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REVIEW ARTICLE

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Can patients with low-risk prostate cancer really benefit from radical treatment?: A systematic review and network meta-analysis

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Abstract

Radical prostatectomy, radiotherapy and active surveillance are three widely used treatment options for patients with low-risk prostate cancer, but the relative effects are controversial. We searched PubMed, Embase and Web of Science until June 2020, focusing on the studies comparing the effect of radical prostatectomy, radiotherapy and active surveillance in patients with low-risk prostate cancer. Through the random-effects model, dichotomous data were extracted and summarised by odds ratio with a 95% confidence interval. Twenty-two studies containing 185,363 participants were pooled for the comprehensive comparison. The Bayesian mixed network estimate demonstrated the cancer-specific mortality of radical prostatectomy was significantly lower than active surveillance (OR, 0.46; 95% CI 0.34–0.64) and external beam radiation therapy (OR, 0.66; 95% CI 0.46–0.96), but not brachytherapy (OR, 0.63; 95% CI 0.41–1.03). The brachytherapy demonstrated the best treatment ranking probability results in terms of all-cause mortality, while no significant difference was observed when compared with other three treatment modalities. Brachytherapy and radical prostatectomy were associated with a similar risk of cancer-specific mortality, and both of them were significantly superior to active surveillance and external beam radiation therapy; nevertheless, there was no significant difference among the aforementioned treatment methods in all-cause mortality.

KEYWORDS

active surveillance, brachytherapy, clinical outcomes, prostatectomy, prostatic neoplasms

1 | BACKGROUND

Prostate cancer (PCa) is the most frequently diagnosed malignant tumour in men around the world and also the second leading cause of cancer-related mortality (Miller et al., 2018) globally causing >300,000 deaths/year in recent years. As PCa initial screening by measuring prostate-specific antigen (PSA) levels has become increasingly widespread, most of the patients are diagnosed at the early stage of prostate cancer and classified as low-risk level based on National Comprehensive Cancer Network (NCCN), which means they could be cured by radical prostatectomy (RP)—the complete removal of the prostate and seminal vesicles. Consequently, RP has become the gold standard for the surgical treatment of localised prostate cancer. Apart from prostatectomy, radiotherapy

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is another widely applied therapeutic option for low-risk prostate cancer. Radiation therapy is commonly delivered through external beam radiotherapy (EBRT) or via radioactive seeds implanted within the prostate (brachytherapy). Nevertheless, the majority of low-risk prostate tumours are intended to be indolence; thus, many patients might have a chance to avoid radical treatment. Active surveillance (AS) is the most common conservative treatment that offers patients a chance to defer radical treatment in the absence of tumour progression.

Several previous studies, though with different methods and qualities, have attempted to represent clinical and functional outcomes of the interventions for low-risk PCa, came to different conclusion. Since the major outcomes of three clinical trials (SPCG-4, PIVOT and PROTECT) (Bill-Axelson et al., 2014; Donovan et al., 2016; Wilt et al., 2017) are completely different, the optimal extent regarding which treatment should be performed is a long-standing debate. Up to now, there is still no determined consensus on the optimal therapy for patients with localised low-risk prostate cancer; treatment selection is mainly based on clinical condition, experience of the physician and clinical criteria. Previous systematic reviews on treatments of prostate cancer have historically focused on 1 or 2 interventions; that is, they have not provided the comparative effectiveness of all available strategies. Therefore, we conducted this systematic review and network meta-analysis (NMA) to provide comparison on the relative efficacy and prognosis benefits of RP, AS and radiotherapy on CSM and ACM.

2 | METHOD

This study followed PRISMA recommendations (preferred reporting items for systematic reviews and meta-analyses) and was performed according to the methods and guidelines from the Cochrane handbook. Ethical approval is not necessary since it is a systematic review and meta-analysis does not contain any private information of participants or violate their human rights. To make sure the data of the included studies were reliable and veritable, we systematically searched PubMed, Embase and Web of Science to include all published potentially appropriate studies that at least make comparison between two of aforementioned treatment methods (RP, radiotherapy and AS) in treating low-risk prostate cancer from January 2004 to June 2020. The search strategy is consisted of the Mesh Word of the following term (prostate cancer, radical prostatectomy, radiotherapy, brachytherapy [BT], external beam radiation therapy and active surveillance) with CSM and/or ACM as endpoints. We also searched proceedings from relevant references of each study to avoid missing potentially eligible research and the language was restricted to English. Unpublished trials, abstracts, case report, letters to editor, commentary and cluster randomised trials were excluded in the present study. The search results would be imported into EndNote x9 software to remove duplicate literature. All titles and abstracts were screened by two independent authors for eligibility, and any content of disagreement or uncertainty was solved through discussion. Similar procedures were followed to select eligible records which met our inclusion or exclusion criteria through full-text screening. Another two authors independently reviewed the main reports and supplementary materials to extract the relevant information from the included trials. The corresponding authors of the included studies were contacted for additional information on trials if necessary. If a research was published more than once, we only included the first one. When there were multiple studies from the same institutions or authors at the same period, we only included the largest study to avoid duplication of patients. The eligibility criteria for this study were strictly according to the PICOS principles. The PICOS research question was whether patients with low-risk prostate cancer (population) could get better results for prognosis (outcome) through radical prostatectomy (intervention) when compared with active surveillance and radiotherapy (comparison intervention) in observational and randomised control trail studies (study design).

The inclusion criteria for the initially screened articles were as follows: (a) patients were classified as low risk based on NCCN, (b) articles should contain the clinical data of ACM or CSM to extract the useful data for odds ratio (OR), and (c) patients were regularly followed up longer than 1 year. We excluded trials with (a) studies that do not provide available data or cannot be extracted, (b) studies focused only on high-risk or intermediate-risk prostate cancer, (c) participants with multiple forms of cancer, (d) patients treated with multiple strategies and (e) 100 or fewer participants.

The possible causes of clinical or methodological heterogeneity were investigated through subgroup analysis and sensitivity analysis. According to study type, the patients were divided into two subgroups, a RCT and an observational study groups. In addition, subgroup analysis was further conducted according to different type of radiotherapy (RT) across the entire cohort to explore whether the statistical significance existed between BT and EBRT so that the best clinical choice could be identified. To further identify potential sources of heterogeneity, we also performed a meta-regression for the efficacy outcomes with at least 10 studies through Stata 12 using 5 variables (publication year, age of participants, follow-up period, research quality, study design).

All included observational studies were evaluated for risk of bias by two reviewers through Newcastle–Ottawa Scale (NOS) (Wells et al., 2000) with ≥7 score representing high-quality, while the assessment for RCT studies was based on Cochrane Collaboration's tool for risk of bias (Higgins et al., 2011). RCTs were evaluated in terms of random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and anything else, ideally pre-specified (other bias). There are three levels: low, unclear or high risk for the quality of RCT evidence. Any discrepancies were resolved by consensus or arbitration of a third author. The funnel plot was applied to evaluate the publication bias of a meta-analysis, and Egger test was reported with a $p < .05$ being considered statistically significant. Study design, radiation modality,

number and age of participants, regime, and outcome data of each treatment were extracted from each included study. Pairwise meta-analysis was generated at first between direct comparisons with Stata 13 (Stata Corp). Bayesian network meta-analysis in random-effect model was conducted by R version 3.4.1 software with the packages GeMTC (MRC Biostatistics Unit) recalling JAGS (version 4.3.0) based on 20,000 tuning iterations for each four Markov chain Monte Carlo (MCMC) chains with a burn-in period of the initial 5,000 iterations; the number of chains was 4 with variance scaling factor = 2.5. The detailed R code is provided in Appendix S1. To avoid the violation of the transitivity assumption in network meta-analyses, we only included studies focusing on low-risk prostate cancer (patients with clinical stage T1 to T2a, grade group 1 and serum PSA level <10 ng/ml) with plausible range of covariate distribution and comparable study design. A covariate-adjusted arm-based 3-level hierarchical Bayesian random-effects model was also applied for this network meta-analysis to guarantee the precision of the estimates. MCMC convergence was evaluated through the potential scale reduction factor (PSRF) of the Brooks–Gelman–Rubin method, and PSRF closer to 1 represents the better convergence (Brooks & Gelman, 1998). Based on the closed loops of the network connections, node-splitting analysis was also generated to explore the statistical inconsistency (White, 2011). The dichotomous variables were expressed in the form of OR as an effect indicator, and 95% CI was included as effect analysis statistics. The size of heterogeneity across studies was evaluated with I^2 statistic. $I^2 > 50\%$ was considered as substantial heterogeneity (Higgins et al., 2003). The rank probabilities were applied to reveal the hierarchy of different treatment, and a lower rank probability value symbolised a better rank of method. If a therapy had a lowest probability of ranking first than all the other methods, then it would be considered as the most effective one. Based on our pooled result, rank 1 was the best and rank N was the worst. Rank probability plots would indicate potential efficacy when two treatments had no statistical significance, though it should be treated carefully (Du et al., 2019).

