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Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

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Background: Many radiation regimens for treating prostate cancer have been used over the years, but which regimen is optimal for localised or locally advanced prostate cancer lacks consensus. We performed a network meta-analysis to identify the optimal radiation regimen.

Methods: We systematically reviewed data from 27 randomised controlled trials and could group seven radiation regimens as follows: low- and high-dose radiation therapy (LDRT and HDRT), LDRT + short- or long-term androgen deprivation therapy (LDRT + SADT and LDRT + LADT), HDRT + SADT, hypofractionated radiotherapy (HFRT), and HFRT + SADT. The main outcomes were overall mortality (OM), prostate-specific antigen (PSA) failure, cancer-specific mortality, and adverse events.

Results: For the network meta-analysis of 27 trials, LDRT + LADT and LDRT + SADT were associated with decreased risk of OM as compared with LDRT alone as was LDRT + LADT compared with HDRT. Apart from HFRT, all other treatments were associated with decreased risk of PSA failure as compared with LDRT. HFRT + SADT was associated with decreased risk of cancer-specific mortality as compared with HFRT, LDRT + SADT, HDRT, and LDRT.

Conclusions: HFRT + SADT therapy might be the most efficacious treatment but with worst toxicity for localised or locally advanced prostate cancer, and HDRT showed excellent efficacy but more adverse events.

In 2013, prostate cancer was diagnosed in 238 590 Americans, and 29 720 died of the disease (Siegel *et al*, 2013). Indeed, in 2008, the incidence and mortality rates of prostate cancer were the second and sixth highest among cancers for males in the world (Jemal *et al*, 2011). Approximately 90% of men have disease confined to the prostate gland (clinically localised disease). Prostate cancer incidence increased and disease-specific mortality rate decreased after the introduction of the prostate-specific antigen (PSA) blood test and with early interventions (Jemal *et al*, 2006).

Many methods for treating prostate cancer have been used for many years, but we lack high-quality evidence that one method is better than another (Heidenreich *et al*, 2011). The main options for localised prostate cancer are active surveillance, radical prostatectomy, and radiotherapy (RT) with or without adjuvant androgen deprivation therapy (ADT). For locally advanced prostate cancer, the treatment is mainly RT with hormone therapy (Heidenreich *et al*, 2011; Mottet *et al*, 2011). Many factors, including medical factors, patient preference, and resource availability, decide the choice of treatment (Cooperberg *et al*, 2010; Bosco *et al*, 2012; Kollmeier and Zelefsky, 2012).

With the development of technology and knowledge of radiation oncology, such as 3D conformal RT (3D-CRT) and intensity-modulated RT (IMRT) with their high dose and high precision, hundreds of clinical trials have been conducted to compare RT regimens with or without ADT for localised prostate

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cancer, with the aim to determine the optimal treatment with a balance of efficacy and tolerability.

With the development of evidence-based medicine, meta-analysis has become a dependable way to clarify clinical concerns or controversy. However, traditional head-to-head meta-analysis cannot reveal the relative effect of different treatment methods for localised prostate cancer. Randomised control trials (RCTs) usually contain two or a few arms, and trials cannot compare all possible treatment regimens. Fortunately, network meta-analysis can simultaneously combine both direct and indirect evidence from studies addressing the same clinical question to assess the relative efficacy of each treatment, while respecting randomisation (Lumley, 2002; Lu and Ades, 2006; Salanti *et al*, 2008).

In this study, we used network meta-analysis to identify the optimal radiation method for prostate cancer, comparing the relative efficacy and safety of different RT regimens. We evaluated hypofractionated RT (HFRT) and high- and low-dose RT (HDRT and LDRT) with or without ADT (long- or short-term ADT (LADT and SADT)).

MATERIALS AND METHODS

Literature search. We performed a literature search of MEDLINE via PubMed to identify RCTs of RT for localised prostate cancer published through July 2013. We used the following MeSH terms and free text words: (1) RT, radiation, irradiation, brachytherapy, 'proton beam', and 'dose fractionation'; (2) localised, locally, localisation, local; and (3) 'prostatic neoplasms/RT'[Majr]. Then we used the sensitivity- and precision-maximising version (2008 revision) to filter trials according to the Cochrane Handbook for Systematic Reviews of Interventions (JPT and Green, 2011). In addition, we reviewed reference lists of retrieved reviews or meta-analyses to identify further studies.

