toxicity in the included studies, but it

does not measure incontinence which could be the most common adverse event post-prostatectomy.[102]

Methodologically, we used informative prior distributions based on external evidence for heterogeneity variances, to increase precision in their estimation and improve estimation of treatment differences. Data-based informative priors have previously been considered by Lu & Ades,[101] who used them for the between-study correlation structure. To our knowledge, our paper is the first application of network meta-analysis incorporating data-based informative priors for between-study heterogeneity.

Our findings have implications for research funding prioritisation and study design; and for clinical practice. The study identified particular 'weak links' in the network of comparative treatment options, which might be prioritized for future investment in randomized controlled trials. This is particularly the case for studies comparing HIFU (which currently is bereft of any comparative evidence) or brachytherapy against other treatment options, and also for trials examining the comparative efficacy and safety of prostatecotmy versus conformal radiotherapy modalities. For clinicians, and for men diagnosed with prostate cancer, our findings highlight that the optimal treatment options may be different in respect of different outcomes: patients need to be given appropriate information about the uncertainty surrounding treatment choice currently, and be allowed to opt for 'trade-offs' between efficacy and safety outcomes as they judge appropriately.[95] Observational studies have consistently shown that radical prostatectomy has better cause-specific mortality outcomes compared with radiotherapy.[96-99,103]

In conclusion, clinically important information from high quality randomized trials is still needed to inform decision making regarding primary treatment options for men with localized prostate cancer. The findings of this study highlight the importance of informed patient choice and shared-decision making about treatment modality and acceptable trade-offs

between multiple outcomes. The upcoming results of the ProtecT study,[13] which is evaluating effectiveness of multiple therapies in men with PSA-detected localized prostate cancer, together with other treatment studies in progress, will hopefully contribute to the evidence base. It is however unlikely that evidential uncertainty about all relevant and important outcomes will be resolved by these trials, and an updated network meta-analysis incorporating new evidence may be useful to synthesize the new with the existing evidence. We demonstrate a high degree of uncertainty about treatment superiority in the management of localized prostate cancer. Clinicians and patients need to grapple with this uncertainty in the context of shared-decision making.

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Figure Legends

Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis

Figure 2. Risk of bias assessments for the included randomized trials

Figure 3. Network of comparisons of treatments for localized prostate cancer showing numbers of trials in which each pairwise comparison had been made

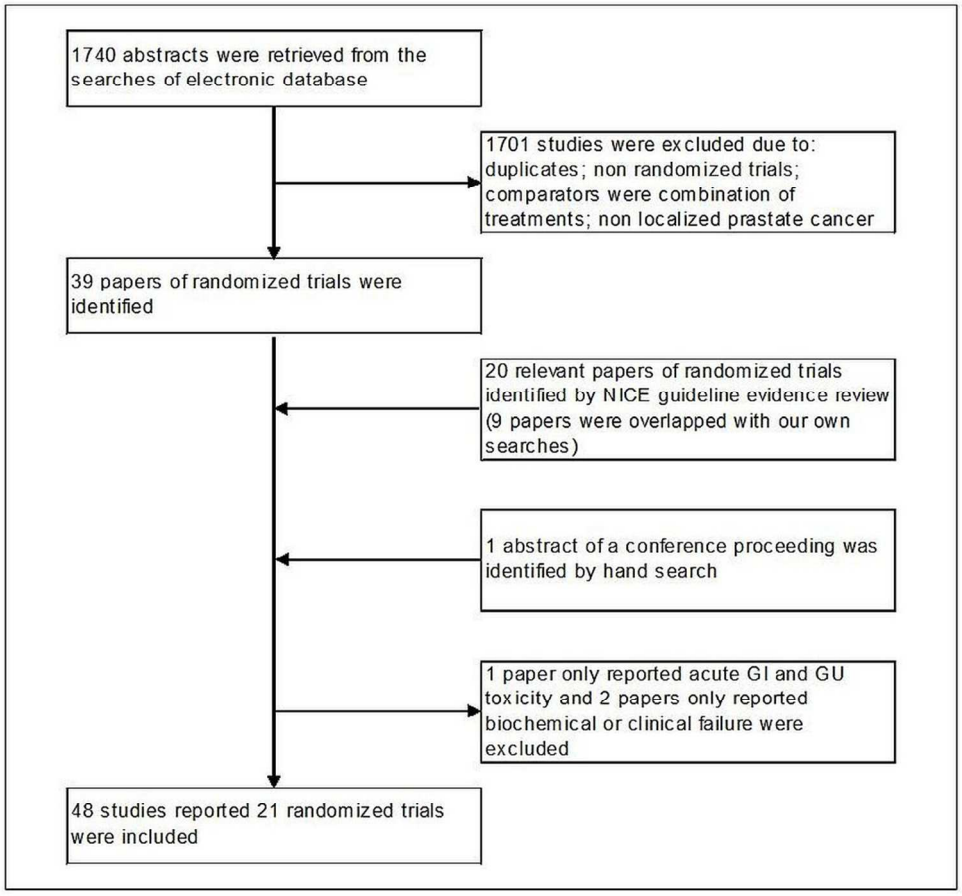
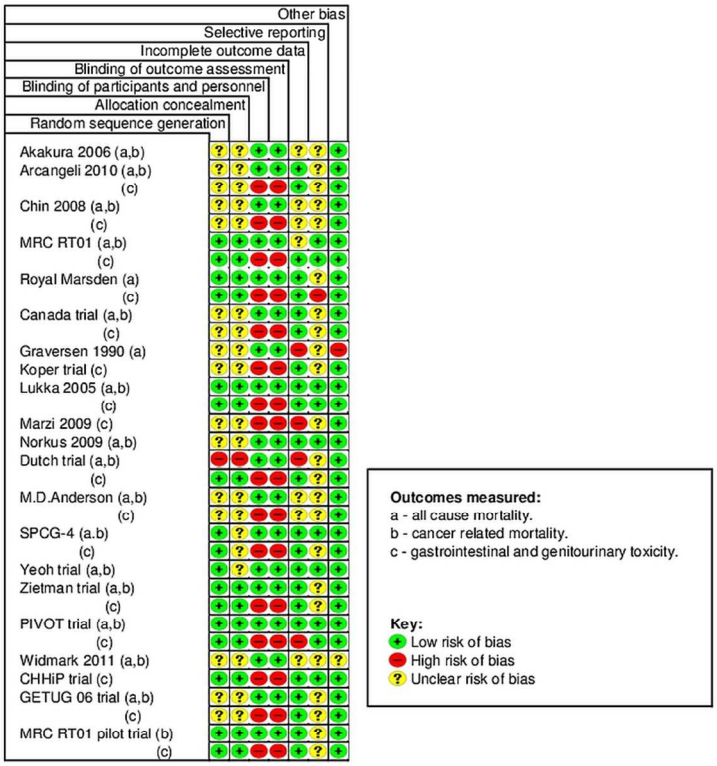


