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ORIGINAL ARTICLE

Prostate Cancer

The role of radical prostatectomy and definitive external beam radiotherapy in combined treatment for high-risk prostate cancer: a systematic review and meta-analysis

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The first-line treatment options for high-risk prostate cancer (PCa) are definitive external beam radiotherapy (EBRT) with or without androgen deprivation therapy (ADT) and radical prostatectomy (RP) with or without adjuvant therapies. However, few randomized trials have compared the survival outcomes of these two treatments. To systematically evaluate the survival outcomes of high-risk PCa patients treated with EBRT- or RP-based therapy, a comprehensive and up-to-date meta-analysis was performed. A systematic online search was conducted for randomized or observational studies that investigated biochemical relapse-free survival (bRFS), cancer-specific survival (CSS), and/or overall survival (OS), in relation to the use of RP or EBRT in patients with high-risk PCa. The summary hazard ratios (HRs) were estimated under the random effects models. We identified heterogeneity between studies using *Q* tests and measured it using I^2 statistics. We evaluated publication bias using funnel plots and Egger's regression asymmetry tests. Seventeen studies (including one randomized controlled trial [RCT]) of low risk of bias were selected and up to 9504 patients were pooled. When comparing EBRT-based treatment with RP-based treatment, the pooled HRs for bRFS, CSS, and OS were 0.40 (95% confidence interval [CI]: 0.24–0.67), 1.36 (95% CI: 0.94–1.97), and 1.39 (95% CI: 1.18–1.62), respectively. Better OS for RP-based treatment and better bRFS for EBRT-based treatment have been identified, and there was no significant difference in CSS between the two treatments. RP-based treatment is recommended for high-risk PCa patients who value long-term survival, and EBRT-based treatment might be a promising alternative for elderly patients.

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INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer deaths in males around the world, with 1 276 106 diagnosed cases and 358 989 deaths worldwide in 2018,[1] accounting for a greater global burden of cancer than that in 2012.[2] High-risk PCa, defined as prostate-specific antigen (PSA) >20 ng ml^{-1} or Gleason score >7 or clinical stage (T) >T2c according to the 2018 European Association of Urology (EAU) guidelines, accounts for 15% of the confirmed cases.[3] Definitive external beam radiotherapy (EBRT) with or without androgen deprivation therapy (ADT) and radical prostatectomy (RP) with or without adjuvant therapies are two common treatment options for patients with high-risk PCa. We designated them as EBRT-based therapy and RP-based therapy. Because high-risk PCa is prone to recurrence and metastasis after treatment, an increasing number of studies have focused on this issue in recent years. To date, only a few studies comparing EBRT-based therapy and RP-based therapy have been published, and the majority are small studies with conflicting results or that lack adequate follow-up periods. Due to the lack of solid evidence, the current guidelines do not provide clear recommendations with regard to patient selection criteria for each treatment. It is still uncertain as to which therapy is better for high-risk patients in terms of efficacy. Through a comprehensive database search, we only identified three systematic reviews focused on localized PCa or locally advanced PCa[4–6] and two systematic reviews of high-risk prostate cancer published in 2014 and 2015, respectively.[7,8] Since then, several new studies on this topic have been published; we therefore systemically searched and analyzed the available literature to evaluate the efficiency of EBRT-based therapy compared with RP-based therapy using more comprehensive outcome measures including biochemical relapse-free survival (bRFS), cancer-specific survival (CSS), and overall survival (OS).

MATERIALS AND METHODS

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement,[9] we conducted a search using various

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combinations of Medical Subject Headings (MeSH) for "prostatic neoplasms," "prostatectomy," "radiotherapy," and "cohort studies," as well as non-MeSH terms for "radical prostatectomy," "prostate cancer surgery," "radiotherapy," "outcome," "survival/mortality," and "androgen deprivation therapy." PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched for studies indexed from January 1, 1998, to April 30, 2019, with no limitation on the publication language. As a supplement, we also contacted some authors for study details. Following the literature search, all duplicates were excluded in Endnote and retrieved publications were subject to initial assessment of the title or abstract. Publications of radiotherapy only with brachytherapy were excluded. To ensure comprehensive coverage, references from included studies, review articles, editorials, commentaries, and conference publications were reviewed and cross-referenced. The computerized search was executed by investigators independently. Any discrepancy was resolved by consensus, with the participation of an interinvestigator.

Data extraction

Two reviewers collected data independently using predesigned abstraction forms. When there were disagreements in data extraction, a consensus was achieved with a third reviewer. Variables including the first author, study characteristics, participant characteristics, and survival outcomes were extracted and are summarized in **Table 1**.

Outcome measures

High-risk PCa was defined as PSA >20 ng ml^{-1} or Gleason score >7 or T >T2c according to the EAU guidelines. Biochemical recurrence in RP patients was defined as postoperative PSA ≥0.2 ng ml^{-1} or at initiation of salvage RT or salvage ADT. Biochemical recurrence in EBRT patients was defined as PSA ≥ nadir +2 ng ml^{-1} or at initiation of local salvage or salvage ADT. We chose bRFS, CSS, and OS as the endpoints of this study. The primary outcomes of this analysis were the effects of RP-based therapy on bRFS, CSS, and OS and the effects of EBRT-based therapy on bRFS, CSS, and OS. For studies that reported hazard ratio (HR), the adjusted HRs were extracted. For other studies that did not report HR, we first processed the survival curves with Engauge Digitizer 4.1 (UpdateStar, Berlin, Germany) and then calculated HRs of each outcome according to the widely used method that Tierney *et al*.[10] reported.