3 | RESULTS

3.1 | Eligible studies and characteristics

A summary of the selection results is demonstrated as a PRISMA flow diagram, representing as a visual flow chart in Figure 1. After removing the duplicates, we identified 2,334 records from the initial title and abstract screening process, retrieved and reviewed 74 articles in full-text assessment for eligibility, among which 52 were

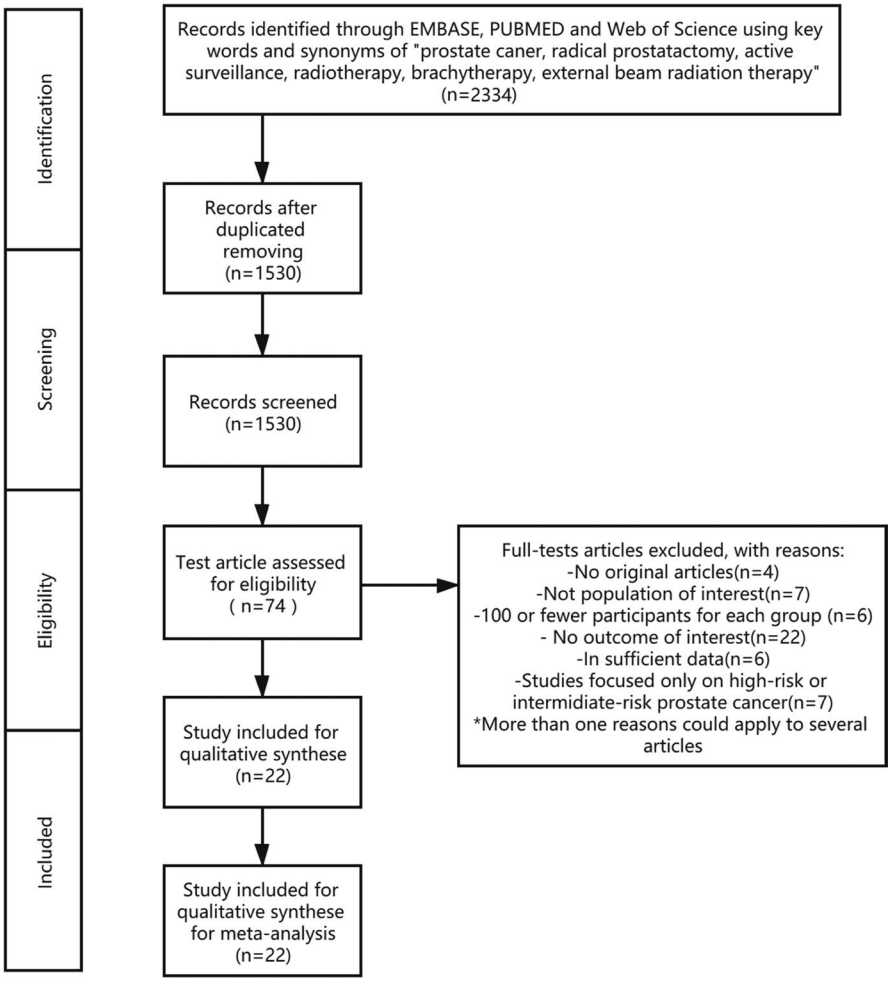


FIGURE 1 Flow chart of identification and selection of included studies

excluded based on the following reasons: no original articles ($n = 4$), not population of interest ($n = 7$), 100 or fewer participants ($n = 6$), no outcome of interest ($n = 22$), insufficient data ($n = 6$), studies focused only on high-risk or intermediate-risk prostate cancer ($n = 7$). Finally, 22 RCTs and retrospective articles (Abdollah et al., 2012; Aizer et al., 2009; Albertsen et al., 2007; Arvold et al., 2011; Bill-Axelson et al., 2014; Colberg et al., 2007; Degroot et al., 2013; Fosså et al., 2014; Giberti et al., 2009; Hamdy et al., 2016; Hayashi et al., 2019; Hoffman et al., 2013; Ladjevardi et al., 2010; Merglen et al., 2007; Merino et al., 2013; Patrick & Walsh, 2005; Resnick et al., 2013; Rice et al., 2013; Stattin et al., 2010; Taguchi et al., 2015; Tward et al., 2010; Wong et al., 2006) were included in our NMA with a total of 185,363 patients treated by at least one of the three treatment strategies. Sixteen trials (Aizer et al., 2009; Albertsen et al., 2007; Arvold et al., 2011; Degroot et al., 2013; Fosså et al., 2014; Giberti et al., 2009; Hamdy et al., 2016; Hayashi et al., 2019; Ladjevardi et al., 2010; Merglen et al., 2007; Merino et al., 2013; Patrick & Walsh, 2005; Resnick et al., 2013; Rice et al., 2013; Stattin et al., 2010; Taguchi et al., 2015) investigated RP versus RT, whereas 11 trials (Abdollah et al., 2012; Albertsen et al., 2007; Bill-Axelson et al., 2014; Fosså et al., 2014; Hamdy et al., 2016; Ladjevardi et al., 2010; Merglen et al., 2007; Stattin et al., 2010; Tward et al., 2010; Wilt et al., 2017; Wong et al., 2006) compared RP with AS. Table 1 demonstrates individual data and detail information on characteristics of the 22 included studies. The 22 included studies were conducted in eight countries on five continents and were published from 2004 to 2019. The median sample size was 1,548 patients (range: 147–60,290). Nine of the studies (Aizer et al., 2009; Bill-Axelson et al., 2014; Colberg et al., 2007; Degroot et al., 2013; Giberti et al., 2009; Merglen et al., 2007; Rice et al., 2013; Taguchi et al., 2015; Wilt et al., 2017) included <1,000 patients and four (Abdollah et al., 2012; Ladjevardi et al., 2010; Tward et al., 2010; Wong et al., 2006) included more than 20,000. The median follow-up period based on individual patient data (interquartile range) was 7.05 years (3.8–15). For the two types of outcome, 16 studies (Abdollah et al., 2012; Aizer et al., 2009; Albertsen et al., 2007; Arvold et al., 2011; Bill-Axelson et al., 2014; Degroot et al., 2013; Fosså et al., 2014; Giberti et al., 2009; Hamdy et al., 2016; Hoffman et al., 2013; Merglen et al., 2007; Merino et al., 2013; Resnick et al., 2013; Stattin et al., 2010; Tward et al., 2010; Wilt et al., 2017) provided CSM, 14 studies (Abdollah et al., 2012; Bill-Axelson et al., 2014; Fosså et al., 2014; Hayashi et al., 2019; Ladjevardi et al., 2010; Merino et al., 2013; Patrick & Walsh, 2005; Resnick et al., 2013; Rice et al., 2013; Stattin et al., 2010; Taguchi et al., 2015; Tward et al., 2010; Wilt et al., 2017; Wong et al., 2006) reported ACM, and nine studies (Abdollah et al., 2012; Bill-Axelson et al., 2014; Fosså et al., 2014; Merino et al., 2013; Patrick & Walsh, 2005; Resnick et al., 2013; Stattin et al., 2010; Tward et al., 2010; Wilt et al., 2017) included both of them. Most of the studies (19 of 22) reported the mean or median ages of participants, which ranged from 50 to 74.1 (mean age: 65.2 years). Two separate networks were created, one comparing CSM and one in which ACM was compared after treatments.