Figure 1. Flow chart of the inclusion process of the studies for network meta-analysis
90x83mm (300 x 300 DPI)

Figure 2. Risk of bias assessments for the included randomized trials



Risk of bias assessments for the included randomized trials
90x116mm (300 x 300 DPI)

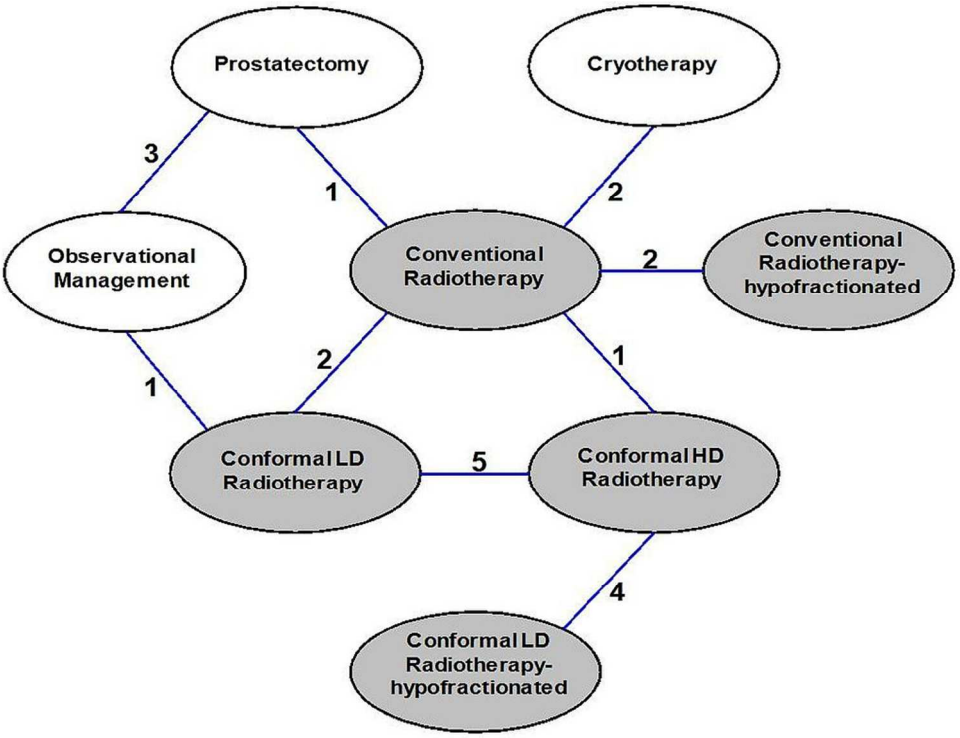


Figure 3. Network of comparisons of treatments for localized prostate cancer
90x69mm (300 x 300 DPI)