Statistical analyses

HRs were used to analyze survival outcomes. Extracted data were pooled into the meta-analysis by Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). We calculated the estimated effects of the two treatments on survival outcomes by log(HR) and standard error (s.e.). Between-study heterogeneity was identified by the *Q*-test and then estimated by the DerSimonian–Laird method and quantified by I^2 values.[11] We employed the random effects models for each of our analyses, under which we assumed that the true effect size might differ from study to study. Then, we ran an influence diagnostic for each outcome measure. Given the identified clinical heterogeneity, subgroup analyses were performed. We assessed publication bias using funnel plots and used Egger's test to statistically examine the funnel plot asymmetry.[12]

Quality assessment

Two independent reviewers assessed the methodological quality of the included randomized controlled trial (RCT) by Jadad Scale,[13] and the methodological quality of retrospective studies was assessed according to the Newcastle–Ottawa Scale. This scale assesses the risk of bias in three domains: (1) selection of the study groups, (2) comparability of groups, and (3) ascertainment of exposure and outcome.[14] Studies were considered as having a low risk of bias (overall scores >7), moderate risk of bias (overall scores 4–6), and high risk of bias (overall scores <4). According to our assessment, the follow-up duration was adequate if the median or mean follow-up was more than 5 years.

RESULTS

Search results

A flowchart of the literature search is shown in **Figure 1**. The primary database search resulted in 4890 records, from which 1660 duplicated records were excluded. A total of 3057 records were excluded following the title and abstract review. Of the 173 articles subjected to full-text assessment, 156 studies were excluded: 38 were review articles; 7 were from duplicate study cohorts; 37 reported unrelated exposure or outcomes; 47 involved incomparable patient populations; and 27 articles were case reports, letters, or editorial comments. In total, 17 publications involving 9504 patients were included.[15–31]

Characteristics and quality of studies

Of the 9504 included patients (**Table 1**), 3921 (41.3%) underwent EBRT-based treatment. ADT was administered to 3717 (94.8%) of the 3921 patients receiving EBRT-based treatment. In addition, 286 (7.3%) patients received salvage therapies, among which 177 (4.5%), 20 (0.5%), and 89 (2.3%) received salvage ADT, salvage local therapy, and salvage systemic therapy, respectively. Moreover, patients treated with EBRT-based treatment were generally older compared with patients treated with RP-based treatment in all of the included studies.

The remaining patients received RP-based treatment. Adjuvant ADT, adjuvant EBRT, and adjuvant systemic therapy were given to selected patients; however, we were unable to extract the exact number of patients under each therapy due to the lack of treatment details in the articles. In addition, some patients received salvage therapies after RP, such as salvage ADT (9.0%), salvage EBRT (not available), salvage local therapy (5.2%), and salvage systemic therapy (2.8%).

Duration of follow-up and inclusion criteria varied from study to study (**Table 1**). The definition of high-risk PCa has changed over time; however,

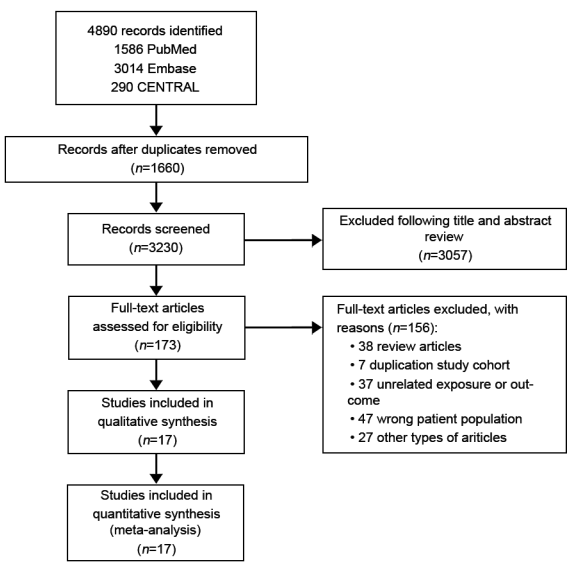

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining the search strategy and final included and excluded studies. CENTRAL: Cochrane Central Register of Controlled Trials databases.

