Urologia Internationalis

Original Paper

Urol Int 2021;105:370–379
DOI: 10.1159/000508415

Received: October 31, 2019
Accepted: April 30, 2020
Published online: December 10, 2020

Impact of Radiotherapy on Prognosis in Patients Diagnosed with Metastatic Prostate Cancer: A Systematic Review and Meta-Analysis

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Keywords
Local therapy · Radiotherapy · Brachytherapy · Metastatic prostate cancer · Meta-analysis

Abstract

Background: It has been reported that compared with no local therapy (NLT), patients treated with local therapy (LT) using radiotherapy (RT) possess higher survival rate in metastatic prostate cancer (mPCa). The aim of this meta-analysis was to evaluate the impact of RT on prognosis in patients with mPCa. ***Methods:*** We retrieved the literature in PubMed, Embase, and Cochrane Library databases until June 2019 using structured search terms. Several studies were included, which evaluated patients with mPCa who received RT versus NLT. ***Results:*** A total of 14,542 patients were analyzed in 7 included papers (2 randomized controlled trials [RCTs] and 5 cohort retrospective studies [CRS]), and 2,232 mPCa patients were treated with RT and 12,310 with NLT. The data of RCTs and CRS were analyzed separately. In RCTs, RT was associated with no significant difference in overall survival (OS) (pooled hazard ratio [HR] = 0.96; 95% confidence interval [CI]: 0.85–1.09; $p = 0.55$; $I^2 = 42\%$) relative to NLT, while survival benefit was observed in the low-metastatic burden group (pooled HR = 0.68; 95% CI: 0.54–0.86; $p = 0.001$; $I^2 = 0\%$), and no survival benefit was observed in the high-metastatic burden group (pooled HR = 1.07; 95% CI: 0.92–1.24; $p = 0.39$; $I^2 = 0\%$). In CRS, RT results in lower cancer-specific mortality (CSM) (pooled HR = 0.49; 95% CI: 0.34–0.75; $p < 0.00001$; $I^2 = 0\%$) and higher OS (pooled HR = 0.61; 95% CI: 0.55–0.68; $p < 0.00001$; $I^2 = 0\%$) relative to NLT. Subsequent analysis demonstrated that high level of M-stage or N-stage was associated with increased CSM (pooled HR = 2.08; 95% CI: 1.69–2.55; $p < 0.00001$; $I^2 = 0\%$ and pooled HR = 1.16; 95% CI: 1.03–1.30; $p < 0.00001$; $I^2 = 0\%$; respectively). ***Conclusions:*** Our observations in aggregate indicated that RT at least does not appear to be harmful and may be beneficial for low-metastatic burden patients and better condition patients. More prospective and randomized studies evaluating RT for mPCa are warranted.

Shuai Liu and Xiao-ying Wang contributed to this work equally.
Study registration: PROSPERO registration No.: CRD42019123871.

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Introduction

Prostate cancer (PCa) is one of the most frequent malignancies in males in the world [1]. Although the widespread use of prostate-specific antigen (PSA) testing had led to reducing PCa mortality [2], still about 20% of patients have local lymph node or distant metastasis at diagnosis and about 4% have distant metastasis [1], which was associated with a poor prognosis [3]. Radical prostatectomy (RP) and radiotherapy (RT) were standard treatment options for men diagnosed with localized PCa. However, in metastatic prostate cancer (mPCa), androgen deprivation therapy (ADT) with or without chemotherapy was recommended by the EAU guidelines for mPCa [4], while local therapy (LT) was not usually taken into account.