Study selection. Studies had to be RCTs, blinded or not, of previously untreated adults with localised prostate cancer without metastasis. Each arm had to involve an RT regimen, regardless of dosage or technique. We included reports published in English and reporting at least one of the outcomes mentioned below.

Exclusion criteria were a study of the imaging technique or radiation technique; the outcomes of interest not reported or insufficiently reported, such as outcomes from the first report or a subset of patients; abstracts from scientific meetings; and main therapy regimens being, for example, brachytherapy, cryoablation, different targets, fast neutrons, pion therapy, or β-carotene therapy to decrease the rate of side effects.

Three investigators (ZZ, JZ, and YL) independently reviewed the titles and abstracts for potential articles, then read the full text, with decisions made by consensus or consultation with a fourth investigator (MC). If results of study were reported several times, we chose the latest publication.

Data extraction and quality assessments. Three investigators independently extracted the following data: first author, publication year, and study location; study period and institution, length of follow-up; and patient charactertics, number of outcomes of interest, and interventions. We assessed the risk of bias by using the Cochrane Collaboration risk of bias tool to assess random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential biases (JPT and Green, 2011). We did not assess blinding because blinding was not practicable in these trials. Disagreements during extraction were discussed with a fourth author.

Outcomes of interest included overall mortality (OM; from any cause), prostate cancer-specific mortality (CSM), PSA failure (biochemical failure), genitourinary (GU), and gastrointestinal (GI) toxicity grade $\geqslant 2$ according to Radiation Therapy Oncology Group morbidity scales/European Organization for Research and Treatment of Cancer scoring criteria (Cox *et al*, 1995), or the National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria. Prostate-specific antigen failure was determined as proposed by the American Society for Radiation Oncology (ASTRO), with $\geqslant 3$ consecutive increases in PSA level (Cox and Kaplan, 1997) or the ASTRO Phoenix definition ($\geqslant$ nadir $+2\,\mathrm{ng\,ml^{-1}}$) (Roach III *et al*, 2006).

Interventions. Hypofractionated RT was defined as dose per fraction >2.0 Gy and conventional RT as dose per session 1.8–2.0 Gy. High-dose radiation therapy was defined as total dose >74 Gy and LDRT as total dose $\leqslant 70$ Gy. High-dose radiation therapy and LDRT for localised prostate cancer could consist of photon or proton therapy combined with conventional and conformational techniques to deliver external-beam RT. Reports of RCTs that compared RT alone or with ADT (regardless of drug and dosage) for localised prostate cancer were included. Trials exploring SADT *vs* LADT, (regardless of absolute values) with RT for localised or locally advanced prostate cancer were included.

Statistical analysis. We grouped regimens such as LDRT, HDRT, LDRT + SADT, or + LADT, HDRT + SADT, HFRT, and HFRT + SADT. We chose a dichotomous outcome for OM instead of overall survival because hazard ratios and *P*-values were reported for a few trials but most reports described OM. The number of patients was calculated on an intention-to-treat basis: the analysis of efficacy data was based on the total number of randomly assigned participants, regardless of how the investigators of the original study analysed the data. We used a conservative approach and imputed outcomes for the missing participants, assuming that they did not respond to treatment (Cipriani *et al*, 2009). For outcomes, if only percentages were reported, the actual number of events were estimated and rounded to the nearest whole number.

We performed a pair-wise meta-analysis by synthesising results of studies that compared the same interventions with a random-effect model to incorporate the assumption that different studies assessed different yet related treatment effects (DerSimonian and Laird, 1986; Borenstein *et al*, 2011). We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs). Heterogeneity was evaluated by the inconsistency statistics (I^2), with values $<25\%$ considered low heterogeneity and $>50\%$ high heterogeneity (Higgins *et al*, 2003).

We used Bayesian network meta-analysis to incorporate both direct and indirect treatment comparisons for estimating the treatment effect between all interventions and ranked treatments in order (Lu and Ades, 2004). We compared outcome variables with a random-effect model. Each analysis was based on non-informative priors for effect sizes and precision. The estimates were obtained by the Markow Chain Monte Carlo method with 10 000 initial iterations to burn in and the next 30 000 iterations for estimations. The posterior mean of the residual deviance and deviance information criteria were used to evaluate the goodness of fit of the model. A model has good fit when residual deviance approximates the number of data points (Spiegelhalter *et al*, 2002). Conventionally, the results are presented by summarising the posterior distribution of the parameters of interest with means and 95% credible intervals. We also assessed the probability that each RT regimen was best in terms of efficacy, second best, third best, and so on, by calculating the OR for each regimen compared with control group. We ranked treatment regimens in terms of safety with the same methods. The LDRT group was considered the control group.