Table 1: Characteristics of included studies

Study	*Country (study interval)*	*Inclusion criteria (PSA, ng ml^{-1})*	*Median follow-up (EBRT vs RP, month)*	*Study size (EBRT vs RP, n)*	*Median age (EBRT vs RP, year)*	*Adjuvant therapies (EBRT vs RP, %)*	*Salvage therapies (EBRT vs RP, %)*	*Outcome*
Akakura *et al.*[15] 1999	Japan (1989–1993)	B2 and C*	58.5 versus 58.5	46 versus 49	68.7 versus 68.1	ADT: 100.0 versus 100.0	–	CSS
Saito *et al.*[23] 2006	Japan (1992–2003)	T3, any GS	55.0 versus 55.0	78 versus 30	69.3 versus 64.0	ADT: 100.0 versus 100.0	–	CSS, OS
Arcangeli *et al.*[16] 2009	Italy (2003–2007)	GS ≥8 or PSA >20 or T ≥T3	38.6 versus 33.8	162 versus 122	75.0 versus 65.5	ADT: 100.0 versus -; EBRT: 0 versus 68.0	–	bRFS
Boorjian *et al.*[19] 2011	USA (1988–2004)	PSA ≥20 or T ≥T3 or GS ≥8	72.0 versus 122.4	344 versus 1238	68.8 versus 66.0	ADT: 56.5 versus 29.6; EBRT: 0 versus 6.9; Both: 0 versus 4.1	ADT: 16.6 versus 0; EBRT: 0 versus 20.4	CSS, OS
Kevin *et al.*[31] 2013	USA (1996–2010)	PSA ≥20 or T ≥T3 or GS ≥8	53.3 versus 53.3	655 versus 900	67.9 versus 61.4	ADT: 99.0 versus 25.0	–	bRFS
Lee *et al.*[22] 2014	Korea (1996–2009)	PSA ≥20 or T ≥T3 or GS ≥8	76.0 versus 76.0	125 versus 251	68.6 versus 67.5	ADT: 100.0 versus 0	EBRT: 0 versus 10.4	CSS
Koie *et al.*[21] 2014	Japan (2004–2012)	PSA ≥20 or T=T2c, T3 or GS ≥8	37.6 versus 31.5	78 versus 78	73.5 versus 71.0	ADT: 100.0 versus 100.0	–	bRFS, OS
Yamamoto *et al.*[24] 2014	Japan (1994–2005)	T3	85.0 versus 93.0	119 versus 112	72.0 versus 67.0	ADT: 95.8 versus 76.8	ADT: 26.9 versus 31.2; EBRT: 0 versus 4.5	CSS, OS
Yamamoto *et al.*[25] 2016	Japan (2007–2013)	PSA ≥20 or T=T3a or GS ≥8	54.5 versus 59.1	43 versus 71	73.0 versus 70.0	ADT: 100.0 versus 0	ADT: -; EBRT: 0 versus -	bRFS
Baker *et al.*[17] 2016	USA (2001–2014)	GS ≥8	61.0 versus 61.0	71 versus 50	69.6 versus 60.9	ADT: 95.8 versus 36.0; EBRT: 0 versus 44.0	EBRT: - versus 27.0	bRFS
Kishan *et al.*[20] 2017	USA (2000–2013)	GS 9–10	50.4 versus 58.8	230 versus 170	69.9 versus 61.9	ADT: 93.9 versus 0; EBRT: 0 versus 12.3; NAST: 0 versus 10.6; AST: 0 versus 7.1	ADT: 19.7 versus 30.1; EBRT: 0 versus -; LT: 0.9 versus 42.9	bRFS, CSS, OS
Ciezki *et al.*[18] 2017	USA (1996–2012)	PSA ≥20 or T ≥T3 or GS ≥8	63.5 versus 63.5	734 versus 1308	68.5 versus 62.0	ADT: 93.0 versus 19.0	–	bRFS, CSS
Johnstone *et al.*[26] 2006	USA (1995–2001)	T4 or N1, M0	–	257 versus 72	66.8 versus 64.3	ADT: 100.0 versus 0	–	OS
Kim *et al.*[27] 2014	Korea (2001–2011)	PSA ≥20 or T ≥T3 or GS ≥8	48.7 versus 48.8	109 versus 200	71.0 versus 66.0	ADT: 59.0 versus 27.0	–	bRFS, CSS, OS
Kishan *et al.*[28] 2018	USA 2000–2013	GS 9–10	61.2 versus 50.4	734 versus 639	67.7 versus 61.0	ADT: 89.5 versus 0; EBRT: 0 versus 8.7; NAST: 0 versus 19.0; AST: 0 versus 11.3	LT: 2.5 versus 34.1; ST: 12.1 versus 24.1	CSS, OS
Markovina *et al.*[29] 2017	USA (2002–2011)	PSA ≥20 or T ≥T3 or GS≥8	51.4 versus 41.0	62 versus 62	64.2 versus 62.9	ADT: 80.6 versus 6.5	–	OS
Reichard *et al.*[30] 2018	USA (2004–2013)	–	61.0 versus 61.0	74 versus 231	66.2 versus 61.2	ADT: 100.0 versus 0	–	bRFS

*Whitmore–Jewett staging system, PCa of B2 and C can be classified as high-risk PCa according to EAU guidelines (T≥T2c). NAST: neoadjuvant systemic therapy; AST: adjuvant systemic therapy; LT: local therapy; ST: systemic therapy; GS: Gleason score; EBRT: external beam radiotherapy; RP: radical prostatectomy; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; bRFS: biochemical relapse-free survival; CSS: cancer-specific survival; OS: overall survival; TNM: tumor node staging; T: tumor (clinical stage of TNM staging system); PCa: prostate cancer; –: not available.

all the included patients were diagnosed with high-risk PCa according to the 2018 EAU guidelines. We excluded studies that assessed the efficacy of EBRT-based treatment with patients treated with brachytherapy. Ten studies[15–17,19,21,22,24,25,27,28] provided data of EBRT modality, such as conventional EBRT, three dimensional conformal radiation therapy, and intensity modulated radiation therapy. Radiation dosage was only mentioned in 15[15–25,27–29,31] of 17 studies and mostly ranged from 60 to 80 gray (Gy, J kg^{-1}). In addition, considerable variability was found in the use of adjuvant or salvage therapies, regardless of the modality or duration.

Of the 17 studies included, 16 were retrospective[16–31] and one was a RCT.[15] The RCT scored three out of five points (considered as high quality) according to the Jadad Scale. None of the retrospective studies were considered as low quality with a high risk of bias according to the Newcastle–Ottawa Scale assessment (**Table 2**).

bRFS of EBRT-based treatment versus RP-based treatment

Eight studies[16–18,20,21,25,27,30] with a total of 3701 patients were involved in the assessment. Meta-analysis showed that the patients might benefit from EBRT-based treatment with a lower risk of biochemical failure (**Figure 2a**). There was significant heterogeneity among the studies (**Figure 2a**). Due to the small number of studies in the meta-analysis, we were unable to perform subgroup analyses or fit a mixed effects model with potential sources of heterogeneity as the covariates. Leave-one-out analysis showed that the direction and magnitude of HRs were quite consistent after removing any study in the analysis (**Supplementary Figure 1a**).

CSS of EBRT-based treatment versus RP-based treatment

Nine studies[15,18–20,22–24,27,28] with a total of 6516 patients were aggregated to assess the effects of treatment modality on CSS. We did not observe significant differences in CSS between EBRT-based treatment and RP-based treatment (**Figure 2b**). There was significant heterogeneity among the studies (**Figure 2b**). Subgroup analyses should be performed to determine the sources of heterogeneity or a mixed effects model can be fitted with these factors as covariates. However, we did not have enough studies for further assessment. The leave-one-out analysis showed that the studies conducted by Lee *et al.*[22] and Kishan *et al.*[28] had the greatest impacts on the HR estimates, and the result was significant after removing the study conducted by Kishan *et al.*[28] mainly because they employed local and systematic treatment as adjuvant or salvage therapy (**Supplementary Figure 1b**).