Appendix 1. Full search strategy for Medline made on 12 Sep 2012

1	"watchful wait$".ti,ab	1408
2	(watch$ adj2 wait$).ti,ab	1795
3	"observation".ti,ab	201605
4	"watchful surveillance".ti,ab	3
5	"watchful monitoring".ti,ab	14
6	"active surveillance".ti,ab	2609
7	"active monitoring".ti,ab	177
8	"expectant manag$".ti,ab	1501
9	"expectant monitoring".ti,ab	18
10	"expectant surveillance".ti,ab	3
11	"deferred treatment$".ti,ab	174
12	"deferred therap$".ti,ab	53
13	"delayed treatment$".ti,ab	1752
14	"delayed therap$".ti,ab	264
15	"conservative monitoring".ti,ab	10
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	209461
17	exp PROSTATIC NEOPLASMS/	83203
18	PROSTATIC INTRAEPITHELIAL NEOPLASIA/	1124
19	pin.ti,ab	9241
20	((prostat$ adj3 (cancer$ OR carcinoma$ OR malignan$ OR tumo?r$ OR neoplas$ OR intraepithelial$ OR adeno$))).ti,ab	85456
21	17 OR 18 OR 19 OR 20	109867
22	RANDOMIZED CONTROLLED TRIALS AS TOPIC/	82900
23	RANDOMIZED CONTROLLED TRIAL/	336590
24	RANDOM ALLOCATION/	75700
25	DOUBLE BLIND METHOD/	116906
26	SINGLE BLIND METHOD/	16674
27	CLINICAL TRIAL/	473817
28	"clinical trial, phase i".pt	12527
29	"clinical trial, phase ii".pt	20003
30	"clinical trial, phase iii".pt	7335
31	"clinical trial, phase iv".pt	739
32	"controlled clinical trial".pt	85134
33	"randomized controlled trial".pt	336590
34	"multicenter study".pt	149366
35	"clinical trial".pt	473817
36	exp CLINICAL TRIALS AS TOPIC/	260613
37	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36	933873
38	(clinical ADJ trial$).ti,ab	185348
39	((singl$ OR doubl$ OR treb$ OR tripl$) AND (blind$3 OR mask$3)).ti,ab	129000
40	PLACEBOS/	31302
41	placebo$.ti,ab	144213
42	"randomly allocated".ti,ab	14778
43	(allocated adj2 random$).ti,ab	17183
44	38 OR 39 OR 40 OR 41 OR 42 OR 43	383691
45	37 OR 44	1064978
46	(case AND report).ti,ab	372325
47	LETTER/	776512

48	HISTORICAL ARTICLE/	286394
49	46 OR 47 OR 48	1422877
50	45 NOT 49	1033939
51	CRYOTHERAPY/	3337
52	CRYOSURGERY/	10459
53	HYPOTHERMIA, INDUCED/	15628
54	cryoablat$.ti,ab	1810
55	(cryo$ ADJ ablat$).ti,ab	351
56	cryotreatment$.ti,ab	65
57	cryotherap$.ti,ab	4776
58	cryotherm$.ti,ab	212
59	(cryo$ ADJ surgery).ti,ab	149
60	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59	31372
61	((cryo$ OR hypotherm$ OR freez$) adj5 prostat$).ti,ab	709
62	60 AND 21	916
63	61 OR 62	1089
64	PROSTATECTOMY/	19443
65	prostatectom$.ti,ab	18653
66	resection.ti,ab	170070
67	64 OR 65 OR 66	192628
68	(radical OR complete$ OR total OR "en bloc").ti,ab	2057017
69	67 AND 68	69466
70	(LRP OR TLRP OR RALRP OR RAP OR RRP OR RPP OR EERP).ti,ab	7847
71	"heilbronn technique".ti,ab	8
72	70 OR 71	7853
73	69 OR 72	76420
74	exp RADIOTHERAPY/	125988
75	"radiation therap$".ti,ab	46061
76	"radiation treatment$".ti,ab	6068
77	radiotherap$.ti,ab	103759
78	exp RADIOTHERAPY PLANNING/	11242
79	irradiation.ti,ab	133551
80	RADIOTHERAPY, ADJUVANT/	15412
81	74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80	307483
82	META-ANALYSIS AS TOPIC/	12419
83	"meta analy$".ti,ab	45804
84	metaanaly$.ti,ab	1171
85	META-ANALYSIS/	36142
86	(systematic ADJ review$1).ti,ab	37644
87	(systematic ADJ overview$1).ti,ab	489
88	exp REVIEW LITERATURE AS TOPIC/	6486
89	82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88	93039
90	cochrane.ab	22743
91	embase.ab	20328
92	(psychlit OR psyclit).ab	865
93	(psychinfo OR psycinfo).ab	7698
94	(cinahl OR cinhal).ab	7537
95	"science citation index".ab	1633
96	bids.ab	331
97	cancerlit.ab	560
98	90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97	37065
99	"reference list$".ab	7905