One key assumption of the network meta-analysis is the consistency between direct and indirect evidence, that is, whether the information of both sources of evidence are similar enough to be combined (Caldwell *et al*, 2010; Dias *et al*, 2011).

This assumption was checked by the Bucher method (Bucher *et al*, 1997). Moreover, we calculated the difference between direct and indirect evidence in all closed loops in the network; inconsistent loops were identified with a significant (95% credible interval that excludes 0) disagreement between direct and indirect evidence (Salanti *et al*, 2009).

We performed a sensitivity analysis by repeating the main computations using a fixed-effect model and a subgroup analysis by population (locally advanced or localised).

The results shown are from random-effect models with homogeneous between-trial variability. STATA 12.0 (Statacorp, College Station, TX, USA) was used for pair-wise meta-analysis, then R software (http://www.R-project.org, the R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) for network meta-analysis.

Role of the funding source. There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Characteristics of included trials. The electronic search yielded 1442 records, and after screening titles and abstracts, 204 records remained. We added another 18 articles from reviews, for 222 full-text articles assessed for eligibility. Finally, after excluding 161 articles, 61 reports assessing results of 27 RCTs (Zagars *et al*, 1988; Pilepich *et al*, 1995; Shipley *et al*, 1995; Pollack *et al*, 1996; Bolla *et al*, 1997; Lawton *et al*, 1997; Pilepich *et al*, 1997; Granfors *et al*, 1998; Nguyen *et al*, 1998; Pollack *et al*, 2000; Storey *et al*, 2000; Lawton *et al*, 2001; Pilepich *et al*, 2001; Bolla *et al*, 2002; Pollack *et al*, 2002; Hanks *et al*, 2003; Lamb *et al*, 2003; Yeoh *et al*, 2003; Ataman *et al*, 2004; Beckendorf *et al*, 2004; Crook *et al*, 2004; D'Amico *et al*, 2004; Laverdiere *et al*, 2004; Christie *et al*, 2005; Dearnaley *et al*, 2005; Denham *et al*, 2005; Lawton *et al*, 2005; Lukka *et al*, 2005; Peeters *et al*, 2005; Pilepich *et al*, 2005; Sathya *et al*, 2005; Zietman *et al*, 2005; Granfors *et al*, 2006; Peeters *et al*, 2006; Yeoh *et al*, 2006; Dearnaley *et al*, 2007; Al-Mamgani *et al*, 2008; D'Amico *et al*, 2008; Horwitz *et al*, 2008; Kuban *et al*, 2008; Roach *et al*, 2008; Bolla *et al*, 2009; Crook *et al*, 2009; Marzi *et al*, 2009; Strigari *et al*, 2009; Norkus *et al*, 2009a, 2009b; Alexander *et al*, 2010; Arcangeli *et al*, 2010; Bolla *et al*, 2010; Heemsbergen *et al*, 2010; Zietman *et al*, 2010; Al-Mamgani *et al*, 2011; Arcangeli *et al*, 2011; Armstrong *et al*, 2011; Beckendorf *et al*, 2011; Denham *et al*, 2011; Jones *et al*, 2011; Yeoh *et al*, 2011; Arcangeli *et al*, 2012; Dearnaley *et al*, 2012) were used in the network meta-analysis, for 13 364 patients with local or locally advanced prostate cancer randomly assigned to receive one of the seven RT regimens examined (Figures 1 and 2). The median age of patients ranged from 65 to 75 years and median follow-up ranged from 1 to 14.5 years, mostly were from 5 to 10 years.

Morbidity of adverse events was not reported consistently, and some reports described GI or GU toxicity as grade 1 to 4 and others as $\geqslant 2$ or $\geqslant 3$ grade. We calculated the number of adverse events for the $\geqslant 2$ grade GI or GU toxicity. The number of outcome events included in the analysis was as follows: 3795 OM, 4530 PSA failure, 1241 CMS, 3523 acute GI (AGI) events, 3,316 acute GU (AGU) events, 2387 late GI (LGI) events, and 2276 late GU (LGU) events.