Primary tumors could be metastasized through circulating tumor cells, and treating the primary tumor might be beneficial to patients with mPCa as tumor self-seeding leading to local progression [5]. The LT of the primary tumor that could benefit patients with metastatic disease had been verified for a variety of tumors, such as renal, breast, and ovarian cancer [6]. Recent studies [7, 8] showed controversial results in relation to the advantage of LT associated with ADT on overall survival (OS) and cancer-specific survival (CSS). Although previous meta-analyses [9, 10] have clarified that LT was beneficial for survival in patients with mPCa, LT using RT of mPCa was still a controversial topic that needed further assessment; hence, we decided to perform a meta-analysis to clarify the impact of RT on OS and cancer-specific mortality (CSM) in patients diagnosed with mPCa.

Methods

Search Strategy

We searched PubMed, Embase, and Cochrane Library to identify pertinent literature published until June 9, 2019, using structured search terms (see Table 1).

Inclusion and Exclusion Criteria

The main selection criteria were as follows: (1) randomized controlled trials (RCTs) or cohort retrospective studies (CRS) [11] and language restricted to English; (2) patients diagnosed with mPCa; (3) focused on the relationship of RT for mPCa. The exclusion criteria were as follows: (1) reviews or letters or case reports or comments or editorials; (2) animal studies; (3) lack of key data or fail to acquire full data; (4) irrelevant to mPCa or RT.

Selection Process

Two reviewers (S.L. and X.-Y.W.) accomplished the selection of articles according to title. If the theme was related to RT in mPCa patients, the abstract was read. Abstracts were analyzed by 3 authors (S.L., T.-B.H., and L.-B.T.), and if considered eligible by at least 2 researchers, the full article was obtained. Disagreements were disposed by discussion or resolved by another reviewer (Z.-Z.X.).

Data Extraction

Data extraction was performed by X.-Y.W. and confirmed independently by X.-X.M. It mainly contains the following information: hazard ratios (HRs) with 95% confidence intervals (95% CIs) comparing men who underwent RT of the primary tumor with those who did not.

Quality Evaluation

RCTs were evaluated using the Cochrane Risk of Bias Tool [12], and the CRS were analyzed using the Newcastle-Ottawa Scale [13].

Analysis

All statistical analyses were conducted by using Stata 12.0 (Stata Corporation, College Station, TX, USA) and RevMan 5.3 software from Cochrane Library. The inverse variance test was used to pool HRs with 95% CI, and the results were exhibited by forest plot. Heterogeneity was considered acceptable when $p > 0.1$ or $I^2 \leq 50\%$, and in those cases, a fixed-effects model was used. Heterogeneity was considered elevated when $p < 0.1$ or $I^2 > 50\%$. Differences in ethnicity, Gleason score, M-stage, and N-stage were used for subgroup analysis to identify the cause of heterogeneity, and in those cases, a random-effects model was used. Sensitivity analysis was conducted to access the stability of results by deleting 1 single study each time to figure out the impact of the individual to overall. Publication bias was assessed by Egger's and Begg's tests, and publication bias would exist if $p < 0.05$. In addition, the data of RCTs and CRS were analyzed separately [14].

Results

A total of 9,631 studies were comprehensively identified by the initial database search. After the exclusion of 1,073 duplicate articles, 8,538 records were excluded based on the titles or abstracts for various reasons (reviews, letters, case reports, or unrelated to mPCa or unrelated to RT). After reading the remaining 20 articles in full text, 13 articles were excluded because 2 studies focused on the effect of prior LT on mPCa [15, 16], 2 studies focused on the effect of LT on mPCa [7, 8], 4 studies of repeated research [17–20], 3 repeated data studies [21–23], and 2 papers did not provide adequate data [24, 25]. Finally, 7 studies [26–32] contributed to the systematic review and meta-analysis (Fig. 1).