100	bibliograph$.ab	10314
101	hand-search$.ab	3303
102	"relevant journals".ab	586
103	"manual search$".ab	1920
104	99 OR 100 OR 101 OR 102 OR 103	21486
105	"selection criteria".ab	16935
106	"data extraction".ab	8148
107	105 OR 106	23737
108	REVIEW/	1733836
109	107 AND 108	15770
110	COMMENT/	517077
111	LETTER/	776512
112	EDITORIAL/	317040
113	ANIMAL/	5040870
114	HUMAN/	12536636
115	113 NOT (113 AND 114)	3686418
116	110 OR 111 OR 112 OR 115	4846136
117	89 OR 98 OR 104 OR 109	118824
118	117 NOT 116	110572
119	ULTRASOUND, HIGH-INTENSITY FOCUSED, TRANSRECTAL/	306
120	((high intensity adj2 ultraso$)).ti,ab	2103
121	HIFU.ti,ab	1012
122	((high intensity focused ultrasound)).ti,ab	1381
123	"focal therapy".ti,ab	295
124	119 OR 120 OR 121 OR 122 OR 123	2619
125	21 AND 50 AND 124	**99**
126	16 AND 21 AND 50 AND 63 [Limit to: Publication Year 2005-Current]	**10**
127	16 AND 21 AND 50 AND 73 [Limit to: Publication Year 2005-Current]	**94**
128	16 AND 21 AND 50 AND 81 [Limit to: Publication Year 2005-Current]	**82**
129	50 AND 63 AND 81 [Limit to: Publication Year 2005-Current]	**27**
130	50 AND 63 AND 73 [Limit to: Publication Year 2005-Current]	**14**
131	21 AND 50 AND 73 AND 81 [Limit to: Publication Year 2005-Current]	**267**
132	(21 AND 50 AND 81) NOT (128 OR 131) [Limit to: Publication Year 2005-Current]	**947**
133	16 AND 21 AND 63 AND 118 [Limit to: Publication Year 2005-Current]	**5**
134	16 AND 21 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**25**
135	16 AND 21 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**27**
136	63 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**14**
137	63 AND 73 AND 118 [Limit to: Publication Year 2005-Current]	**12**
138	21 AND 73 AND 81 AND 118 [Limit to: Publication Year 2005-Current]	**56**
139	(21 AND 81 AND 118) NOT (135 OR 138) [Limit to: Publication Year 2005-Current]	**61**

Appendix 2. Characteristics of included studies

Comparison	Trial title	Author, year	Country	Population	No.of men	Interventions and Comparisons	Outcomes	Follow up
Observational management v Prostatectomy (3 trials)	Graversen 1990 (1 paper)	Graversen 1990	USA	Dates of enrolment to study: Between May 1967 and March 1975; Setting: Multi-centre (15 participating hospitals); Age: All age; Disease status: stage I or II (T0 – T2).	142	1. Watchful waiting (74 men) 2. Prostatectomy (68 men)	Overall survival.	15 years.
	PIVOT trial (1 paper)	Wilt 2012	USA	Dates of enrolment to study: Nov 1994 to Jan 2002; Setting: multicentre; Mean age: 67yr; Disease status: T1-T2NxM0.	731	1. Observation (367 men) 2. Prostatectomy (364 men)	All cause mortality; Cancer caused mortality; Bone metastases; Urinary incontinence; Bowel dysfunction; Erectile dysfunction.	10 years.
	Scandinavian Prostate Cancer Group Study No 4 (SPCG-4) (6 papers)	Bill-Axelson 2005, 2008, 2011; Johansson 2009, 2011 Steineck 2002;	Sweden, Finland, Iceland	Dates of enrolment to study: Oct 1989 to Feb 1999; Setting: Multi-centre (14 participating hospitals); Age: Mean age 64.7; Disease status: T0d, T1, T2.	695	1. Watchful waiting (348 men) 2. Prostatectomy (347 men)	Death due to prostate cancer; All-caused mortality; Distance metastasis; Local progression; overall distress from all bowel symptoms, overall distress from all urinary symptoms.	8.2 - 12.8 years.
Observational management v Conformal LD radiotherapy (1 trial)	Widmark 2011 (1 paper)	Widmark 2011	Sweden, Denmark and Norway	Dates of enrolment to study: Apr 1986 to Jan 1997; Setting: unknown; Age: up to 75; Disease status: T1b-T2, pN0, G1-G2, M0.	214	1. Watchful waiting (107 men) 2. 3D conformal radiotherapy, either 64 Gy in 32 fractions with 2cm margin, or 64-68 Gy with 1.5cm margin (107 men)	All-cause mortality, Prostate cancer mortality, Distant progression, Recurrence free survival, Clinical progression, Biochemical progression, Local progression.	20 years.

Prostatectomy v Conventional radiotherapy (2 trials)	Akakura 2006(1 paper)	Akakura 2006	Japan	Dates of enrolment to study: 1989 to 1993; Setting: Multi-centre; Age: Mean 68.1, SD 7.0 in surgery group; mean 68.7, SD 6.6 in radiation group; Disease status: T2b-3N0M0, no evidence of lymph node metastasis.	95	1. Prostatectomy (46 men).2. Conventional radiotherapy (49 men): Irradiation by linear accelerator with a 40-50 Gy beam to the whole pelvis followed by a 20 Gy boost to the prostatic area for 6-7 weeks fractionated five times per week. All men received an initial treatment with 8 weeks of neoadjuvant endocrine therapy.	Biochemical progression-free survival at 10 years; Clinical progression-free survival at 10 years; Cause-specific survival at 10 years; Overall survival at 10 years; Adverse effects.	Median follow-up was 102 months.
Cryotherapy v Conventional radiotherapy (2 trials)	Canada trial (3 papers)	Donnelly 2007, 2010; Robinson 2009	Canada	Dates of enrolment to study: Dec 1997 to Feb 2003; Setting: Tom Baker Cancer Center, Calgary, Canada; Age: Median 69.4, range 52.8-81.4 in CT group; median 68.6, range 53.2-78.6 in EBRT group; Disease status: T2 - T3.	244	1. Cryotherapy (122 men). 2. Conventional EBRT (122 men): dose of 68 Gy given in 2 Gy fractions daily, 5 days per week, later increased to 70 Gy and later 73.5 Gy.	Treatment Failure; 5 year overall survival; Biopsy rate at 36 months; Disease-specific survival at 5 years; Genitourinary and gastrointestinal adverse effects; Quality of life.	Median follow-up was 82 months.
	Chin 2008 (1 paper)	Chin 2008	Canada	Setting: London Health Sciences Centre, University of Western Ontario; Age: Median age 70 in each group; Disease status: T2 - T3.	64	1. Cryotherapy (33 men). 2. Conventional EBRT (31 men): 66 Gy in 33 fractions.	Biochemical disease-free survival at 4 years; Overall survival at 4 years; Disease specific survival at 4 years; Positive biopsy rate; Gastrointestinal toxicity; Genitourinary toxicity; Hormonal adverse effects.	Mean follow-up 37 months.