OS of EBRT-based treatment versus RP-based treatment

When nine studies[19–21,23,24,26–29] on 4612 patients were pooled, EBRT-based treatment was associated with a significantly increased risk of overall mortality compared with RP-based treatment (**Figure 2c**). There was no significant heterogeneity among the studies (**Figure 2c**). In addition, the leave-one-out analysis showed that the direction and magnitude of HR were quite consistent after removing any study in the analysis (**Supplementary Figure 1c**).

Influence diagnostics

Influence diagnostics were conducted for three outcomes (**Supplementary Figure 1**). For bRFS, Ciezki *et al.*[18] had a large influence on the model fit and was considered as an outlier. Removal of this study would significantly reduce the amount of heterogeneity. For CSS, Lee *et al.*[22] and Kishan *et al.*[28] had a large influence on the model fit and Lee *et al.*[22] was considered an outlier. Removing the two studies would significantly reduce the amount of heterogeneity. For OS, Boorjian *et al.*[19] and Kishan *et al.*[28] had a large influence on the model fit and Kishan *et al.*[28] was considered an outlier.

Publication bias

Funnel plot and Begg's test were used to assess publication bias. The funnel plot was quite symmetrical (**Figure 2**), indicating the absence of publication bias in the present meta-analysis. Egger's test again supported the conclusion for bRFS (P = 0.6789), CSS (P = 0.7111), and OS (P = 0.9506).

DISCUSSION

Unlike low-risk localized PCa, there is no established treatment option for high-risk PCa patients. The widely performed treatment options for high-risk PCa include EBRT-based treatment (mostly plus ADT) and RP-based treatment. However, the current guidelines from the EAU, the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN)[32] are inconsistent with regard to which treatment should be used as the first-line treatment for high-risk PCa. In the current meta-analysis, the definition of high-risk

Table 2: Newcastle–Ottawa Scale for risk of bias assessment of studies included in the meta-analysis

Study	*Selection*				*Comparability*	*Outcome*			*Total*
	Representativeness of exposed cohort	*Selection of nonexposed*	*Ascertainment of exposure*	*Outcome not present at start*		*Assessment of outcome*	*Adequate follow-up length*	*Adequacy of follow-up*	
Saito *et al.*[23] 2006	1	1	1	1	2	1	1	1	9
Arcangeli *et al.*[16] 2009	1	1	1	1	1	1	0	1	7
Boorjian *et al.*[19] 2011	1	1	1	1	2	1	1	1	9
Kevin *et al.*[31] 2013	1	1	1	1	2	1	1	0	8
Lee *et al.*[22] 2014	1	1	1	1	2	1	1	1	9
Koie *et al.*[21] 2014	1	1	1	1	2	1	0	1	8
Yamamoto *et al.*[24] 2014	1	1	1	1	1	1	1	1	8
Yamamoto *et al.*[25] 2016	1	1	1	1	1	1	1	1	8
Baker *et al.*[17] 2016	1	1	1	1	1	1	1	1	8
Kishan *et al.*[20] 2017	1	1	1	1	1	1	1	1	8
Ciezki *et al.*[18] 2017	1	1	1	1	1	1	1	1	8
Johnstone *et al.*[26] 2006	1	1	1	1	1	1	0	1	7
Kim *et al.*[27] 2014	1	1	1	1	1	1	0	1	7
Kishan *et al.*[28] 2018	1	1	1	1	1	1	0	1	7
Markovina *et al.*[29] 2017	1	1	1	1	2	1	0	1	8
Reichard *et al.*[30] 2018	1	1	1	1	1	1	1	0	7