A total of 14,542 patients were analyzed in 7 included papers (2 RCTs [31, 32] and 5 CRS [26–30]): 2,232 mPCa patients were treated with RT and 12,310 with NLT. Data were all directly obtained from articles. The characteristics of these included studies are summarized in Table 2. The HRs and 95% CIs of different levels of Gleason score,

Table 1. Literature search criteria

Database	Search criteria	Results
PubMed	((Metastatic) AND (("Radiotherapy" [Mesh]) AND ((((((((((((((((((radiotherapies) OR radiation therapy) OR radiation therapies) OR therapies, radiation) OR therapy, radiation) OR radiation treatment) OR radiation treatments) OR treatment, radiation) OR radiotherapy, targeted) OR radiotherapies, targeted) OR targeted radiotherapies) OR targeted radiotherapy) OR targeted radiation therapy) OR radiation therapies, targeted) OR targeted radiation therapies) OR therapies, targeted radiation) OR therapy, targeted radiation) OR radiation therapy, targeted))) AND (("prostatic Neoplasms" [Mesh]) AND ((((((((((((((((prostate neoplasms) OR neoplasms, prostate) OR neoplasm, prostate) OR prostate neoplasm) OR neoplasms, prostatic) OR neoplasm, prostatic) OR prostatic neoplasm) OR prostate cancer) OR cancer, prostate) OR cancers, prostate) OR prostate cancers) OR cancer of the prostate) OR prostatic cancer) OR cancer, prostatic) OR cancers, prostatic) OR prostatic cancers) OR cancer of prostate))	1,213 studies
Cochrane Library	#1: MeSH descriptor: [Prostatic neoplasms] explode all trees; #2: (Prostatic):ti,ab, kw OR (prostate):ti,ab, kw (word variations have been searched) in trials; #3: ("cancer"):ti,ab, kw OR (Neoplasm):ti,ab, kw (word variations have been searched) in trials; #4: #2 AND #3 in Trials; #5: #1 OR #4 in trials; #6: MeSH descriptor: [Radiotherapy] explode all trees; #7: (radiotherapy):ti,ab, kw OR (radiation Therapy):ti,ab, kw (word variations have been searched) in trials; #8: #6 OR #7 in trials; #9: (metastatic):ti,ab, kw (word variations have been searched) in trials; #10: #5 AND #8 AND #9 in trials	477 studies
Embase	#1: "prostate cancer"/exp; #2: "Prostatic neoplasms":ab,ti; #3: "Cancer of prostate":ab,ti; #4: "prostate cancer":ab,ti; #5: #1 OR #2 OR #3 OR #4; #6: "radiotherapy"/exp; #7: "Radiation therapy":ab,ti; #8: "radiotherapies":ab,ti; #9: "Treatment radiation":ab,ti; #10: #6 OR #7 OR #8 OR #9; #11: "metastasis"/exp; #12: #5 AND #10 AND #11; #13: #5 AND #10 AND #11 AND [embase]/lim	7,941 studies