Many RT techniques were used, such as IMRT, 3D-CRT, and conventional RT, and the radiation dose ranged from the lowest, 55 Gy to the highest, 80 Gy. Most trials used conventional fractionation, and some trials compared hypofractionation (2.7–4.5 Gy f^{-1}) to conventional fractionation (1.8 or 2 Gy f^{-1}).

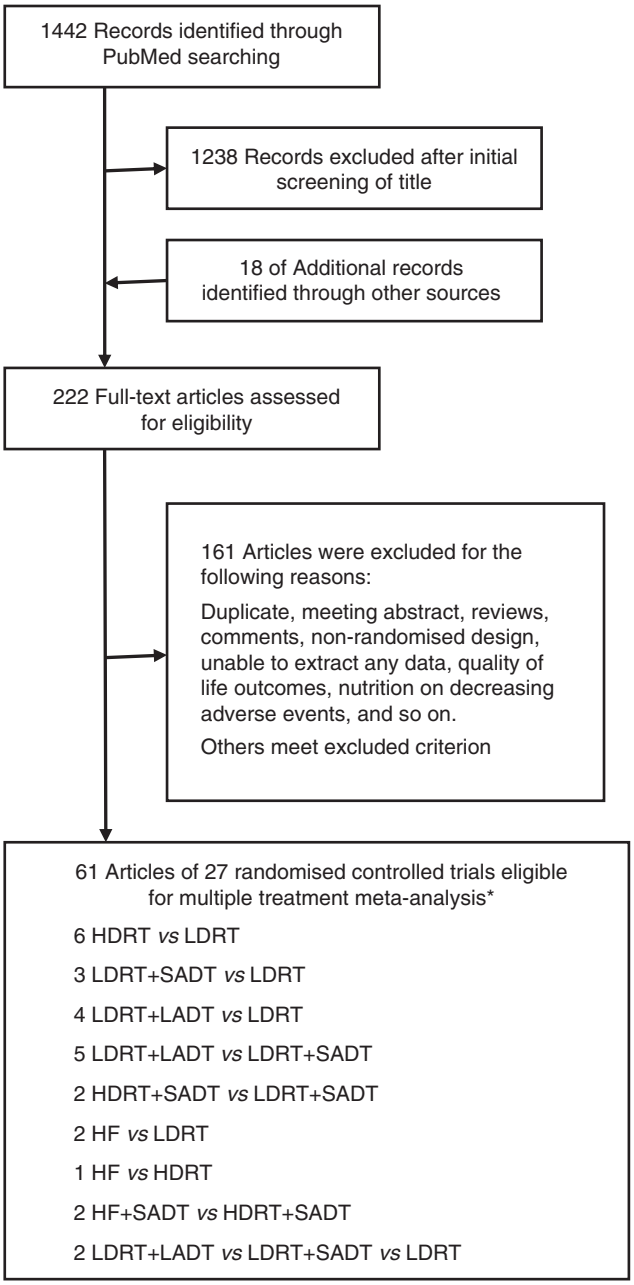

Figure 1. Study selection process. '*' Indicates 27 randomised trials that correspond to 56 groups because two three-arm studies were included in this network meta-analysis.

Patients with RT plus ADT experienced different ADT durations. Most began at 3 to 6 months before RT to the end of RT, so SADT duration was <10 months, whereas LADT duration was 2–3 years or the whole life (orchiectomy). The main characteristics of the included studies are in Supplementary Table 1.

The overall methodological quality was moderate (Supplementary Table 2). All included studies were RCTs, but most studies did not report the techniques for randomisation and concealment. When the article reported concealment carried out by a central office, we judged this as no bias.

Comparison of efficacy and safety. We directly compared efficacy and safety outcomes (Table 1 and Supplementary Table 3), showing that PSA control was associated with HDRT rather than LDRT, LDRT + SADT than LDRT, LDRT + LADT than LDRT + SADT, and HDRT + SADT than LDRT + SADT.

For OM and CSM, LDRT + SADT and LDRT + LADT were better than LDRT alone. In addition, LDRT + LADT was better than LDRT + SADT for CSM. Hypofractionated RT produced more AGU events than LDRT but less than HDRT. High-dose radiation therapy was associated with increased risk of LGI and LGU events as compared with LDRT, and LDRT + SADT was associated with increased risk of LGU events as compared with LDRT + SADT. Overall, heterogeneity was high for most safety outcomes and moderate for efficacy outcomes. With direct comparisons, I^2 values were >75% for the comparisons LDRT + LADT and LDRT + SADT for PSA failure and AGU events.