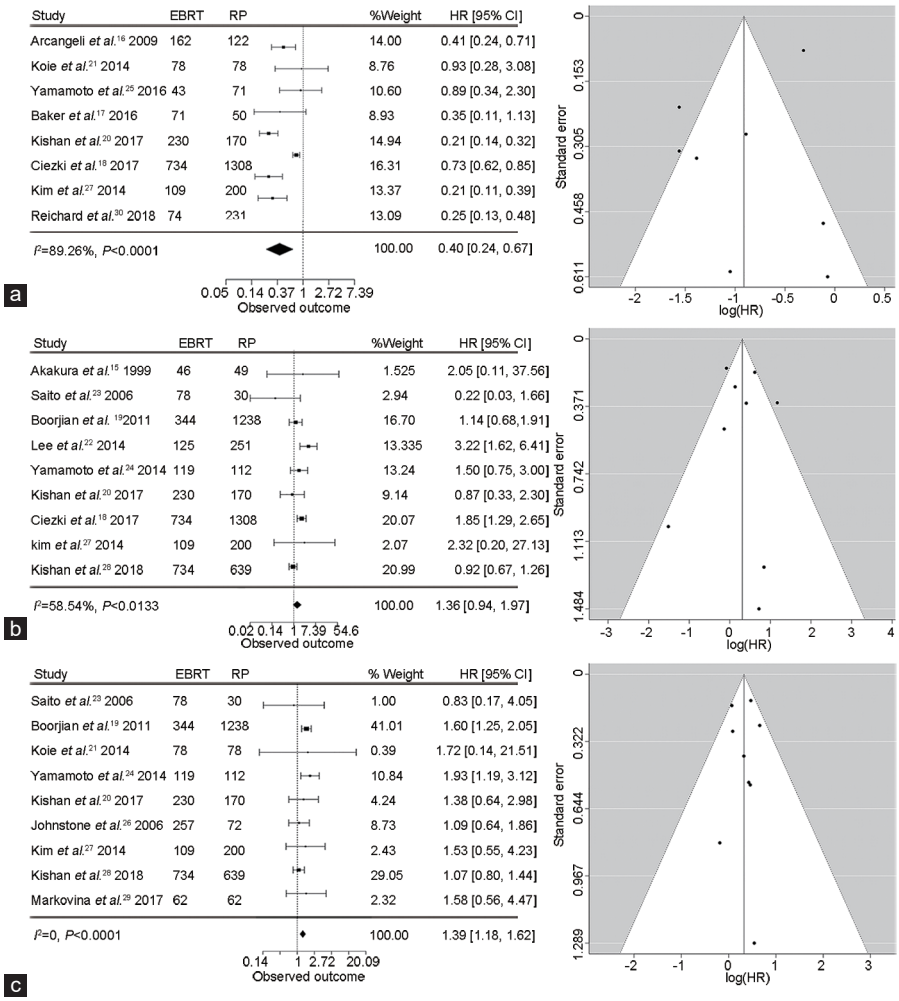

Figure 2: Forrest plot and funnel plot assessing the risk of (**a**) bRFS, (**b**) CSS, and (**c**) OS following EBRT-based and RP-based treatment. CI: confidence interval; EBRT: external beam radiotherapy; RP: radical prostatectomy; HR: hazard ratio; bRFS: biochemical relapse-free survival; CSS: cancer-specific survival; OS: overall survival.

PCa varied considerably in the included 17 studies, but all of them met the criteria of the 2018 EAU guidelines.

By reviewing and summarizing the 17 previously published studies with low-to-moderate risk of bias, we identified that EBRT-based treatment was associated with better bRFS than RP-based treatment. Conversely, RP-based treatment was associated with a significantly better OS than EBRT-based treatment. Moreover, the analysis showed no statistically significant difference between the two treatments in terms of CSS, which is in contradiction with a previous meta-analysis.[7] It suggested that EBRT-based treatment might be associated with a higher risk of cancer-specific mortality after controlling for related bias. Thus, more studies need to be included in this analysis. In addition, we have compared the two treatment modalities by the 5-year bRFS rates, the 5-year CSS rates, and the 5-year OS rates; most studies reported better 5-year CSS rates, better 5-year OS rates, and worse 5-year bRFS rate for RP-based treatment (**Table 3**).

After a thorough search of published meta-analyses on this topic, our study represents the most comprehensive and up-to-date review. There were three previous meta-analyses[4–6] examining the survival outcomes among patients with localized or locally advanced PCa treated with surgery or radiotherapy. Lei *et al*.[8] conducted a meta-analysis comparing the survival outcomes among patients with high-

Table 3: Absolute 5-year survival rates for included studies

Study	*5-year bRFS (%)*		*5-year CSS (%)*		*5-year OS (%)*	
	EBRT	*RP*	*EBRT*	*RP*	*EBRT*	*RP*
Akakura *et al*.[15] 1999	–		84.6	96.6	–	–
Saito *et al*.[23] 2006	–	–	96.6	93.8	94.9	87.3
Arcangeli *et al*.[16] 2009	74.6	54.2	–	–	–	–
Boorjian *et al*.[19] 2011	–	–	96.0	97.3	88.2	92.3
Kevin *et al*.[31] 2013	74.0	61.0	–	–	–	–
Lee *et al*.[22] 2014	–	–	88.3	96.5	–	–
Koie *et al*.[21] 2014	78.8	81.8	–	–	92.3	98.6
Yamamoto *et al*.[24] 2014	–	–	85.7	93.1	79.9	96.6
Yamamoto *et al*.[25] 2016	20.9	59.2	–	–	–	–
Baker *et al*.[17] 2016	92.8	57.7	–	–	–	–
Kishan *et al*.[20] 2017	71.9	26.4	91.6	91.7	79.9	90.3
Ciezki *et al*.[18] 2017	74.0	65.0	94.7	97.2	–	–
Johnstone *et al*.[26] 2006	–	–	–	–	72.6	71.1
Kim *et al*.[27] 2014	82.0	30.4	94.8	96.3	84.4	94.4
Kishan *et al*.[28] 2018	–	–	87.0	88.0	82.0	83.0
Markovina *et al*.[29] 2017	79.0	42.0	–	–	81.0	86.1
Reichard *et al*.[30] 2018	33.0	2.0	–	–	100.0	94.0

EBRT: external beam radiotherapy; RP: radical prostatectomy; bRFS: biochemical relapse-free survival; CSS: cancer-specific survival; OS: overall survival; –: not available.

risk PCa treated with RP, EBRT, brachytherapy, ADT, and watchful waiting, which revealed that RP or (EBRT plus ADT) gave the best prognosis in patients with high-risk PCa. Furthermore, RP had significantly better OS and CSS than EBRT (with or without ADT). Another meta-analysis conducted by Petrelli *et al*.[7] also found better OS and CSS for patients treated with RP compared with EBRT; however, the odds ratios (OR) they used had natural limitations compared with the time-to-event outcome measures in our study. In addition, by including higher-quality studies published in recent years, we have updated the two meta-analyses in high-risk patients and added another outcome measure for bRFS.

Evidence of significant between-study heterogeneity was identified in the statistics for our pooled analysis of bRFS and CSS. The potential source of heterogeneity might be mainly differences in study design, baseline characteristics, and treatment modality. The studies that caused more heterogeneity were identified through the influence diagnostics. Among the included studies, the surgical approach, EBRT dosage, and modality varied, and the use of adjuvant or salvage therapy also differed. In addition, the duration and drug category of the adjuvant ADT or salvage ADT was diverse, further complicating the potential source of heterogeneity.