3.2 | Risk of bias assessment

Risk of bias assessment of the included studies is presented in Figure 2. The majority of RCTs were of high quality, while Hamdy et al. (2016) are of unknown risk as it had more than three domains judged as unclear risk. All six included RCT studies (Bill-Axelson et al., 2014; Degroot et al., 2013; Fosså et al., 2014; Hamdy et al., 2016; Resnick et al., 2013; Wilt et al., 2017) were of low risk in random sequence generation domain. Five were considered as low risk of bias from allocation concealment domain, while one study (Wilt et al., 2017) was classified as unknown risk of bias in this domain. One study (Fosså et al., 2014) was open-label and therefore rated as high risk on the domain of performance bias. In the NOS system for retrospective studies, nine (Abdollah et al., 2012; Albertsen et al., 2007; Arvold et al., 2011; Colberg et al., 2007; Hoffman et al., 2013; Merglen et al., 2007; Patrick & Walsh, 2005; Stattin et al., 2010; Wong et al., 2006) of these 15 retrospective studies were of high quality, as shown by NOS scores ≥7. There were no studies that we should clearly have excluded due to poor quality or the differences in baseline characteristics.

3.3 | Pairwise meta-analysis of CSM

The forest plots of meta-analysis comparing RP versus AS and RP versus RT in terms of CSM are presented in Figures 3–6. As can be seen from pairwise comparison, RP was associated with a declined CSM compared with RT and AS (AS OR, 0.40; 95% CI, 0.37–0.44 $I^2 = 1\%$; RT: OR, 0.65; 95% CI, 0.50–0.85 $I^2 = 60\%$). In subgroup analysis based on radiotherapy modalities, RP showed significant CSM advantage over EBRT alone (OR, 0.60; 95% CI, 0.43–0.84 $I^2 = 43\%$), while RP failed to show superiority in the BT subgroup (OR, 0.75; 95% CI, 0.54–1.04 $I^2 = 36\%$). As for the meta-regression, our results showed that none of the aforementioned variables (publication year, age of participants, follow-up period, research quality, study design) was the source of heterogeneity for both RP versus AS and RP versus RT subgroups. Meta-regression for CSM is summarised in Appendices S2 and S3.

3.4 | Pairwise meta-analysis of ACM

On ACM analysis, no significant alteration was detected in RP group when compared with AS (OR, 0.78; 95% CI, 0.57–1.05 $I^2 = 100\%$) and radiotherapy (OR, 1.14; 95% CI, 0.97–1.32 $I^2 = 82\%$) as shown in Figures 3, 4, 5 and 7. With regard to radiotherapy modality subgroup analysis, BT presented promising reductions in ACM compared with RP (OR, 1.67; 95% CI, 1.30–2.15 $I^2 = 80\%$), while on the other hand, no significant difference between RP and EBRT was observed (OR, 0.87; 95% CI, 0.71–1.06 $I^2 = 77\%$) in ACM analysis.

As for the subgroup analysis according to study design, our results indicated that there were no statistical differences between the RCT group and observational group for each pairwise comparison with

TABLE 1 Characteristics of included studies and the main characteristic

Author	Year	Follow-up (RP/RT/AS)	Study type	Age	Radiation modality	Sample size			Country	NOS
						RP	RT(BT/EBRT)	AS		
Hayashi	2019	6.4/4.5/5.5	Retro	66/73/70	Intensity-modulated radiation therapy/ brachytherapy	462	319/1,036		Japen	6
Wilt	2017	12.7	RCT	67		364		357	USA	Low risk
Hamdy	2016	10	RCT	50–69	Three-dimensional conformal radiotherapy 74 Gy/37 fractions	553	545	545	UK	Unknown risk
Taguchi	2015	4.4/3.7	Retro	66/70	External beam radiotherapy	568	322		Japen	5
Axelson	2014	13.4	RCT	65		347		348	Sweden	Low risk
Fossa	2014	13.5	RCT	62/66/69	Not specified	895	1,339	1,252	Norway	Unknown risk
Hoffman	2013	15	RCT	NG	External beam radiotherapy	1,164	491		USA	Low risk
DeGroot	2013	4.25	RCT	69.2/62.8	External beam radiotherapy	518	458		Canada	Low risk
Merino	2013	7.6/6.3	Retro	63/70	Intensity-modulated radiotherapy 76 Gy	993	207		Chile	6
Rice	2013	6.4	Retro	72.2/74.1	External beam radiotherapy	194	252		USA	6
Abdollah	2011	7.1	Retro	69.8/73.5	Not specified	22,244		22,450	Italy	7
Arvold	2011	4.2	Retro	62.9/71	Brachytherapy	2,935	5,902		USA	7
Stattin	2010	8.2	Retro	61.2/63.4/64.7	Not specified	3,399	1,429	2,021	Sweden	7
Ladjevardi	2010	4.0/4.4/4.8	Retro	65.2	External beam radiotherapy/brachytherapy	8,884	3,462	9,016	Sweden	6
Aizer	2009	3.8/3.3	Retro	NG	Intensity-modulated radiation therapy	204	352		USA	5
Giberti	2009	5	RCT	65.2/65.6	Brachytherapy	89	85		Italy	Low risk
Merglen	2007	6.7	Retro	71	External beam radiation	158	152	378	Canada	7
Albertsen	2007	13.3	Retro	65/70	External beam radiation	802	702	114	Canada	7
Colberg	2007	13	Retro	59/67	Brachytherapy	391	350		USA	7
Tward	2006	3.8	Retro	NG	Brachytherapy	34,758	6,637	18,895	USA	6
Wong	2006	12	Retro	72.9/71.0		13,292		12,608		7
Patrick and Walsh	2004	7	Retro	61.8/69.4	Brachytherapy	746	733		USA	7

Abbreviations: AS, active surveillance; BT, brachytherapy; EBRT, external beam therapy; NG, not given; RCT, randomised controlled trial; Retro, retrospective study; RP, radical prostatectomy; RT, radiotherapy.

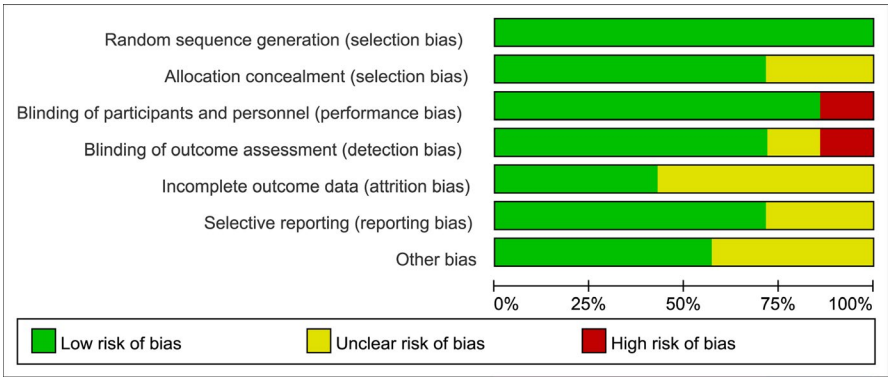


FIGURE 2 Risk of bias for the included RCT studies

$p > .05$ and through our subgroup analysis, heterogeneity could be reduced to an acceptable range ($I^2 < 50\%$). Furthermore, sensitivity analysis was performed to assess the influence of individual study on the overall meta-analysis results by excluded one study once a time, and the 'remove-one' sensitivity analysis suggested that our findings are convincible. In meta-regression, both RP versus AS and RP versus RT failed to provide the sufficient data for meta-regression so that the meta-regression could not be conducted.

The funnel plot and Egger's test also did not indicate a major publication bias with p value = .250 (CSM) and p value = .139 (ACM) respectively (Figure 8a,b).