Network meta-analysis findings. The network meta-analysis results were based on a random-effects model (Table 2 and Supplementary Table 4) because they generally showed better goodness of fit and more conservative estimates than fixed-effect models (Supplementary Table 5).

The risk of OM was lower with LDRT + LADT and LDRT + SADT as compared with LDRT (ORs 0.64 (0.53–0.77) and 0.75 (0.61–0.88)) and LDRT + LADT as compared with HDRT (OR 0.72 (0.53–0.97)). For PSA failure, apart from HFRT, all treatments were associated with decreased risk as compared with LDRT. Moreover, HFRT + SADT was associated with decreased risk of PSA failure as compared with HFRT, LDRT + SADT, HDRT and LDRT, and LDRT + LADT as compared with LDRT + SADT, HDRT, and LDRT. However, HFRT alone was associated with increased risk of PSA failure as compared with HDRT + SADT, LDRT + LADT, and LDRT + SADT (ORs 2.98 (1.33–5.84), 2.46 (1.42–4.01), and 1.72 (1.01–2.92), respectively). Hypofractionated RT + SADT was associated with decreased risk of CSM as compared with HFRT, LDRT + SADT, HDRT and LDRT (ORs 0.24 (0.02–0.96), 0.23 (0.02–0.85), 0.17 (0.01–0.62), and 0.14 (0.01–0.50), respectively). High-dose radiation therapy + SADT, LDRT + LADT, and LDRT + SADT were associated with decreased risk of CSM as compared with LDRT (ORs 0.43 (0.19–0.85), 0.48 (0.35–0.63), and 0.6 (0.42–0.78), respectively) as was LDRT + LADT compared with HDRT (OR 0.56 (0.32–0.93)). We found no significant associations for AGI and AGU or for LGU and LGI events in the random-effects models, except for HDRT associated with increased risk of LGI events as compared with LDRT (OR 1.85 (1.35–2.53)).

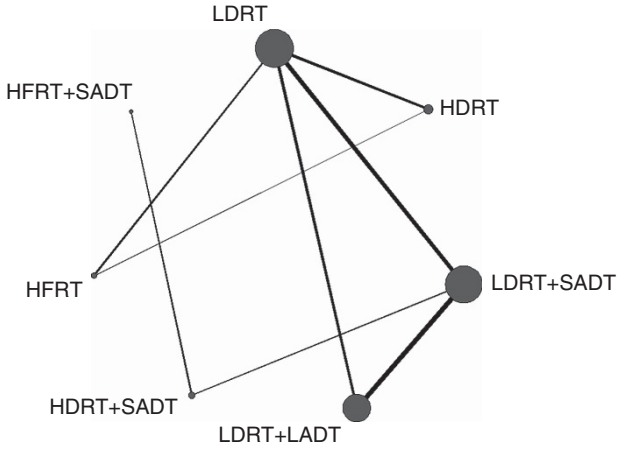

Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size).

We also ranked treatments and estimated the cumulative probabilities of being the best treatment using random-effect models under the Bayesian framework (Supplementary Table 6). Furthermore, we estimated an inconsistency factor for each closed loops as the difference between direct and indirect estimates and the corresponding 95% CI. Inconsistent loops are inconsistency factors with 95% CIs incompatible with zero. We found no inconsistent loops per network (Supplementary Table 7).

We performed a sensitive analysis using fixed-effect models (Supplementary Tables 8 and 9). However, random and fixed-effects models produced different results. More than 50% of patients were at the T3 or T4 tumor node metastasis stage in both trial arms, considered mainly locally advanced prostate cancer; similarly, trials of mainly T1 or T2 stage patients were considered as early-stage (localised prostate cancer) trials. We performed the subgroup analysis by early or locally advanced stage (Supplementary Tables 10, 11, and 12). All seven RT treatments were used in early-stage trials, and only four treatments (LDRT, HDRT, LDRT + SADT, and LDRT + LADT) in locally advanced-stage trials. In early-stage trials, OM and CSM did not differ by treatment method. Hypofractionated RT was associated with increased risk of PSA failure as compared with all other treatments except LDRT. In late-stage trials, LDRT + LADT was associated with decreased risk of OM, CSM, and PSA failure as compared with other treatments.