It is unclear why the EBRT group showed better bRFS and the RP group showed better OS. Potential explanations include: (1) patients receiving EBRT were generally older than those undergoing RP, and age could be a risk factor for comorbidities and worse OS; (2) patients who initially received RP still had the chance to undergo salvage EBRT, while those who have undergone EBRT rarely received salvage RP even if the treatment failed, and the relatively high biochemical recurrence rate after RP might account for the higher use of salvage therapies; (3) EBRT and ADT drugs have greater toxicity and long-term side effects, which might contribute to the worse OS of EBRT-based treatment; (4) surgery could reduce a greater tumor burden than EBRT, which might account for the better OS; (5) postradiotherapy patients are diagnosed as a biochemical failure with a higher PSA level and are often given a longer duration of ADT; therefore, the EBRT group would show better bRFS.

In this study, we performed a comprehensive search of published studies, undertook a careful selection of studies, and conducted strict quality assessment of included studies to draw robust conclusions comparing EBRT- and RP-based treatments. However, there are several limitations in our meta-analysis, including the lack of information on the methodological quality among the included studies, the significant between-study differences in treatment modality, and the small number of studies that limited our ability to assess the potential sources of heterogeneity. However, this meta-analysis, with nearly 10 000 patients, is the most up-to-date review analyzing the outcomes of high-risk PCa patients treated by EBRT- or RP-based treatment. The conclusion of this study is important for clinicians in choosing the best treatment plan for high-risk PCa patients.

CONCLUSION

We identified better OS for RP-based treatment and better bRFS for EBRT-based treatment in high-risk PCa. RP-based treatment showed no significant superiority compared with EBRT-based treatment with regard to CSS. The results suggested that BP-based treatment would be more preferential for populations that valued longer survival, and EBRT-based treatment might be a promising alternative option for older populations. Large-scale RCT and observational studies with adequate duration of follow-up were needed to attain a comprehensive comparison between EBRT and RP for high-risk PCa.

AUTHOR CONTRIBUTIONS

XC wrote the first draft of the paper. XC, ZCH, LY, WZL, and JWC obtained data. XC and ZHW analyzed the results. YHW, MP, ZCH, LY, and YJL commented in detail on the drafts. YHW, ZHW, and MP reviewed the manuscript. YHW conceived the idea for the study. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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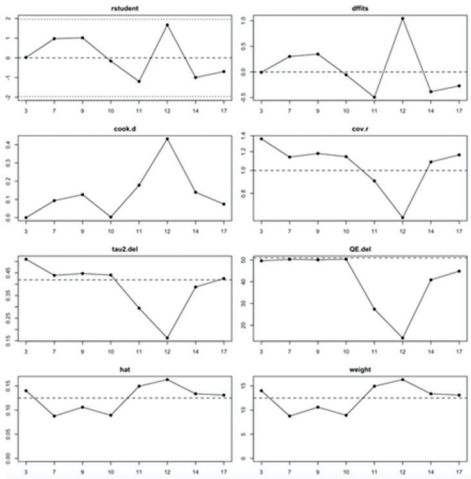
Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
3 Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol* 2010; 28: 1117–23.
4 Chen L, Li Q, Wang Y, Zhang Y, Ma X. Comparison on efficacy of radical prostatectomy versus external beam radiotherapy for the treatment of localized prostate cancer. *Oncotarget* 2017; 8: 79854–63.
5 Fahmy O, Khairul-Asri MG, Hadi SH, Gakis G, Stenzl A. The role of radical prostatectomy and radiotherapy in treatment of locally advanced prostate cancer: a systematic review and meta-analysis. *Urol Int* 2017; 99: 249–56.
6 Wallis CJ, Saskin R, Choo R, Herschorn S, Kodama RT, *et al*. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2016; 70: 21–30.
7 Petrelli F, Vavassori I, Coinu A, Borgonovo K, Sarti E, *et al*. Radical prostatectomy or radiotherapy in high-risk prostate cancer: a systematic review and meta-analysis. *Clin Genitourin Cancer* 2014; 12: 215–24.
8 Lei JH, Liu LR, Wei Q, Yan SB, Song TR, *et al*. Systematic review and meta-analysis of the survival outcomes of first-line treatment options in high-risk prostate cancer. *Sci Rep* 2015; 5: 7713.
9 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.
10 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8: 16.
11 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–60.
12 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–101.
13 Clark HD, Wells GA, Huët C, McAlister FA, Salmi LR, *et al*. Assessing the quality of randomized trials: reliability of the Jadad scale. *Control Clin Trials* 1999; 20: 448–52.
14 Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, *et al*. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7: iii–x, 1–173.
15 Akakura K, Isaka S, Akimoto S, Ito H, Okada K, *et al*. Long-term results of a randomized trial for the treatment of stages B2 and C prostate cancer: radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities. *Urology* 1999; 54: 313–8.
16 Arcangeli G, Strigari L, Arcangeli S, Petrongari MG, Saracino B, *et al*. Retrospective comparison of external beam radiotherapy and radical prostatectomy in high-risk, clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009; 75: 975–82.
17 Baker C, Strigari L, Arcangeli S, Petrongari MG, Saracino B, *et al*. Pelvic radiotherapy versus radical prostatectomy with limited lymph node sampling for high-grade prostate adenocarcinoma. *Prostate Cancer* 2016; 2016: 2674954.
18 Ciezki JP, Weller M, Reddy CA, Kittel J, Singh H, *et al*. A comparison between low-dose-rate brachytherapy with or without androgen deprivation, external beam radiation therapy with or without androgen deprivation, and radical prostatectomy with or without adjuvant or salvage radiation therapy for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; 97: 962–75.
19 Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, *et al*. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer* 2011; 117: 2830–2.
20 Kishan AU, Shaikh T, Wang PC, Reiter RE, Said J, *et al*. Clinical outcomes for patients with Gleason score 9-10 prostate adenocarcinoma treated with radiotherapy