3.5 | Network meta-analysis for CSM

Network connections of included studies are presented in Figure 9a. According to the available data, compared with EB and AS, RP achieved significantly lower CSM (EBRT: OR, 0.66 0.46–0.97 95% CI; AS: OR, 0.46 0.34–0.64 95% CI), while showed similar results to BT (OR, 0.63 0.41–1.03 95% CI). Compared with AS, EBRT only demonstrated a similar CSM (OR, 0.70 0.45–1.07 95% CI) (Table 2). As illustrated by the rank probabilities, brachytherapy (0%), prostatectomy (0%) and EBRT (4%) are three recommended options for low-risk prostate cancer in terms of ACM (Figure 10a).

3.6 | Network meta-analysis for ACM

A total of 14 studies involved RP, AS, EBRT and BT were included in the network meta-analysis (Figure 9b). Based on our established network, compared with results from the traditional pairwise meta-analysis, although BT failed to show a clinically superior advantage for ACM over other treatment modalities, according to rank probability, BT was still recommended as the optimal choice in terms of ACM followed by RP (2%), EB (43%) and AS (56%). The rank probability plots are displayed in Figure 10b. There is no statistical difference among four treatments in ACM as outcome.

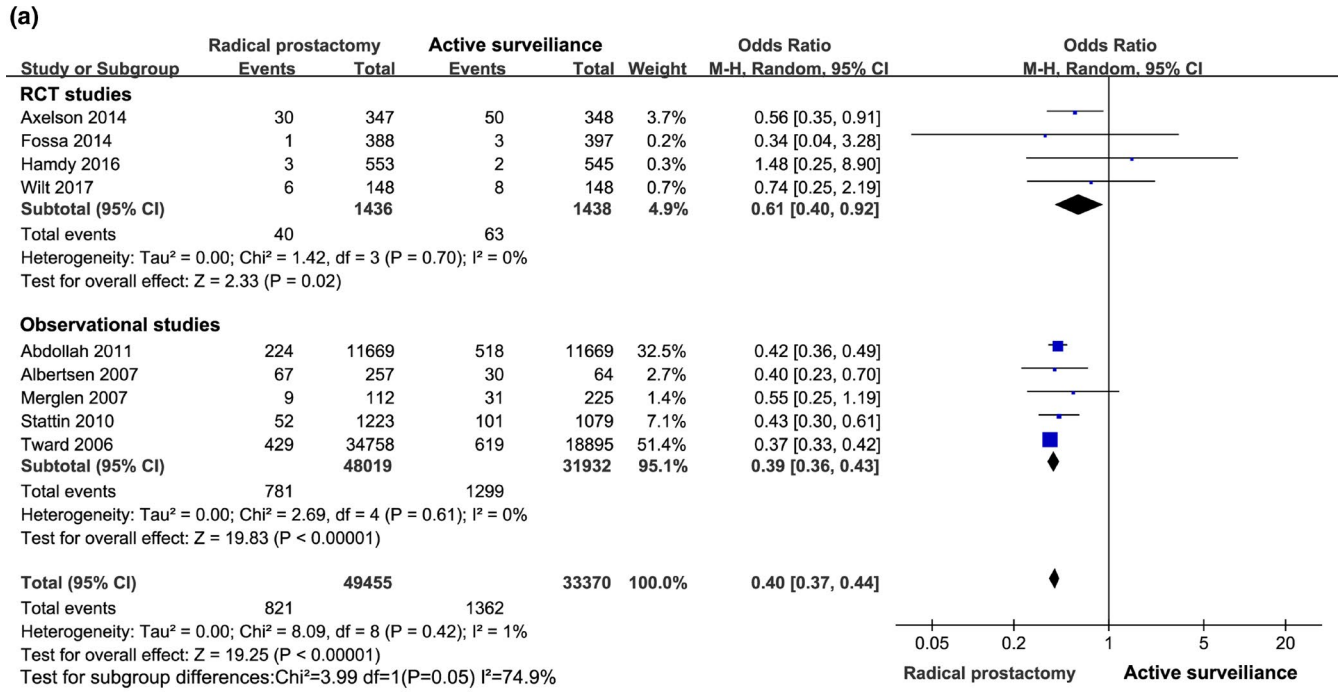
All the PSRFs were close to 1.00, so the model was proven convergent and stable; in terms of the node spilt analysis, all p values exceeded .05 and consistency model was selected. According to our 3-level hierarchical model, whether included study is observational study or RCT would not increase heterogeneity to our meta-analysis; thus, the adjustment is not needed (Appendices S4 and S5).

4 | DISCUSSION

In the management of low-risk prostate cancer, there is always a basic question: Where is the border between evidence-based radical management and overtreatment? It remains controversial about whether the increased detection and treatment of low-risk prostate cancer could benefit overall survival rates since multiple observational studies have proved most of the low-risk cancers are related to minimal risk of cancer-related mortality (D'Amico et al., 2002; Lavallée et al., 2014). Two previous meta-analyses (Luo et al., 2019; Zhang et al., 2020) focusing on the relative efficacy of RP compared radiotherapy with AS were published in 2019 and 2020 respectively. However, to the best of our knowledge, our present study is the first network meta-analysis exploring the prognosis of different treatment in patients with low-risk prostate cancer. Compared with pairwise meta-analysis, network meta-analysis could provide useful information about the effectiveness of treatments that have not been compared head to head.

The major findings of this NMA of different treatment in low-risk prostate cancer can be summarised as follows: first, brachytherapy should be considered as prior choice in terms of low-risk prostate cancer, second, when only focusing on CSM, RP ranked better than EB and AS, and finally, although BT had the highest probability ranked the first best for improving ACM and RP had second highest probabilities of being ranked second, no statistical difference was detected among the four treatments. These results were overall consistent among each endpoint.

The application of AS for low-risk PCa patients inclined from 9.7% in 2004 to 15.3% in 2007 according to SEER and Medicare data (Filson et al., 2014). However, Epstein et al. (1994) indicated that one-third of patients who failed AS underwent RP in the end with seminal vesicle/lymph node involvement or extraprostatic extension. Within 5 years of AS, almost 30% of patients need other treatments, such as surgery or radiotherapy (Moschini et al., 2017). In addition, when compared with RP, patients underwent AS were more likely to develop metastatic disease (Bill-Axelson et al., 2014). However, Venderbos et al. (2017) reported that patients under AS reached



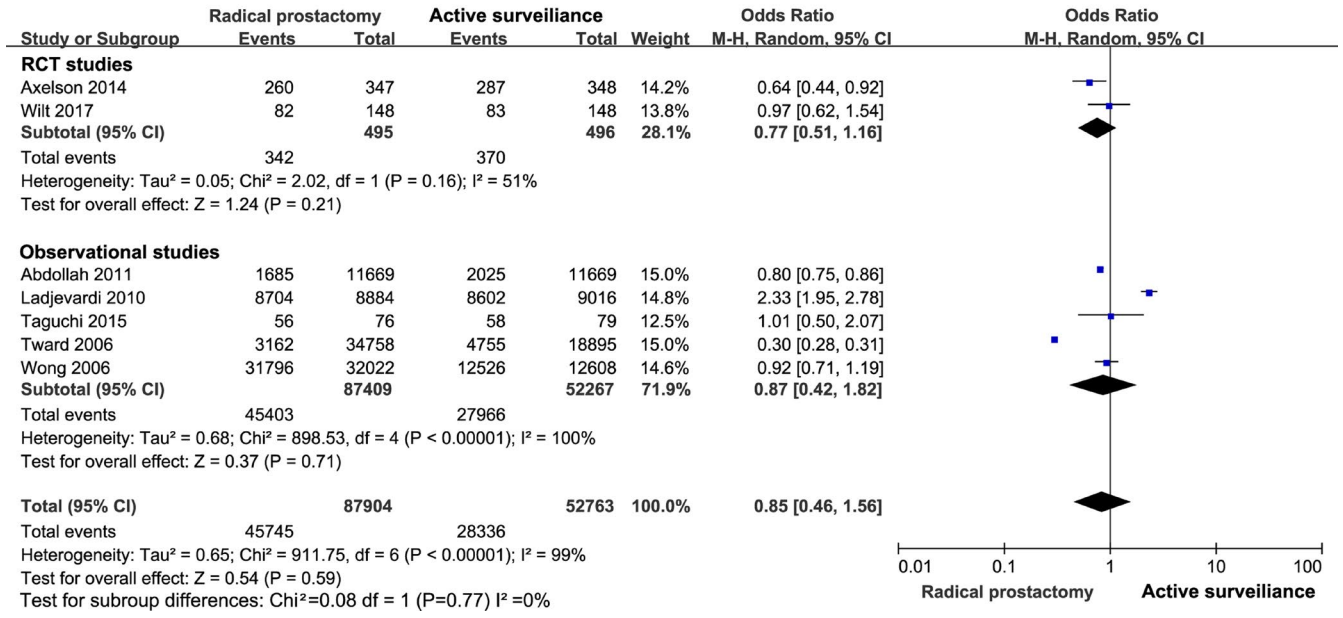


FIGURE 3 (a) Forrest plot assessing the risk of CSM following RP and AS for prostate cancer. (b) Forrest plot assessing the risk of ACM following RP and AS for prostate cancer