Table 1. Efficacy in meta-analysis of direct comparisons

	OM				BF				CSM			
	OR	95% CI	P	I^2	OR	95% CI	P	I^2	OR	95% CI	P	I^2
HDRT *vs* LDRT	0.91	0.72–1.14	0.395	0	0.61	**0.49–0.76**	**0.000**	0	0.92	0.67–1.26	0.586	0
LDRT + SADT *vs* LDRT	0.77	**0.66–0.90**	**0.001**	0	0.48	**0.41–0.57**	**0.000**	0	0.51	**0.38–0.67**	**0.000**	0
LDRT + LADT *vs* LDRT	0.65	**0.48–0.87**	**0.004**	28.20%	-	-	-	-	0.56	**0.38–0.83**	**0.004**	44.20%
LDRT + LADT *vs* LDRT + SADT	0.86	0.71–1.06	0.160	30.90%	0.65	**0.44–0.96**	**0.030**	*82.60%*	0.71	**0.53–0.95**	**0.023**	21.60%
HDRT + SADT *vs* LDRT + SADT	1.1	0.72–1.69	0.671		0.64	**0.48–0.83**	**0.001**	0	0.62	0.21–1.81	0.383	43.80%
HFRT *vs* LDRT	0.86	0.62–1.20	0.380	0	0.84	0.67–1.07	0.151	0	0.67	0.34–1.34	0.257	0
HFRT *vs* HDRT	0.94	0.06–15.42	0.962		0.61	0.10–3.82	0.595		-	-	-	-
HFRT + SADT *vs* HDRT + SADT	0.43	0.17–1.12	0.083		0.63	0.28–1.40	0.258		0.28	0.06–1.37	0.144	

Abbreviations: ADT = androgen deprivation; CI = confidence interval; CSM = cancer-specific mortality; HDRT = high-dose radiotherapy; HFRT = hypofractionated radiotherapy; LADT = long-term androgen deprivation therapy; LDRT = low-dose radiotherapy; OM = overall mortality; PSA = prostate-specific antigen failure; OR = odds ratio; SADT = short-term androgen deprivation therapy. Two three-arm studies comparing LDRT with LDRT + SADT and LDRT + LADT were not included in the pair-wise meta-analysis.

Table 2. Efficacy of the seven radiotherapy regimens in network meta-analysis (OR with 95% CrI)

HFRT + SADT	**0.27**	**0.69**	**0.62**	**0.43**	**0.38**	**0.21**	
	0.07–0.75	0.24–1.55	0.17–1.59	**0.12–1.10**	**0.10–0.98**	**0.06–0.53**	
0.46	**HFRT**	**2.98**	**2.46**	**1.72**	1.51	0.83	
0.12–1.28		**1.33–5.84**	**1.42–4.01**	**1.01–2.92**	0.87–2.46	0.50–1.29	
0.47	1.14	**HDRT + SADT**	0.89	0.62	0.55	**0.31**	
0.15–1.07	0.56–2.08		0.47–1.50	0.36–1.01	0.26–1.02	**0.16–0.53**	PSA
0.62	1.4	1.31	**LDRT + LADT**	**0.7**	**0.63**	**0.34**	
0.17–1.69	0.86–2.06	0.77–2.17		**0.56–0.89**	**0.40–0.96**	**0.26–0.45**	
0.53	1.2	1.12	0.87	**LDRT + SADT**	0.89	**0.49**	
0.15–1.39	0.77–1.78	0.68–1.85	0.73–1.04		0.58–1.33	**0.37–0.63**	
0.44	0.99	0.93	**0.72**	0.83	**HDRT**	**0.57**	
0.13–1.16	0.62–1.51	0.51–1.59	**0.53–0.97**	0.61–1.12		**0.40–0.75**	
0.4	0.89	0.84	**0.64**	**0.75**	0.91	**LDRT**	
0.12–1.07	0.59–1.27	0.49–1.37	**0.53–0.77**	**0.61–0.88**	0.69–1.15		
			OM				