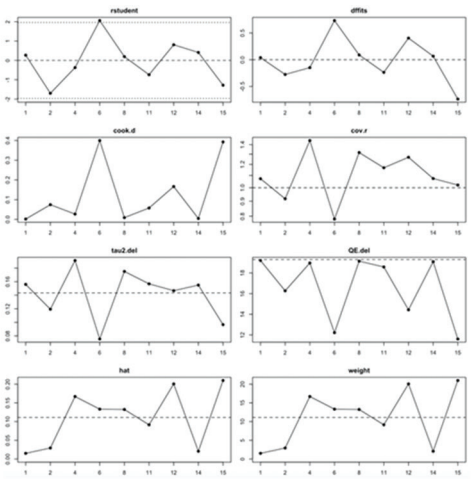
or radical prostatectomy: a multi-institutional comparative analysis. *Eur Urol* 2017; 71: 766–73.
21 Koie T, Ohyama C, Yamamoto H, Imai A, Hatakeyama S, *et al*. Both radical prostatectomy following treatment with neoadjuvant LHRH agonist and estramustine and radiotherapy following treatment with neoadjuvant hormonal therapy achieved favorable oncological outcome in high-risk prostate cancer: a propensity-score matching analysis. *World J Surg Oncol* 2014; 12: 134.
22 Lee JY, Cho KS, Kwon JK, Jeh SU, Kang HW, *et al*. A competing risk analysis of cancer-specific mortality of initial treatment with radical prostatectomy versus radiation therapy in high-risk prostate cancer. *J Urol* 2014; 21: 4026–33.
23 Saito T, Kitamura Y, Komatsubara S, Matsumoto Y, Sugita T, *et al*. Outcomes of locally advanced prostate cancer: a single institution study of 209 patients in Japan. *Asian J Androl* 2006; 8: 555–61.
24 Yamamoto S, Kawakami S, Yonese J, Fujii Y, Urakami S, *et al*. Long-term oncological outcome in men with T3 prostate cancer: radical prostatectomy versus external-beam radiation therapy at a single institution. *Int J Clin Oncol* 2014; 19: 1085–91.
25 Yamamoto Y, Kiba K, Yoshikawa M, Hirayama A, Kunikata S, *et al*. Evaluation of biochemical recurrence in patients with high-risk prostate cancer treated with radical prostatectomy and radiotherapy plus androgen deprivation therapy. *Res Rep Urol* 2016; 8: 225–31.
26 Johnstone PA, Ward KC, Goodman M, Assikis V, Petros JA. Radical prostatectomy for clinical T4 prostate cancer. *Cancer* 2006; 106: 2603–9.
27 Kim YJ, Cho KH, Pyo HR, Lee KH, Moon SH, *et al*. Radical prostatectomy versus external beam radiotherapy for localized prostate cancer: comparison of treatment outcomes. *Strahlenther Onkol* 2014; 191: 321–9.
28 Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, *et al*. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. *JAMA* 2018; 319: 896–905.
29 Markovina S, Meeks MW, Badiyan S, Vetter J, Gay HA, *et al*. Superior metastasis-free survival for patients with high-risk prostate cancer treated with definitive radiation therapy compared to radical prostatectomy: a propensity score-matched analysis. *Adv Radiat Oncol* 2017; 3: 190–6.
30 Reichard CA, Hoffman K, Allen PK, Williams SB, Achim MF, *et al*. Oncologic outcomes in men with high risk prostate cancer eligible for both radical prostatectomy and radiotherapy: the MD Anderson multidisciplinary clinic experience. *J Urol* 2018; 199: 275.
31 Kevin LS, Rahul DT, Cherukuru KR, Stepenson AJ, Klein E, *et al*. High-risk prostate cancer: radiation or surgery? *Int J Radiat Oncol* 2013; 87: 371.
32 Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, *et al*. prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 479–505.



	rstudent	dffits	cook.d	cov.r	tau2.del	QE.del	hat	weight	dfbs	inf
3	0.0224	-0.0064	0.0000	1.3584	0.5101	49.5899	0.1400	14.0032	-0.0064	
7	0.9745	0.3019	0.0934	1.1382	0.4389	50.2550	0.0876	8.7599	0.3001	
9	1.0168	0.3483	0.1265	1.1787	0.4470	50.0257	0.1060	10.5999	0.3467	
10	-0.1631	-0.0558	0.0032	1.1432	0.4403	50.3229	0.0893	8.9255	-0.0555	
11	-1.1978	-0.4933	0.1780	0.9038	0.2942	27.3897	0.1494	14.9392	-0.4830	
12	1.6700	1.0436	0.4322	0.6331	0.1624	14.1433	0.1631	16.3097	0.9276	
14	-0.9958	-0.3851	0.1393	1.0860	0.3875	40.8462	0.1337	13.3704	-0.3849	
17	-0.6956	-0.2711	0.0743	1.1631	0.4248	44.8237	0.1309	13.0922	-0.2711	

	estimate	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
3	0.402	-2.964	0.003	0.221	0.735	49.590	0.000	0.510	87.901	8.265
7	0.371	-3.531	0.000	0.214	0.643	50.255	0.000	0.439	88.061	8.376
9	0.366	-3.516	0.000	0.209	0.641	50.026	0.000	0.447	88.006	8.338
10	0.408	-3.185	0.001	0.235	0.708	50.323	0.000	0.440	88.077	8.387
11	0.449	-3.197	0.001	0.275	0.734	27.390	0.000	0.294	78.094	4.565
12	0.338	-5.177	0.000	0.224	0.510	14.143	0.028	0.162	57.577	2.357
14	0.443	-2.964	0.003	0.259	0.759	40.846	0.000	0.387	85.311	6.808
17	0.432	-2.957	0.003	0.247	0.753	44.824	0.000	0.425	86.614	7.471