statistically and clinically significant better levels in role, social and emotional functioning compared with patients went through RP, maybe that could explain why there is no clinical difference in ACM between AS and RP. Besides, RP has been reported to be related to numerous adverse effects, such as the possibility of erectile and urinary function, which lead to the decline of life quality. Therefore, decisions about the management of low-risk PCa, including AS, should be made with an individualised method such as life expectancy and physical condition after careful risk evaluation. Moreover, risk stratification and prediction model for low-risk cancer patients are still necessary to allow physicians identify patients accurately with a greater risk of progression.

When the decision for an active treatment for low-risk PCa is made by the clinician or chosen by patients, uncertainty about the optimal treatment alternative leads to wide and substantial differences in the application of various interventions. Radiotherapy has been considered as an effective alternative to surgery for curative treatment of low-risk PCa, and Mohler et al. (2016) pointed out radiotherapy is suitable for patients who are unfit or unwilling to surgery, those with less than 10 years' life expectancy or high-risk patients

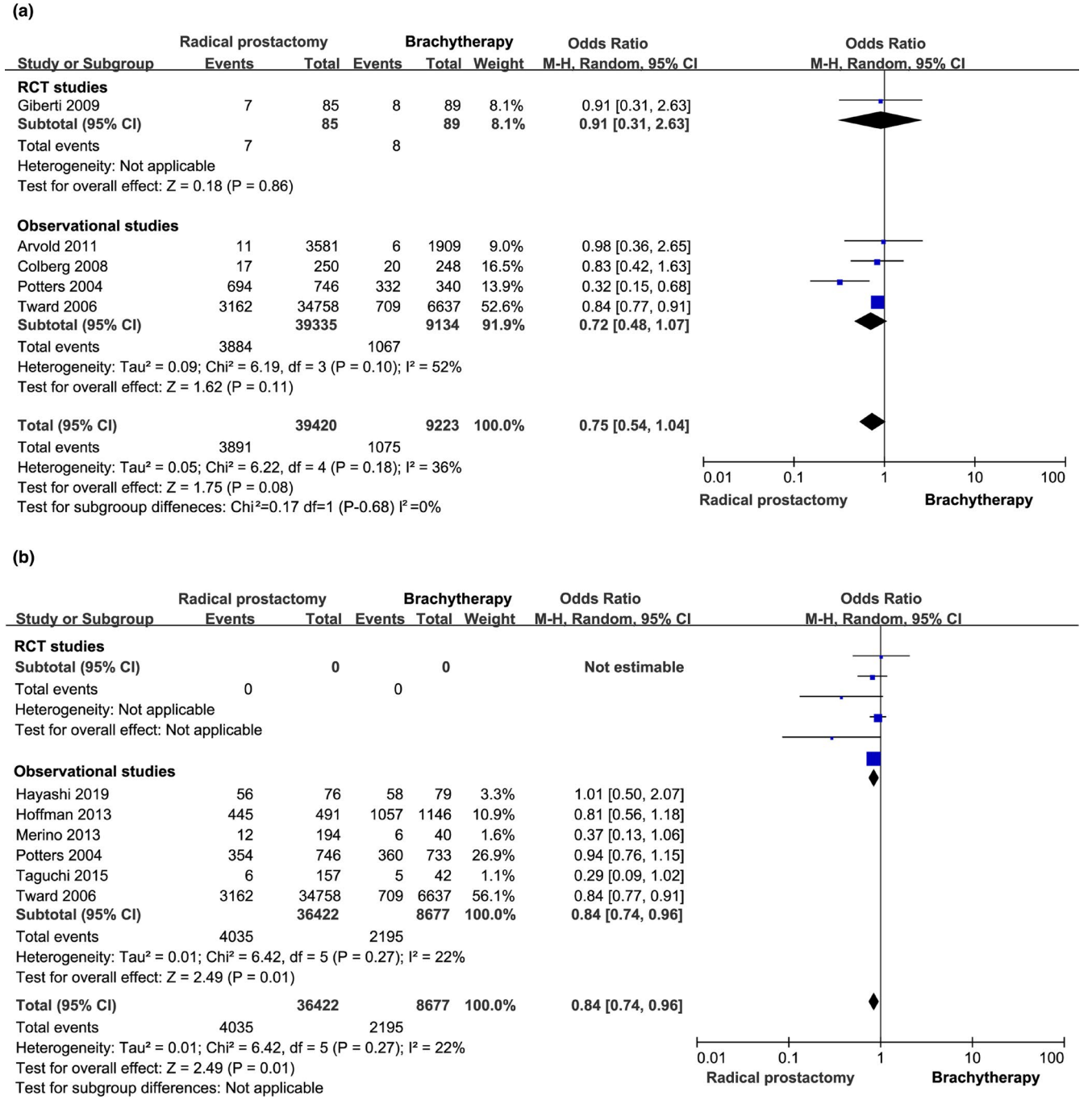


FIGURE 4 (a) Forrest plot assessing the risk of CSM following RP and BT for prostate cancer. (b) Forrest plot assessing the risk of ACM following RP and BT for prostate cancer

suffered from distant metastasis. Prostate cancer brachytherapy, as a new form of radiotherapy, was first conducted by Barringer in 1915 and gradually popularised in the 1970s, when the retro-pubic technology matured (Barringer, 1924). Multiple previous studies have suggested that due to its high-dose gradient, brachytherapy has increasingly become an important part of radiotherapy with reduced total treatment time, increased patient comfort and precise dose distribution (Yoshioka et al., 2014). Abdel-Wahab et al. (2008) reported significantly ($p < .0001$) fewer tumour progression events were detected among patients treated by brachytherapy when compared with EBRT. Thus, the American Brachytherapy Society recommends patients with tumour (T) classifications of T1–T2a, with PSA levels <10 ng/ml and with biopsy Gleason scores 6 have been considered as the most appropriate cohort for brachytherapy alone. BT with or without EBRT has an apparent advantage over EBRT in biochemical control for all risk patients. Recently, the advantage of brachytherapy and EBRT combination therapy has been proved by the ASCENDE randomised trial at a median follow-up of 6.5 years with a significantly lower biochemical failure. This therapeutic strategy could provide broad coverage of extraprostatic tissues while