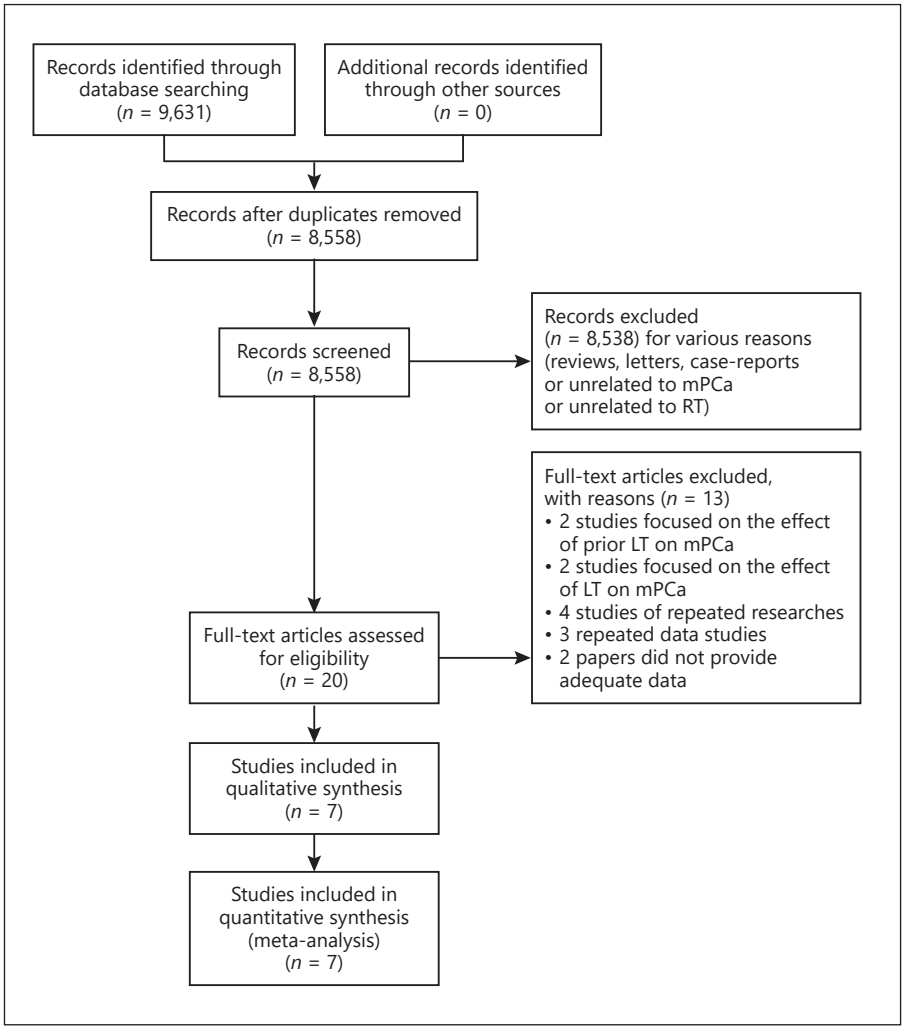


Fig. 1. Selection of studies.

Table 2. Characteristics of included studies

Article	Type of study	Source of HR	Age-I/C, years	Dominant ethnicity	Patients-I/C, *n*	Intervention	Comparison	Median follow-up, months	HR (95% CI)	Outcome
Satkunasivam et al. [26]	CRS	Reported	75.3/78.2	Non-Hispanic whites	195/3,827	PRT	NLT	Unknown	0.64 (0.50–0.82)	CSM^M
Rusthoven et al. [27]	CRS	Reported	66/69	White	538/5,844	PRT	NLT	61	0.624 (0.551–0.706)	OS^M
Cho et al. [28]	CRS	Reported	Unknown	Unknown	38/102	PRT	NLT	34	0.43 (0.22–0.85)	OS^M
Bianchini et al. [29]	CRS	Reported	62.2/63.1	Unknown	38/192	PRT	NLT	54.6	0.53 (0.33–0.85)	OS^M
Pompe et al. [30]	CRS	Reported	Unknown	Caucasian	175/1,100	BT	NLT	31.5	0.62 (0.48–0.81)	CSM^M
Boeve et al. [31]	RCT	Reported	67/67	Unknown	216/216	PRT	NLT	47	1.11 (0.87–1.43)	OS^M
Parker et al. [32]	RCT	Reported	68/68	Unknown	1,032/1,029	PRT	NLT	37	0.92 (0.80–1.06)	OS^M

CRS, cohort retrospective studies; RCT, randomized controlled trial; PRT, prostate radiotherapy; BT, brachytherapy; NLT, no local therapy; OS, overall survival; CSM, cancer-specific mortality; M, multivariate analysis.