HFRT + SADT						
0.24	**HFRT**					
0.02–0.96						
0.32	1.89	**HDRT + SADT**		CSM		
0.03–1.14	0.55–5.00					
0.3	1.5	0.91	**LDRT + LADT**			
0.02–1.08	0.56–3.2	0.38–1.80				
0.23	1.2	0.72	0.8	**LDRT + SADT**		
0.02–0.85	0.45–2.60	0.35–1.37	0.61–1.07			
0.17	0.82	0.51	**0.56**	0.71	**HDRT**	
0.01–0.62	0.29–1.79	0.19–1.08	**0.32–0.93**	0.40–1.13		
0.14	0.7	**0.43**	**0.48**	**0.6**	0.89	**LDRT**
0.01–0.50	0.28–1.50	**0.19–0.85**	**0.35–0.63**	**0.42–0.78**	0.55–1.33	

Abbreviations: ADT = androgen deprivation; CI = confidence interval; CrI = credibility interval; CSM = cancer-specific mortality; HDRT = high-dose radiotherapy; HFRT = hypofractionated radiotherapy; LADT = long-term androgen deprivation therapy; LDRT = low-dose radiotherapy; OM = overall mortality; PSA = prostate-specific antigen failure; OR = odds ratio; SADT = short-term androgen deprivation therapy. Results are the ORs in the column-defining treatment compared with the ORs in the row-defining treatment. ORs <1 favour the column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken (e.g., the OR for LDRT compared with HDRT is 1/0.91 = 1.1). Significant results are in bold. Two three-arm studies comparing LDRT with LDRT + SADT and LDRT + LADT were not included in the pair-wise meta-analysis.

DISCUSSION

Our network meta-analysis was based on 27 RCTs of 13 364 patients who underwent seven RT regimens for prostate cancer. We aimed to synthesise data on RT for prostate cancer to help in choosing a regimen that balances efficacy and safety for treating localised or locally advanced prostate cancer. Low-dose radiation therapy plus ADT might be associated with reduced risk of OM as compared with RT alone. Except for HDRT and HFRT, all RT regimens were associated with decreased risk of CSM as compared with LDRT. In addition, except HFRT as compared with LDRT, all regimens were associated with reduced risk of PSA failure. Hypofractionated RT plus SADT might be the most efficacious for local prostate cancer.

We found no difference among the seven RT regimens in toxicity. However, HDRT or LDRT plus ADT might be associated with reduced risk of acute toxicity as compared with RT alone. Only HDRT alone was associated with increased risk of LGI events as compared with LDRT alone. Low-dose radiation therapy alone might have the lowest late-toxicity rate. The most efficacious treatment (HFRT plus ADT) might not be the best for overall acceptability because of some toxicity.

Hypofractionated RT plus ADT was the most efficient for localised prostate cancer, especially in terms of reduced risk of PSA failure as compared with RT alone, but with the worst toxicity. Hypofractionated RT without ADT was associated with increased risk of OM, CSM, and PSA failure as compared with other treatments except RT alone (low or high dose), as with toxicity outcomes. Our findings may not agree with hypothesis of fewer but larger-than-conventional fractions being equal to high doses with conventional fraction sizes for efficacy with reduced total dose. Patients who received HFRT showed the reverse outcomes with or without short ADT. Notably, HFRT might be associated, but not significantly, with reduced risk of LGU events as compared with other treatments except LDRT alone. An important randomised trial had been published in 2013 comparing conventional fraction RT (2.0 Gy f^{-1}) with HFRT (2.7Gy f^{-1}) (Pollack *et al*, 2013). We could not group the arms in this trial for half of the patients in both arms received short or long ADT. In this trial, the hypofractionation regimen did not result in a significant reduction in biochemical and/or clinical disease failure, and this is consistent

with our pair-wise meta-analysis. In a traditional meta-analysis comparing HFRT with conventional fractionated RT, HFRT was associated with AGI toxicity, especially as compared with HDRT, and HFRT for localised prostate cancer was not superior to conventional therapy (Botrel *et al*, 2013). To some extent, these data are consistent with our network meta-analysis results. However, in our pair-wise meta-analysis, HFRT was associated with reduced risk of AGU events as compared with HDRT and increased risk of AGU events as compared with LDRT. We classified seven groups for only one trial included in each traditional meta-analysis and excluded the trials in the Botrel's meta-analysis because they did not meet inclusion criteria.