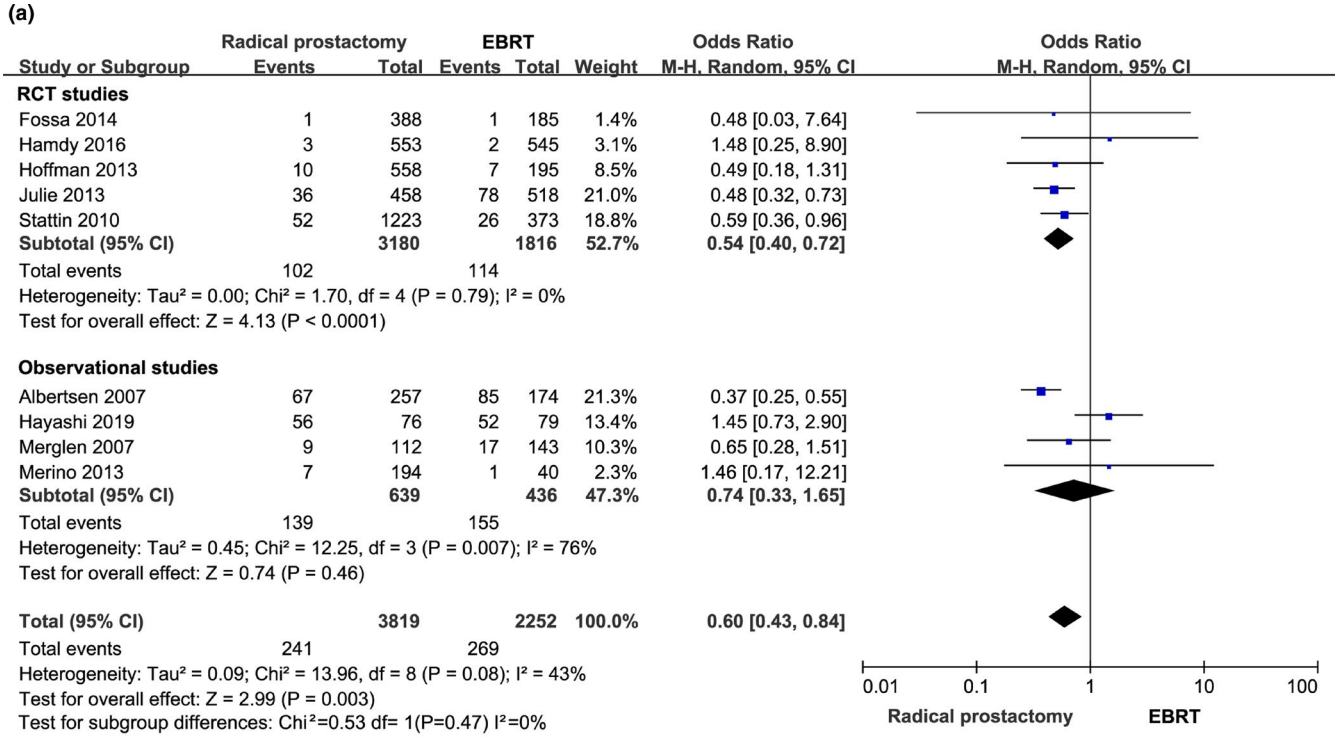


FIGURE 5 (a) Forrest plot assessing the risk of CSM following RP and EBRT for prostate cancer. (b) Forrest plot assessing the risk of ACM following RP and EBRT for prostate cancer

ensuring an extremely conformal, high-dose boost of radiation to the prostate. In addition, brachytherapy also can be used as a salvage treatment after failed radiation therapy due to relatively little long-term toxicity (Burri et al., 2010).

Radiotherapy was also associated with several distinct adverse effect profiles, and Jani and Hellman (2003) indicated when compared with EBRT, brachytherapy could improve sexual dysfunction and incontinence rates and increase the rate of urinary retention but reduce rectal-related adverse effects. Complications requiring unplanned procedures may occur after brachytherapy and could be significantly increased after brachytherapy when combined with EBRT. Hoskin et al. (2012) indicated that the incidence of early grade 3 or higher genitourinary and gastrointestinal morbidity was 3%–7% with acute grade 1 genitourinary toxicity and grade 3 chronic urinary toxicity which may occur lately and be problematic. Regardless of radiation treatment technique in the low-risk PCa cohort, clinical doctors must strictly follow normal tissue dose constraints when performing the treatment process. Brachytherapy development also

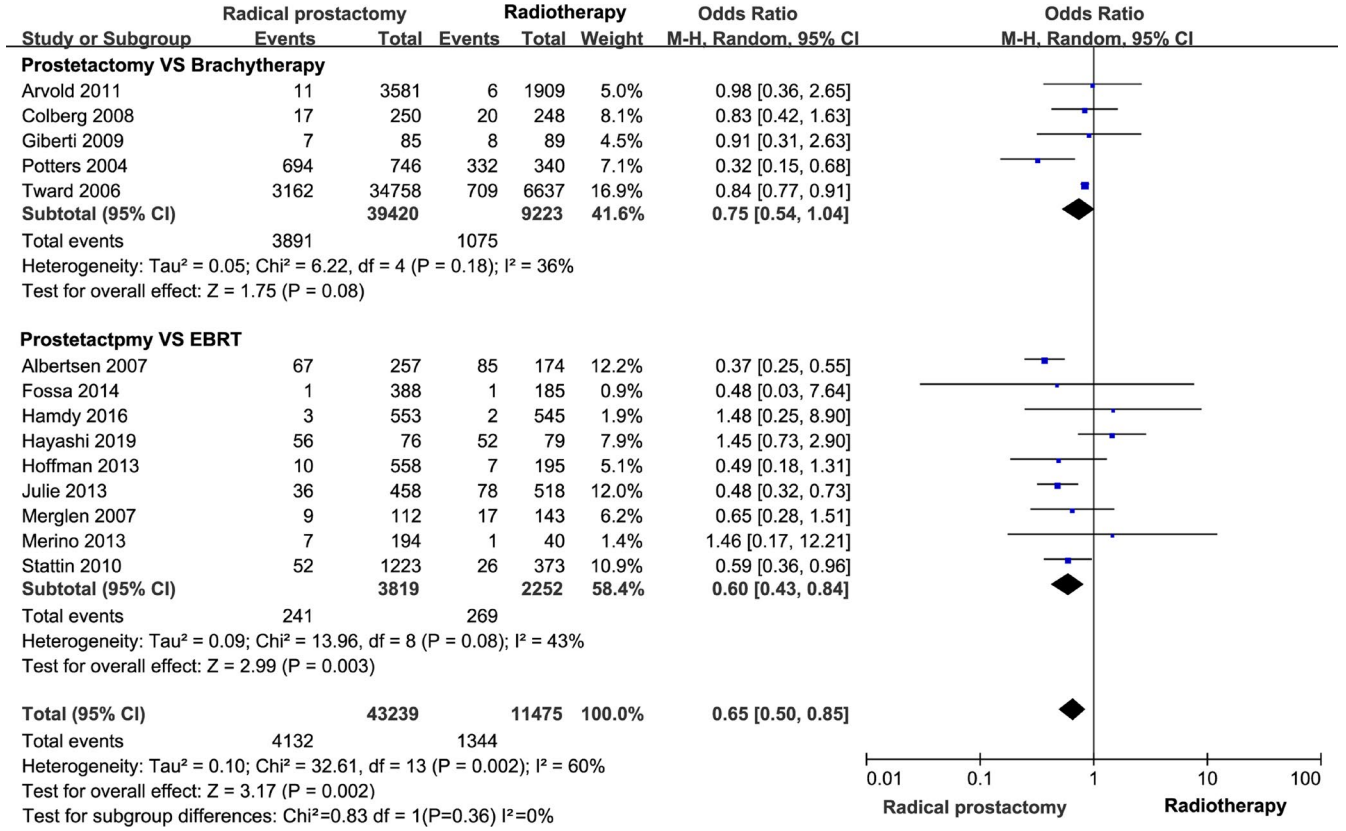


FIGURE 6 Forrest plot assessing the risk of CSM following RP and radiotherapy for prostate cancer