Conventional radiotherapy v Conventional radiotherapy-hypofractionated (2 trials)	Yeoh trial (4 papers)	Yeoh 2003, 2006, 2009, 2011	Australia	Dates of enrolment to study: July 1996 to Aug 2003; Setting: Department of Radiation Oncology and Gastroenterology, Royal Adelaide Hospital; Age: Median age 69 (44 ~ 82 yrs); Disease status: T1, T2, N0 M0.	217	1. Conventional EBRT: 64 Gy in 32 fractions within 6.5 weeks (109 men). 2. Hypofractionated EBRT: 55 Gy in 20 fractions within 4 weeks (108 men).	Gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival rate; biochemical ±clinical relapse; biochemical ±clinical relapse-free survival; cancer-related mortality.	5 years.
	Lukka 2005 (1 paper)	Lukka 2005	Canada	Dates of enrolment to study: March 1995 – December 1998; Setting: 8 Ontario regional cancer centres and 8 additional Canadian centres; Age: Mean 70.3, range 53-84 in group 1; mean 70.0, range 53-84 in group 2; Disease status: T1, T2.	936	1. Conventional EBRT (470 men): 66 Gy in 33 fractions over 45 days. 2. Hypofractionated EBRT (466 men): 52.5 Gy in 20 fractions over 28 days.	Composite of biochemical or clinical failure (BCF); local persistence of tumour on biopsy of the prostate at 2 years; overall survival; acute and late radiation-induced toxicity; prostate cancer-related mortality.	Median follow-up was 5.7 years.
Conventional radiotherapy v Conformal LD radiotherapy (2 trials)	Koper trial (2 papers)	Koper 1999, 2004	Nether-lands	Dates of enrolment to study: June 1994 to March 1996; Setting: Erasmus Medical Center/Daniel den Hoed Cancer Center; Mean age: group1: 70 (6.4); group 2: 69.5 (6.1); Disease status: T1-T4 N0M0.	266	1. Conventional radiotherapy (134 men); 2. Conformal radiotherapy (129 men). All men were treated to a dose of 66 Gy, using the same planning procedure, treatment technique, linear accelerator, and portal imaging procedure.	Gastrointestinal (GI) and genitourinary (GU) toxicity.	2 years.
	Royal Marsden and Institute of Cancer Research study (2 papers)	Dearnaley 1999; Tait 1997	UK	Dates of enrolment to study: 1988 to 1995; Setting: Tertiary care, single centre; Median age (range): 69 (51-80) in group 1, 68 (50-83) in group 2; Disease status: T1-T4 N0M0.	225	1. Conventional radiotherapy (111 men): 60 to 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy (114 men): 60 to 64 Gy in 2 Gy fractions.	Overall survival; Biochemical progression free survival; Late GI toxicity; Late GU toxicity.	2 - 5 years.