Table 3. HRs and 95% CIs of different levels of Gleason score, M-stage, and N-stage of included studies

Article	Type of study	Source of HR	Gleason score	HR (95% CI)	M-stage	HR (95% CI)	N-stage	HR (95% CI)	Outcome
Satkunasivam et al. [26]	CRS	Reported	≥7 versus ≤6	1.66 (1.32–2.1)	M1c versus M1a	1.93 (1.49–2.51)	N1 versus N0	1.13 (0.98–1.29)	CSM^M
Rusthoven et al. [27]	CRS	Reported	Unknown	Unknown	Unknown	Unknown	N1 versus N0	1.053 (0.973–1.140)	OS^M
Cho et al. [28]	CRS	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	OS^M
Bianchini et al. [29]	CRS	Reported	≥8 versus <8	1.29 (0.94–1.77)	Unknown	Unknown	Unknown	Unknown	OS^M
Pompe et al. [30]	CRS	Reported	≥7 versus <7	2.37 (1.94–2.88)	M1c versus M1a	2.35 (1.68–3.28)	N1 versus N0	1.22 (1.00–1.48)	CSM^M
Boeve et al. [31]	RCT	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	OS^M
Parker et al. [32]	RCT	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	OS^M

CRS, cohort retrospective studies; RCT, randomized controlled trial; OS, overall survival; CSM, cancer-specific mortality; M1a, metastasis in pelvic lymph nodes; M1c, distant metastasis; M, multivariate analysis.

M-stage, and N-stage are described in Table 3. For these enrolled studies, we made a detailed analysis of bias (Table 4; Fig. 2).

OS Related to mPCa in the CRS and RCTs

Association between OS and RT in the CRS: 3 CRS showed higher OS in patients with mPCa submitted to RT in relation to NLT (pooled HR = 0.61; 95% CI: 0.55–0.68; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3a). In RCTs, no significant differences were observed in OS of patients submitted to RT (pooled HR = 0.96; 95% CI: 0.85–1.09; $p = 0.55$; $I^2 = 42\%$) compared with NLT, while RT results in higher OS relative to NLT in the low-metastatic burden group (pooled HR = 0.68; 95% CI: 0.54–0.86; $p = 0.001$; $I^2 = 0\%$) (Fig. 3a).

CSM Related to mPCa in the CRS

During the analysis of CSM related to mPCa in the CRS, the results of 2 observational studies showed that RT for mPCa was linked to decreased CSM compared with NLT (pooled HR = 0.63; 95% CI: 0.53–0.75; $p < 0.00001$; $I^2 = 0\%$) (Fig. 3c). Furthermore, we reached the conclusion that high level of M-stage or N-stage was associated with increased CSM (pooled HR = 2.08; 95% CI: 1.69–2.55; $p < 0.00001$; $I^2 = 0\%$ and pooled HR = 1.16; 95% CI: 1.03–1.30; $p < 0.00001$; $I^2 = 0\%$; respectively) (Fig. 4).

Table 4. Risk-of-bias assessment of the CRS

Studies	Selection				Comparability	Outcome			Total score
	exposed cohort	nonexposed cohort	ascertainment of exposure	outcome of interest		assessment of outcome	length of follow-up	adequacy of follow-up	
Satkunasivam et al. [26]	*	*	*	*	**	–	–	–	6
Rusthoven et al. [27]	*	*	*	*	**	*	*	–	8
Cho et al. [28]	*	*	*	*	**	*	–	–	7
Bianchini et al. [29]	*	*	*	*	**	*	*	*	9
Pompe et al. [30]	*	*	*	*	**	*	*	–	8

CRS, cohort retrospective studies.

Sensitivity Analysis

Sensitivity analysis was conducted to estimate the stability of results by deleting 1 study in each turn to investigate the influence of a single study on the overall pooled. In the CRS with OS groups, the results did not alter significantly in the sensitivity analysis, suggesting that no individual study significantly influenced the pooled HR or the 95% CI; scilicet, our results were robust (Fig. 3d).

Publication Bias

There was no apparent publication bias by inspection of the funnel plot among the OS in CRS (Egger's test, $p = 0.135$; Begg's test, $p = 0.296$) (Fig. 5).