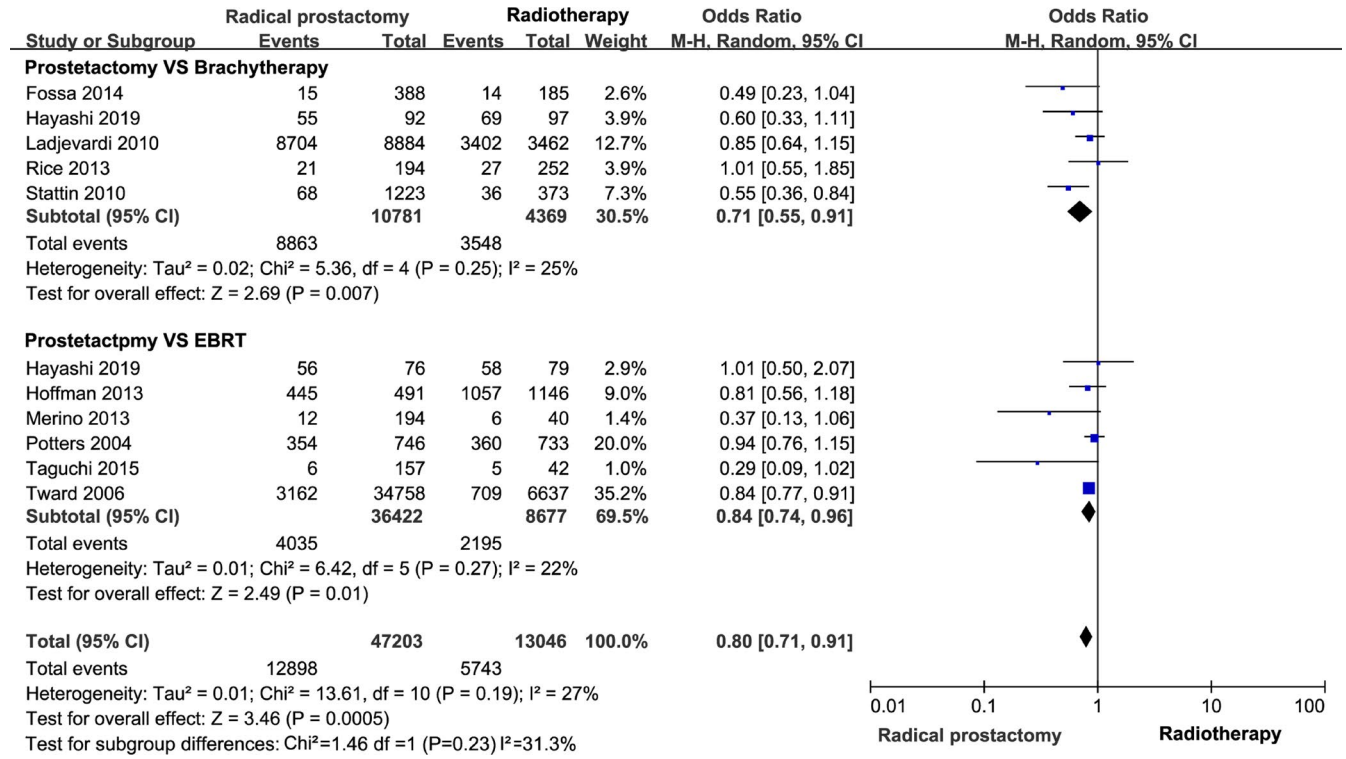


FIGURE 7 Forrest plot assessing the risk of ACM following RP and radiotherapy for prostate cancer

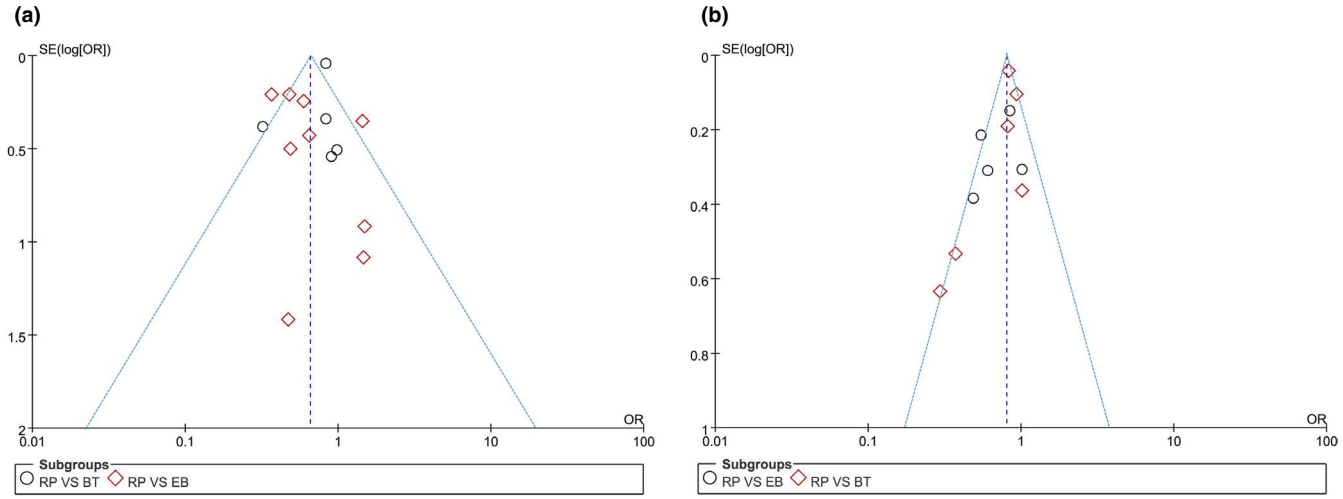


FIGURE 8 (a) Funnel plots for included studies CSM. (b) Funnel plots for included studies ACM

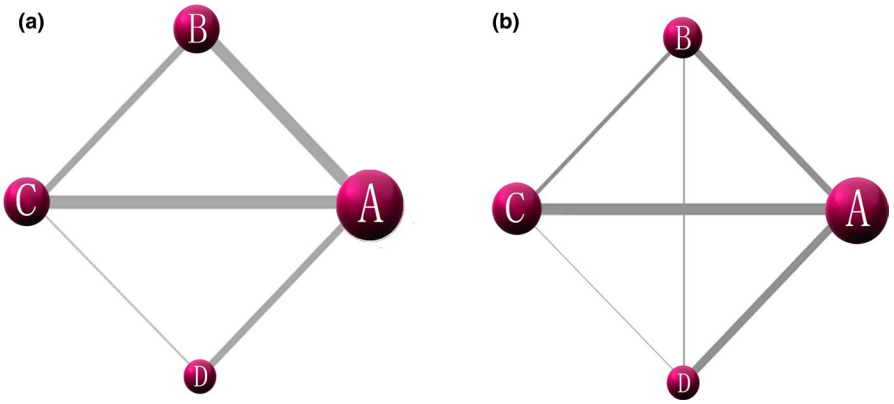


FIGURE 9 Network diagram of CSM (left) and ACM (right). (A) Radical prostatectomy, (B) brachytherapy, (C) external beam radiation therapy and (D) active surveillance. Each circle represents an intervention; each line represents a comparison between interventions, with the lines with width representing the number of trials with the direct comparisons in question (i.e. thicker width represents a direct comparison with larger numbers of trials)

TABLE 2 (a) Pooled OR for CSM. (b) OR for ACM

a			
RP	0.63 (0.41–1.03)	0.66 (0.46–0.97)	0.46 (0.34–0.64)
1.60 (0.97–2.46)	BT	0.41 (0.24–0.77)	0.29 (0.17–0.51)
1.52 (1.03–2.17)	2.43 (1.29–1.42)	EBRT	0.70 (0.45–1.07)
2.19 (1.56–2.98)	3.50 (1.97–5.75)	1.44 (0.94–2.22)	AS
b			
RP	0.64 (0.24–1.85)	0.45 (0.12–1.68)	0.58 (0.22–1.56)
1.56 (0.54–4.23)	BT	0.28 (0.06–1.41)	0.37 (0.10 = 1.46)
2.24 (0.60–8.84)	3.51 (3.71–16.28)	EBRT	0.77 (0.17–3.60)
1.73 (0.64–4.48)	2.70 (0.68–9.67)	1.29 (0.28–5.98)	AS

Abbreviations: AS, active surveillance; BT, brachytherapy; EBRT, external beam therapy; RP, radical prostatectomy.