Conformal LD radiotherapy v Conformal HD radiotherapy (5 trials)	Dutch trial (7 papers)	Al-Mamgani 2008, 2011; Heemsbergen 2007; Peeters 2005, 2006a,b; van der Wielen 2008	Netherlands	Dates of enrolment to study: between June 1997 and February 2003; Setting: multicenter; Age: mean 68.6 and 68.8, range 50.3-82.9 and 48.7-83.6; Disease status: T1-T4.	669	1. 3D conformal radiotherapy 68 Gy (331 men). 2. 3D conformal radiotherapy 78 Gy (333 men).	freedom from failure; biochemical progression free survival; clinical progression free survival; overall survival; late GI toxicity; late GU toxicity; prostete cancer related deaths.	2 - 7 years.
	MRC RT01 pilot trial (1 paper)	Dearnaley 2005	UK	Dates of enrolment to study: between Jul 1995 and Dec 1997; Setting: Royal Marsden NHS Trust and Institute of Cancer Research; Age: median 66 and 69; Disease status: T1b-T3b N0 M0.	127	1. Conformal radiotherapy, standard dose (64 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (63 men): 74 Gy in 2 Gy fractions.	Biochemical (PSA) failure; Local or metastatic failure; Hormone therapy restarted; acute GU toxicity; acute GI toxicity; late GU toxicity; late GI toxicity; prostate cancer caused deaths.	5 years.
	MRC RT01 (3 papers)	Dearnaley 2007a,b; Syndikus 2010.	UK	Dates of enrolment to study: Jan 1998 to Dec 2002; Setting: multi-centre; Age: median 67 (IQR 63-71); Disease status: T1b-T3a N0 M0.	843	1. Conformal radiotherapy, standard dose (421 men): 64 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (422 men): 74 Gy in 2 Gy fractions.	Biochemical-progression-free survival; 5-year overall survival; Progression-free survival; Freedom from local progression; Freedom from salvage androgen suppression; Metastases-free survival; Bowel dysfunction; Urinary or bladder dysfunction; Sexual dysfunction; prostate cancer mortality.	5 years.
	GETUG 06 Tial (2 papers)	Beckendorf 2004, 2011	France	Dates of enrolment to study: Sep 1999 to Feb 2002; Setting: Multicentre; Age: mean 67; Disease status: T1b-T3a, N0M0.	306	1. Conformal radiotherapy, standard dose (153 men): 70 Gy in 2 Gy fractions. 2. Conformal radiotherapy, high dose (153 men): 80 Gy in 2 Gy fractions.	Biochemical relapse alone; PSA and clinical relapse; Free from relapse; All cause death; Cancer cause death; RTOG rectal and urinary toxicity grade 2 and worse.	61 months.
	Zietman trial (2 papers)	Zietman AL, 2005, 2010	USA	Dates of enrolment to study: between Jan 1996 and Dec 1999; Setting: 2 US academic institutions; Age: 67 (45~91) in 70.2 Gy arm, 66 (47~78) in 79.2 Gy arm; Disease status: T1-T2, N0, Nx.	393	1. External beam radiation 70.2 Gy (197 men); 2. External beam radiation 79.2 Gy (195 men).	Freedom from biochemical failure 5 yrs after treatment (measured by PSA level); Acute and late GU and GI morbidity, overall survival, prostate cancer-related mortality.	5.5 - 8.9 years.

Conformal HD radiotherapy v Conformal LD radiotherapy-hypofractionated (4 trials)	Arcangeli 2010 (2 papers)	Arcangeli 2010, 2011	Italy	Dates of enrolment to study: Jan 2003 to Dec 2007; Setting: single centre; Mean age: 75 years; Disease status: no evidence of distant metastases.	168	1. hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week): 83 men. 2. conventional fractionation radiotherapy (80 Gy/40 fractions/8 weeks): 85 men.	Acute and late GU and GI toxicity; biochemical failure; freedom from biochemical failure; distant metastasis rates; all cause mortality; cancer related mortality.	4 years.
	Marzi 2009 (1 paper)	Marzi 2009	Italy	Dates of enrolment to study: March 2003 to June 2008; Setting: single centre; Age: all; Disease status: T1-T4.	162	1. Conformal radiotherapy hypofractionated: 62 Gy in 20 fractions over 5 weeks (57 men); 2. Conformal radiotherapy: 80 Gy in 40 fractions over 8 weeks (57 men).	Late rectal toxicity.	Median followup was 30 months.
	Norkus 2009 (2 papers)	Norkus 2009 a,b	Lithuania	Dates of enrolment to study: 2004; Setting: single centre; Age: median 63 (range 53-75) in group 1, median 65 (range 50-78) in group 2; Disease status: T1-T3.	91	1. Hypofractionated external beam radiotherapy: 57 Gy given as 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy (47 men). 2. Conventionally fractionated external beam radiotherapy: 74 Gy given in 37 fractions of 2 Gy (44 men).	Biochemical (PSA) response; acute gastrointestinal (GI) and genitourinary (GU) toxicity; overall survival; prostate cancer-related mortality.	3 - 12 months.
	CHHiP trial (1 paper)	Dearnaley 2012	UK	Dates of enrolment to study: Oct 2002 to Aug 2006; Setting: multicentre; Age: median 67 - 68 (range 44-82); Disease status: T1b – T3a N0M0.	457	1. Conventional fractionation: 74 Gy in 37 fractions at 2 Gy per fraction (153 men). 2. Hypofractionation: 60 Gy in 20 fractions at 3 Gy per fraction (153 men). 3. Hypofractionation: 57 Gy in 19 fractions at 3 Gy per fraction (151 men).	Acute bowel toxicity; Acute bladder toxicity; Late bowel toxicity; Late bladder toxicity; Sexual dysfunction.	50.5 months.
Conventional radiotherapy v Conformal HD radiotherapy (1 trial)	M. D. Anderson randomized dose-escalation trial (4 papers)	Kuban 2008, 2011; Pollack 2002; Storey 2000.	USA	Dates of enrolment to study: 1993 to 1998; Setting: M. D. Anderson Cancer Center, University of Texas; Median age 69 for each arm; Disease status: T1-T3 N0M0.	305	1. Conventional radiotherapy (150 men): 70 Gy, given in daily 2 Gy fractions. 2. 3D conformal radiotherapy (151 men): 78 Gy, given in daily 2 Gy fractions.	freedom from biochemical or clinical failure; freedom from distant metastasis; overall survival; disease-specific survival; late GI toxicity; late GU toxicity; prostate cancer-related mortality.	Median follow-up of 5 - 8 years.