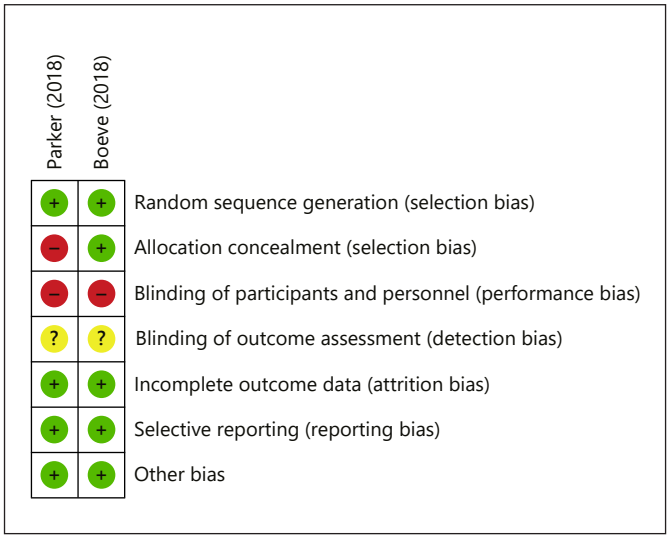


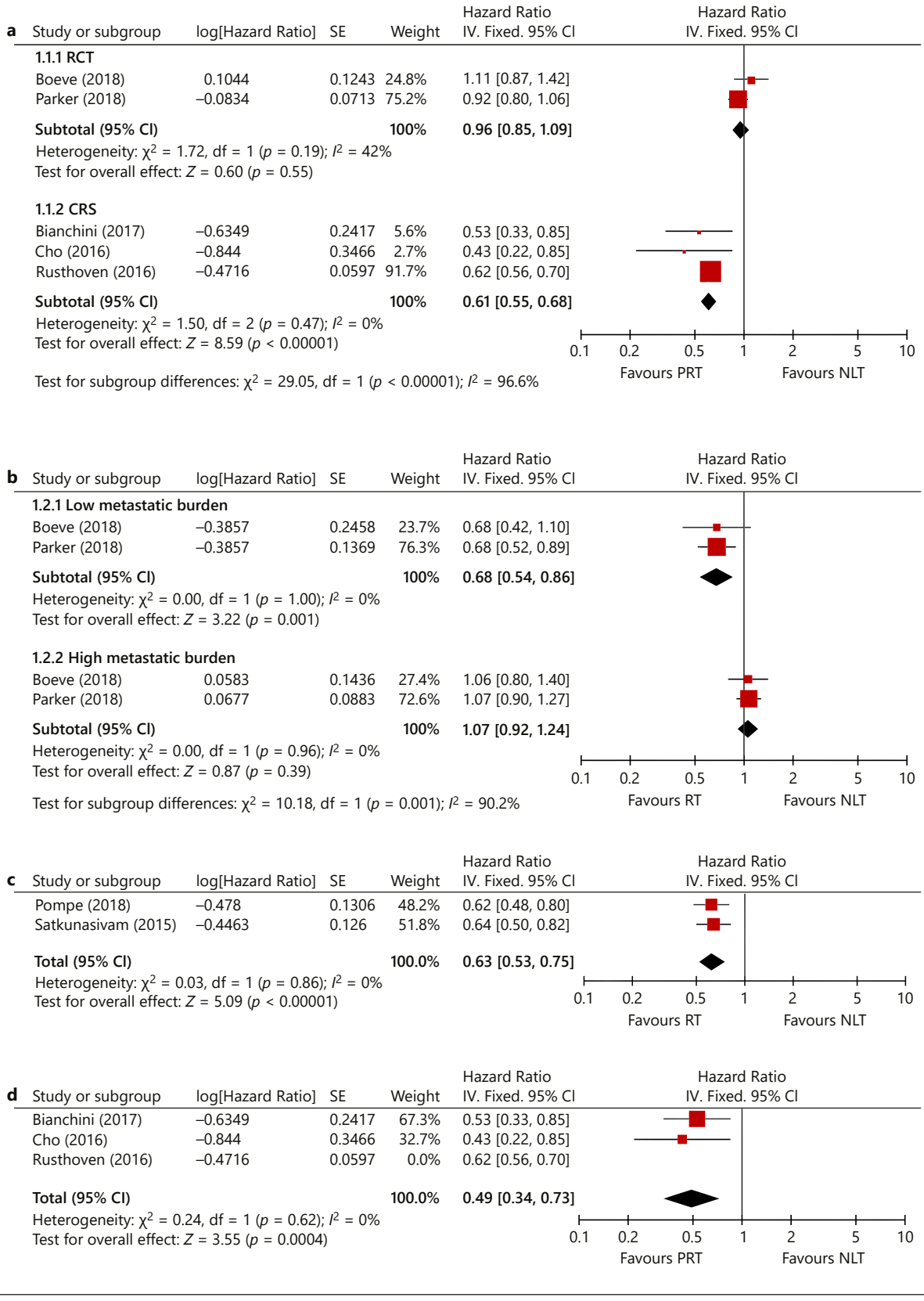
Fig. 2. Risk-of-bias assessment of the RCTs. RCT, randomized controlled trial.