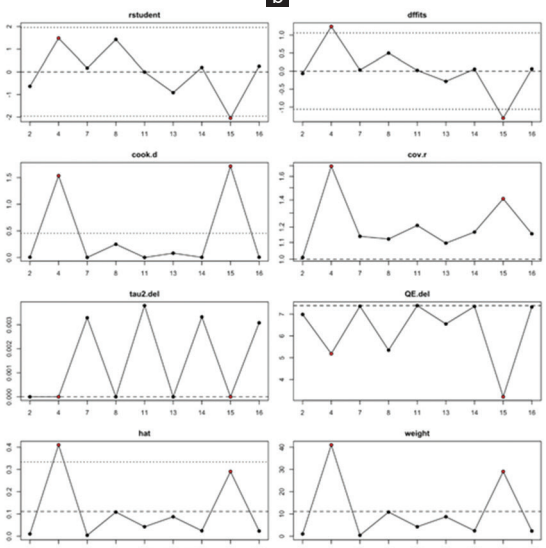
a



	rstudent	dffits	cook.d	cov.r	tau2.del	QE.del	hat	weight	dfbs	inf
1	0.2694	0.0394	0.0016	1.0728	0.1560	19.2070	0.0152	1.5152	0.0384	
2	-1.6995	-0.2756	0.0745	0.9172	0.1194	16.2715	0.0294	2.9437	-0.2888	
4	-0.3727	-0.1479	0.0268	1.4458	0.1912	18.9657	0.1670	16.7038	-0.1489	
6	2.0593	0.7322	0.3997	0.7826	0.0754	12.2210	0.1333	13.3255	0.7630	
8	0.1949	0.0886	0.0088	1.3162	0.1751	19.1435	0.1324	13.2398	0.0878	
11	-0.7400	-0.2361	0.0577	1.1686	0.1568	18.5803	0.0914	9.1430	-0.2333	
12	0.8081	0.4042	0.1665	1.2685	0.1467	14.4315	0.2007	20.0683	0.4050	
14	0.4105	0.0663	0.0044	1.0743	0.1549	19.0903	0.0207	2.0690	0.0648	
15	-1.2790	-0.7361	0.3925	1.0209	0.0967	11.6036	0.2099	20.9917	-0.7058	

	estimate	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
1	1.351	1.541	0.123	0.921	1.981	19.207	0.008	0.156	63.555	2.744
2	1.433	1.993	0.046	1.006	2.041	16.272	0.023	0.119	56.980	2.325
4	1.404	1.496	0.135	0.900	2.189	18.966	0.008	0.191	63.091	2.709
6	1.208	1.134	0.257	0.871	1.675	12.221	0.094	0.075	42.721	1.746
8	1.337	1.344	0.179	0.875	2.043	19.143	0.008	0.175	63.434	2.735
11	1.424	1.735	0.083	0.955	2.123	18.580	0.010	0.157	62.326	2.654
12	1.260	1.090	0.276	0.831	1.911	14.431	0.044	0.147	51.495	2.062
14	1.344	1.514	0.130	0.917	1.971	19.090	0.008	0.155	63.332	2.727
15	1.532	2.239	0.025	1.055	2.225	11.604	0.114	0.097	39.674	1.658

b



	rstudent	dffits	cook.d	cov.r	tau2.del	QE.del	hat	weight	dfbs	inf
2	-0.6371	-0.0640	0.0041	1.0101	0.0000	6.9849	0.0100	0.9998	-0.0640	
4	1.4854	1.2384	1.5337	1.6951	0.0000	5.1844	0.4101	41.0064	1.2384	*
7	0.1694	0.0337	0.0011	1.1389	0.0033	7.3626	0.0039	0.3931	0.0317	
8	1.4300	0.4985	0.2485	1.1215	0.0000	5.3460	0.1084	10.8355	0.4985	
11	-0.0052	0.0225	0.0005	1.2116	0.0038	7.3908	0.0424	4.2413	0.0212	
13	-0.9178	-0.2838	0.0806	1.0956	0.0000	6.5484	0.0873	8.7288	-0.2838	
14	0.1963	0.0564	0.0032	1.1669	0.0033	7.3533	0.0243	2.4282	0.0533	
15	-2.0456	-1.3088	1.7129	1.4094	0.0000	3.2066	0.2905	29.0462	-1.3088	*
16	0.2528	0.0639	0.0041	1.1554	0.0031	7.3280	0.0232	2.3208	0.0606	

	estimate	zval	pval	ci.lb	ci.ub	Q	Qp	tau2	I2	H2
2	1.393	4.078	0.000	1.188	1.633	6.985	0.430	0.000	0.000	1.000
4	1.254	2.147	0.032	1.020	1.541	5.184	0.637	0.000	0.000	1.000
7	1.382	3.749	0.000	1.167	1.636	7.363	0.392	0.003	4.925	1.052
8	1.331	3.339	0.001	1.125	1.574	5.346	0.618	0.000	0.000	1.000
11	1.383	3.644	0.000	1.162	1.646	7.391	0.389	0.004	5.287	1.056
13	1.418	4.125	0.000	1.201	1.673	6.548	0.477	0.000	0.000	1.000
14	1.379	3.682	0.000	1.162	1.636	7.353	0.393	0.003	4.805	1.050
15	1.540	4.501	0.000	1.276	1.859	3.207	0.865	0.000	0.000	1.000
16	1.378	3.693	0.000	1.163	1.634	7.328	0.396	0.003	4.476	1.047

c

Supplementary Figure 1: Influence diagnostics of (**a**) bRFS, (**b**) CSS, (**c**) OS. Influence diagnostics shows plots of the external standardized residuals; the DIFFITs values; the Cook's distances; the covariance ratios; the leave-one-out estimates of the amount of heterogeneity; the leave-one-out values of the test statistics for heterogeneity; the hat values; and the weights. bRFS: biochemical relapse-free survival; CSS: cancer-specific survival; OS: overall survival.