LD: low dose; HD: high dose.

Appendix 3. Assessment of risk of bias for included randomized trials (please refer to www.cochrane-handbook.org for instructions on how to complete the tables).

Outcomes measured:
a - all cause mortality.
b - cancer related mortality.
c - gastrointestinal and genitourinary toxicity.

Study ID: CHHiP trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random permuted blocks were used
Allocation concealment	Low risk	Independent randomisation was via telephone to the ICR-CTSU.
Blinding of participants and personnel	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Blinding of outcome assessment	High risk	Treatment allocation was not masked and, because of the trial's size, assessors could not be blinded to toxicity or clinical assessments.
Incomplete outcome data	Low risk	Losses to follow-up are disclosed
Selective reporting	Low risk	Pre-planned analyses.
Other bias	Low risk	No other sources of bias identified.

Study ID: PIVOT trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome	Low risk	After randomization, a central pathologist reviewed the biopsy and radical-prostatectomy specimens, and a

assessment		central laboratory measured PSA.
Incomplete outcome data	Low risk	Losses to follow-up described and were low
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Randomization was stratified according to site and implemented by means of a central interactive telephone system
Allocation concealment	Low risk	Protocol
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Toxicity outcomes are patient-reported and therefore at high risk of bias.
Incomplete outcome data	High risk	Moderate losses to follow-up, 23% in each group.
Selective reporting	Low risk	Protocol
Other bias	Low risk	Not identified

Study ID: GETUG 06 Tial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	Not stated
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	HIGH risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Lost to follow-up described
Selective reporting	Unclear risk	No protocol available
Other bias	Low risk	Not identified

Study ID: Widmark 2011

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No details available.
Allocation concealment	Unclear	No details available.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect mortality or biochemical/clinical relapse.
Incomplete outcome data	Unclear	No details available.
Selective reporting	Unclear	No details available.
Other bias	Unclear	No details available.

Study ID: Yeoh trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Low risk	Blocked computer-generated random numbers (Yeoh EE 2003)
Allocation concealment	Unclear risk	Not clear
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality
Incomplete outcome data	Low risk	Report Kaplan Meier estimates, log-rank test results.
Selective reporting	Low risk	Pre-specified
Other bias	Low risk	Not identified

Study ID: Royal Marsden trial

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".
Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Randomised permuted blocks design from an independent randomisation service offered by the Clinical trials and Statistics Unit, institute of Cancer Research".

Allocation concealment	Low risk	Allocation carried out by independent randomisation service.
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses of follow-up disclosed, losses were low and balanced between intervention groups.
Selective reporting	High risk	Some cut-off values reporting.
Other bias	Low risk	No other sources of bias identified.

Study ID: Zietman trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and personnel	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Blinding of outcome assessment	Low risk	Unlikely to pose any conceptual risks to the ascertainment of mortality and biochemical outcomes
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	unclear	No clear
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Central randomization
Allocation concealment	Low risk	Randomized by external body: randomized centrally by the American College of Radiology statistical office on protocol 95-09 of the Proton Radiation Oncology Group between January 1996 and December1999.
Blinding of participants and	High risk	Lack of blinding is likely to poses conceptual risks to

personnel		toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Incomplete outcome data	Low risk	Follow-up data completed
Selective reporting	Unclear	No clear
Other bias	Low	Not identified

Study ID: SPCG-4

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Stratification according to tumor grade and randomization center. The randomization list was computer generated, and the block size was unknown to the investigators
Allocation concealment	Unclear	Not stated
Blinding of participants and personnel	Low	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low	"Blinding to analyst". The pathologists were blinded to patient outcome and assignment. Only the results from the central review are used. Members of the endpoint committee were blinded to patients' group assignment and treatment received." Or, "Blinded evaluation (2005)".
Incomplete outcome data	Low	Losses of follow-up disclose
Selective reporting	Low	Outcomes pre-specified
Other bias	Low	Not other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	The randomization list was computer generated (Bill-Axelson,2002)
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	Outcome assessment was obtained by asking patients to return questionnaire after intervention, from which the blinding of assessor is impossible.

Incomplete outcome data	Low risk	88% and 87% of participants return questionnaires from prostatectomy and watchful waiting, respectively.
Selective reporting	Unclear risk	Study report doesn't make clear if this outcom were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Graversen1990

Risk of bias table for outcome a		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	More elderly patients in placebo group
Allocation concealment	Unclear risk	Not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality.
Incomplete outcome data	High risk	Outcome data incomplete.
Selective reporting	Unclear risk	Not stated
Other bias	High risk	31 stage I and 20 stage II patients were assigned to placebo; 31 stage I and 30 stage II patients were assigned to prostatectomy.