Discussion

Contemporarily, LT using RT in patients diagnosed with mPCa was not recommended by the EAU guidelines [4]. Emerging studies had demonstrated that LT using RT in patients with mPCa was beneficial for survival, the 2 single-center CRS [28, 29] observed higher survival in patients treated with RT compared with patients treated with ADT only, while Dall'Era et al. [8] did not observe this. These results are inconsistent and controversy. Therefore, systemically evaluating the efficacy of RT in patients with mPCa is important. Our study was the first meta-analysis that identified RCTs to shed light on the impact of RT on prognosis in patients diagnosed with mPCa.

Using the SEER-Medicare database, Satkunasivam et al. [26] showed that older age, high levels of PSA, more aggressive primary tumor, elevating CCI, and bone radiation within 6 months of diagnosis were independent factors for the increase in prostate CSM of mPCa patients. In the single-institution retrospective analysis, loco-regional treatment (LRT) was more frequently performed in patients with fewer burden disease (35.4 vs. 16.2%; $p < 0.001$), lower PSA at diagnosis (median PSA: 75 vs. 184 ng/mL; $p = 0.005$), and lighter local symptoms (34.2 vs. 4.8%; $p < 0.001$) [29]. Löppenberg et al. [7] and Leyh-Bannurah et al. [21] clarified that patients with fewer primary tumors and good health conditions appeared to benefit more. Leyh-Bannurah et al. [21] also demonstrated that RP results in lower mortality relative to RT, this may be due to patients receiving RT because of unresectability by RP or high tumor burden in the primary.

In the HORRAD study, no significant difference in OS was found in men with low (<5 metastatic lesions) or high (≥5 metastatic lesions) volume of metastatic disease (HR = 0.68; 95% CI: 0.42–1.10; $p = 0.12$ and HR = 1.06;



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95% CI: 0.80–1.39; $p = 0.68$; respectively) [31]. Another much larger prospective, multicenter randomized STAMPEDE trial demonstrated that RT enhanced 3-year OS in patients with low metastatic burden (except for high metastatic burden) compared with NLT (81 vs. 73%; HR = 0.68; 95% CI: 0.52–0.90; $p = 0.007$), whereas patients with high metastatic burden (>4 bone metastases and 1 was nonaxial bone metastasis or visceral metastasis) did not benefit from RT compared with NLT (53 vs. 54%; HR = 1.07; 95% CI: 0.90–1.28; $p = 0.44$) [32]. The STAMPEDE study defined patients as having high tumor load and low tumor load, as defined by the CHAART-ED study [33], while the HORRAD study defined metastasis as 5 metastatic lesions, a cutoff point. For the different outcomes of RT in men with low metastatic burden in the HORRAD and STAMPEDE trials, Boeri et al. [34] suggested that an insufficient number of patients were included in the HORRAD trials and estimated that >250 men would be needed to include in the research to produce different results. Taken together, both these trials build evidence for RT in patients newly diagnosed with a low metastatic burden or oligometastatic prostate cancer (oPCa).