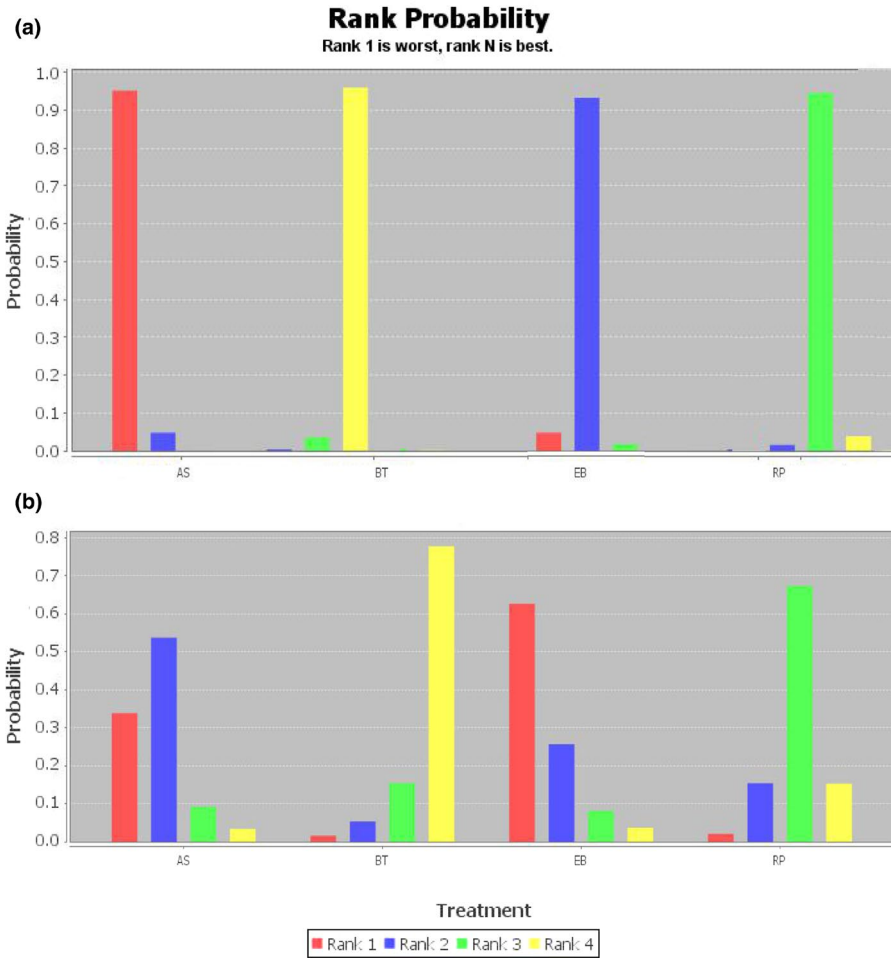


FIGURE 10 Ranking of treatments in terms of CSM and ACM. Each treatment has a probability of being the best treatment (rank 1) or the worst treatment (rank 4)

faces a few challenges due to its nature, such as how to precisely and effectively locate the target lesion and post-implantation surveillance of the nonimplanted prostate tissue. Successful completion of ongoing and new phase III trials will attribute to specify the effect of combination treatment (EBRT and brachytherapy) in the management of low-risk prostate cancer.

Due to its promising rate of bRFS, brachytherapy has become a widely used alternative to surgical treatment. Compared with RP, there are both neglected patient convenience and hospitalisation cost reduction benefits of brachytherapy. Previous research reported that the bRFS rates at 5, 10 and 15 years after surgery and brachytherapy were comparable in patients with low-risk PCa (Prada et al., 2012), which was consistent with our results. Alexianu and Weiss identified the largest available low-risk prostate cancer brachytherapy from the Northwest Hospital in Seattle and compared it with largest RP from the Johns Hopkins Hospital; the 7-year success rate of RP was 97.8% (no PSA >0.2 ng/ml), while in the brachytherapy group, the 7-year freedom from biochemical progression (PSA <0.5 ng/ml) was 79% and when the American Society of Therapeutic Radiation Oncology definition of failure was applied that could rise to 88% (Dallas et al., 2012).

The toxicity adverse event of prostatectomy and radiotherapy has been compared in the ProtecT randomised trial, which demonstrated higher rates of urinary incontinence and sexual dysfunction within the surgery group at a median follow-up of 10 years (Donovan et al., 2016), while RP patients had significantly better prostate cancer index composite Expanded Prostate Cancer Index Composite (EPIC) urinary irritation scores than BT patients; other researchers also indicated the same results (Davis et al., 2001), and thus, we may draw a further conclusion that BT is suitable for patients with localised low-risk prostate cancer who are eager to retain sexual function after treatment. Previous study has proved that brachytherapy for low-risk prostate cancer is better for preserving potency with 3-year potency preservation rate to be 70% (Benoit et al., 2000). In the SEER tumour registry data from the years 1988–2002, cumulatively five randomised controlled trials (Degroot et al., 2013; Fosså et al., 2014; Giberti et al., 2009; Hamdy et al., 2016; Resnick et al., 2013) were performed to compare the efficacy of RT and RP among which only Giberti et al. (2009) compared BT and RT; our network meta-analysis also failed to drawn a definite conclusion with clinical significance according to ACM; thus, it was still difficult to achieve consensus on brachytherapy application in the management of low-risk prostate cancer. Therefore, well-designed prospective population-based trials comparing functional outcomes and side effects between BT and RP are needed.

Although this is the first NMA specific to treatment modality for the management of low-risk prostate cancer, our study has some limitations. The main limitation of the systematic review is

very low quality of the evidence as a result of the sparse data currently available and the small number of RCTs. Some of the included studies were retrospectively designed which may lead to a possible limitation of selection bias, detection bias and performance of analysis bias; thus, a 3-level hierarchical Bayesian model was built to make our results more convincible. Second, Bayesian framework yielded wider CI than pairwise meta-analysis because the framework accounted for the uncertainty in the estimation of the heterogeneity. The estimate of network meta-analysis was less precise than the estimate from the pairwise meta-analysis which may result in inconsistency between our pairwise meta-analysis and network meta-analysis. Third, our study included the time span over 1999–2017, during which patient characteristics and diagnosis approaches may have changed a lot. For instance, some studies were conducted in 1980s, before the popularisation of the PSA blood test. Fourth, bBFS and side effects of each treatment are also crucial indicator related to prognosis of different treatment; however, due to the limited number of quantity of included studies, they were not involved in our article. Last but not least, our research is a network meta-analysis; we could only provide indirectly comparison. Results should be interpreted with caution and cannot replace a direct head-to-head evaluation. Future multi-centre, large sample randomised controlled trials with head-to-head comparisons are still necessary to improve the level of evidence.

5 | CONCLUSION

Choosing the optimal management for low-risk PCa remains a problem for the urologist. In this Bayesian analysis on low-risk PC, the best oncological outcomes were accomplished by RP or BT. BT for low-risk prostate cancer was associated with a similar risk of CSM when compared with RP; both RP and BT demonstrate a significantly increased risk of CSM when compared with EBRT and AS. While in terms of ACM, four treatment modalities posed comparable risks though brachytherapy ranked first in the histogram. For patients with low-risk prostate cancer, the choice of treatment should be done very carefully combined with other factors of patients. Prospective randomised designed trials are still needed to assess the ideal treatment modality for low-risk prostate cancer patients.

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Not applicable.

CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organisation regarding the material discussed in the manuscript.

AUTHOR CONTRIBUTIONS

Protocol/project development: Liang Zhen, Zhou Zhien, Wu Xingcheng, Feng Tianrui; Data collection or management: Li Hanzhong, Yan Weigang; Data analysis: Chen Yuliang, Zhou Yi, Chen Yuliang, Yan Weigang; Manuscript writing/editing: Liang Zhen, Li Hanzhong, Chen Yuliang, Liang Zhen, Zhou Yi; Data analysis and interpretation: Zhou Zhien, Feng Tianrui; Manuscript writing: All authors; Final approval of manuscript: All authors.

DATA AVAILABILITY STATEMENT

All the data generated or analysed during this study are included in the published article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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