Study ID: Canada trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival, biopsy rate, disease-specific survival.
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect treatment failure, overall survival,

		biopsy rate, disease-specific survival.
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk (need further discussion)	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk (need further discussion)	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Losses to follow-up are fairly low
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: MRC RT01

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival
Incomplete outcome data	Unclear risk	Losses to follow-up are disclosed and appear balanced across groups for other outcomes reported, but we can't adjust for losses to follow-up for overall survival since this outcome isn't formally reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol

Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Computer-based minimisation algorithm
Allocation concealmentLow	Low risk	Central allocation
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low risk	Adjustment made for losses to follow-up in calculation of the hazard ratios and cumulative proportions reported.
Selective reporting	Low risk	Outcomes pre-specified in trial protocol
Other bias	Low risk	No other sources of bias identified.

Study ID: Chin 2008

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical disease-free survival, disease specific survival, overall survival and positive biopsy
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		

	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information given
Allocation concealment	Unclear risk	No information given
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified.

Study ID: MRC RT01 pilot trial

Risk of bias table for outcome b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design
Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Blinding of outcome assessment	Low	unlikely to pose any conceptual risks to the ascertainment of biochemical failure or local/metastatic failure
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low	Randomised permuted block design

Allocation concealment	Low	Independent randomisation was undertaken by ICR Clinical Trials and Statistics Unit.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	Low	Losses of follow-up disclosed
Selective reporting	Unclear	Unclear whether outcomes reported were pre-specified in the protocol.
Other bias	Low	Not identified

Study ID: Akakura 2006

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No details given, but may be reported in the earlier design paper
Allocation concealment	Unclear risk	No details given, but may be reported in the earlier design paper
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Blinding of outcome assessment	Low risk	No blinding mentioned, but we judge that lack of blinding is unlikely to affect biochemical progression-free survival, clinical progression-free survival, cause-specific survival and overall survival
Incomplete outcome data	Unclear risk	No information given
Selective reporting	Unclear risk	No information given
Other bias	Low risk	No other sources of bias identified

Study ID: Arcangeli 2010

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information

Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	High risk	Lack of blinding is likely to poses conceptual risks to toxicity assessment
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risk to the toxicity assessment.
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified
Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information
Allocation concealment	Unclear risk	No information
Blinding of participants and personnel	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Blinding of outcome assessment	Low risk	We judge that blinding is less likely to poses high risk on survival and biochemical/clinical outcomes
Incomplete outcome data	Low risk	No lost to follow-up
Selective reporting	Unclear risk	No protocol information
Other bias	Low risk	Not identified

Study ID: Kopper trial

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low	Follow-up completed in (Kopper 2004)

Selective reporting	Unclear	Not clear which outcomes were pre-specified.
Other bias	Low	No other sources of bias identified

Study ID: Lukka 2005

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect overall survival.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to affect measurement of overall survival.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	"Patients were assigned…according to a central computer-generated randomization schedule…"
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Blinding of outcome assessment	High risk	Lack of blinding is likely to pose conceptual risks to the toxicity assessment.
Incomplete outcome data	Low risk	Losses to follow-up are balanced across groups, and taken into account in analysis.
Selective reporting	Low risk	Methods section implies that all outcomes reported were pre-specified and approved by the study Steering Committee. The primary outcome was altered to an outcome of increasing importance in emerging literature, before the data were unblinded.

Other bias	Low risk	No other sources of bias identified.

Study ID: Marzi 2009

Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of adverse effects
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of adverse effects
Incomplete outcome data	High risk	Losses to follow-up are fairly high and no information is given about the patients lost to follow-up.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: Norkus 2009

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear	Methods not stated
Allocation concealment	Unclear	Methods not stated
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease control.
Incomplete outcome data	Low risk	Low losses to follow-up
Selective reporting	Low risk	The two 2009 papers list the planned endpoints and report the early 12-month findings. It's unlikely that other pre-specified outcomes would be omitted at this stage of the trial.
Other bias	Low risk	No other bias identified

Study ID: Dutch trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	Low risk	Not clear but low risk for mortality
Blinding of outcome assessment	Low risk	Not clear but low risk for mortality
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for the rest outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Allocation concealment	Low risk	Random assignment was performed with a minimization technique with stratification for treatment group
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Low risk	Losses to follow-up disclosed.
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.

Study ID: M. D. Anderson trial

Risk of bias table for outcomes a, b		
	Judgement (low/ high/unclear risk)	**Support for judgement**

Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Blinding of outcome assessment	Low risk	Unmasked design, but we judge that lack of blinding is unlikely to pose any conceptual risks to the ascertainment of mortality and disease progression outcomes.
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Not clear which outcomes were pre-specified.
Other bias	Low risk	No other sources of bias identified.
Risk of bias table for outcome c		
	Judgement (low/ high/unclear risk)	**Support for judgement**
Random sequence generation	Unclear risk	No information.
Allocation concealment	Unclear risk	No information.
Blinding of participants and personnel	High risk	Unmasked design, and lack of blinding could influence reporting of toxicity
Blinding of outcome assessment	High risk	No blinding of outcome assessors mentioned, and lack of blinding could influence assessment of toxicity
Incomplete outcome data	Unclear risk	No data on losses to follow-up
Selective reporting	Unclear risk	Cut-points may have been chosen based on significance.
Other bias	Low risk	No other sources of bias identified.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 – 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 – 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 – 7 Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8 – 10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7 – 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9 – 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12 – 14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12 – 14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12 – 21
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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