Hormone therapy has been used for decades as the sole treatment or as an adjuvant to RT for prostate cancer. In our network meta-analysis, overall, RT plus ADT significantly reduced the risk of OM, CSM, and PSA failure as compared with RT alone. Especially LDRT + LADT was associated with reduced risk of OM, CSM, and PSA failure as compared with HDRT or LDRT alone, and might be the second-best therapy for localised or locally advanced prostate cancer. In terms of toxicity, we observed no statistically significant differences among therapies, but the combination regimens might be associated with reduced risk of AGI events as compared with RT alone. In the Bria *et al* study (Bria *et al*, 2009), GU and GI events rates were reduced, but not significantly, with combination therapy, but acute or late toxicity was not described. In our pair-wise meta-analysis, LDRT with SADT or LADT had significant efficacy as compared with LDRT alone, which is similar to the Bria *et al* study (Bria *et al*, 2009).

Although our results confirmed the benefit of combination therapy for localised or locally advanced prostate cancer, the optimal duration of ADT added to RT remains is unknown. In our network meta-analysis and pair-wise meta-analysis, LDRT + LADT was associated with reduced risk of OM, CSM, and PSA failure as compared with LDRT + SADT. However, as compared with HDRT + SADT, LDRT + LADT was associated with increased risk of CSM and PSA failure. The Cuppone *et al* study (Cuppone *et al*, 2010) also favored LADT added to RT for locally advanced prostate cancer. Combined with LDRT, LADT might increase the risk of toxicity as compared with SADT. A spinodal effect might occur with increased duration of adjuvant ADT along with decreased toxicity, and then the spinodal point increases. However, we did not evaluate the optimal timing of ADT.

Our network meta-analysis indicated a trend in that HDRT gave the expect results and increased the early or late toxicity. While Michalski *et al* (Michalski *et al*, 2013) study showed that a trend for clinically reduction in late G2 + GI toxicity with HDRT using IMRT compared with 3D-CRT . And in another review (Bauman *et al*, 2012), the findings were in favour of IMRT over 3D-CRT in the radical treatment of localised prostate cancer when doses were > 70 Gy. However, we excluded the trials comparing different RT technique using same doses, and in most of the trials in our study, the group of HDRT used the 3D-CRT, thereby increasing the toxicity. In pair-wise meta-analysis, HDRT significantly reduced the risk of PSA failure as compared with LDRT, which is consistent with the Viani *et al* (Viani *et al*, 2009).

In the subgroup analysis, the seven treatments were examined in early-stage trials with four treatments in advanced-stage trials. With the advent of PSA screening, stage migration has resulted in the diagnosis of many men with potentially clinically insignificant disease. This finding might explain why no new RT technique was tested for locally advanced prostate cancer.

Our methodological approach was innovative. First, the division of RT methods was more exact and useful than the classes used in pair-wise meta-analysis. Second, to our knowledge, this is the first comparison of direct, indirect, and network approaches. This approach allowed us to incorporate all available evidence to estimate treatments more precisely. Third, for comparing trials with similar clinical features, we excluded trials of branch RT for high dose (> 100 Gy) or ADT alone and included patients with localised or locally advanced prostate cancer.

A possible limitation of the analysis is that we used published data rather than individual patient information. Individual patient data might produce a more detailed appraisal of outcomes for different risk groups. Even with the use of individual patient information in such a complex network of multiple treatments, the power to detect effect modifications might still be limited (Trikalinos and Ioannidis, 2001; Mauri *et al*, 2008). Adequate information about randomisation and allocation concealment was not reported in many included trials that might undermine the validity of overall findings (Cipriani *et al*, 2009). In addition, in a retrospective meta-analysis, selective reporting bias and publication bias cannot be avoided. Finally, in subgroup analysis, we classified the trials subjectively as early- or late-stage, and the results by different follow-up duration. Therefore, our results might over- or underestimate findings and strong inferences should be avoided.

In conclusion, HFRT + SADT might be the most efficacious treatment but with worst toxicity for localised or locally advanced prostate cancer, and HDRT may represent good efficacy but more adverse events. Considering the small number of patients in our HFRT groups and not long enough follow-up duration, more trials with large number of patients should be implemented to evaluate this method. However, with the advent of PSA screening, more patients are showing early-stage cancer, with long-life expectancy, so decreasing adverse events should be a concern with new RT (such as IMRT or Image Guided RT) techniques or regimens.

AUTHOR CONTRIBUTIONS

KL and ZZ were responsible for the study concept and design. ZZ, JZ, YL and MC acquired data, which were analysed and interpreted by ZZ and JZ ZZ drafted the report. ZZ and PG performed the statistical analysis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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