In RCTs, RT enhanced OS in patients with a low metastatic burden relative to NLT, it might suggest that we should pay more attention to mPCa in different states, such as oPCa when choosing treatment strategies. The oPCa is an intermediate state between localized and extensive metastatic PCa. In this state of PCa, although the clinical stage is advanced, the treatment can still be a more effective control. The exact definition of oPCa is still controversial, mainly, the number and site of metastases are not consistent, but its core concept refers to the low tumor burden [35]. Since the focus of oPCa is primarily on the number of metastases, increasingly advanced imaging techniques may be able to better distinguish between different mPCa subtypes [6].

In terms of the safety of RT, in the STAMPEDE study [36], patients in the RT group received local RT of the prostate for either 36 Gy in 6 consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks. There was no significant difference in baseline data between the 2 treatment groups. They found that the patients were well tolerated to RT, the proportion reporting at least 1 severe adverse event was similar by treatment group in the safety population (38 vs. 39%). In the HORRAD study, patients received RT after ADT for 3 months. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 weeks. During the study period, an optional schedule of 57.76 Gy in 19 fractions of 3.04 Gy, 3 times a week for 6 weeks was added. The patients received salvage treatments were similar between treatment groups. It should be noted that in the STAMPEDE study [36], where the standard treatment was ADT with or without docetaxel chemotherapy, 18% of patients in the entire study population received docetaxel chemotherapy, and subgroup analysis of the study showed that combination RT had a survival advantage in patients receiving docetaxel chemotherapy. However, in the study, there was no explanation on the chemotherapy received by patients in the low-tumor burden group, which should be paid attention to in the clinical work. Rusthoven et al. [37] divided patients into high-dose and low-dose groups. Of all, 324 (67%) received higher-dose RT (>65 Gy) and 163 (33%) received lower-dose RT (<65 Gy). In Cho et al.'s study [38], patients received conventional or hypofractionated RT with a median dose of 60 Gy in 24 fractions (varying from 30 Gy/10 fractions to 72.6 Gy/33 fractions) to the prostate (1.8–4 Gy per fraction), while metastatic lesions received a median dose of 40 Gy in 10 fractions (range: 22.5–54 Gy). They found toxicities in the PRT group, and most of the side effects were tolerable.

Obviously, our study was not devoid of limitations. First, the subgroup analysis for a moderate heterogeneity in the RCT group was not implemented because of the insufficient quantity of articles. Second, only 2 studies [24, 26] mentioned different types of RT treatments, so it was not possible to further analyze which type of RT was beneficial for mPCa survival. Finally, these CRS were conducted with a large number of patients but existed with selection bias toward patients with favorable general health. In Satkunasivam's study, in overall 4,069 patients with MPCa, NLT was used in 3,827 (94.05%) patients, while only 88 (2.1%) and 107 (2.6%) patients received IMRT and CRT, respectively. The mismatch in the number of patients enrolled between treatment groups reduced the reliability of the results. In the STAMPEDE and the HORRAD study, there was no significant difference in baseline data between the 2 treatment

Fig. 3. Meta-analysis of prognosis with RT versus NLT. RCTs and CRS (**a**); low metastatic burden and high metastatic burden in RCTs (**b**); meta-analysis of CSM with RT versus NLT in CRS (**c**); sensitivity analysis of OS of patients submitted to RT in relation to NLT in CRS (**d**). RCT, randomized controlled trial; CRS, cohort retrospective studies; OS, overall survival; CSM, cancer-specific mortality; RT, radiotherapy; NLT, no local therapy.

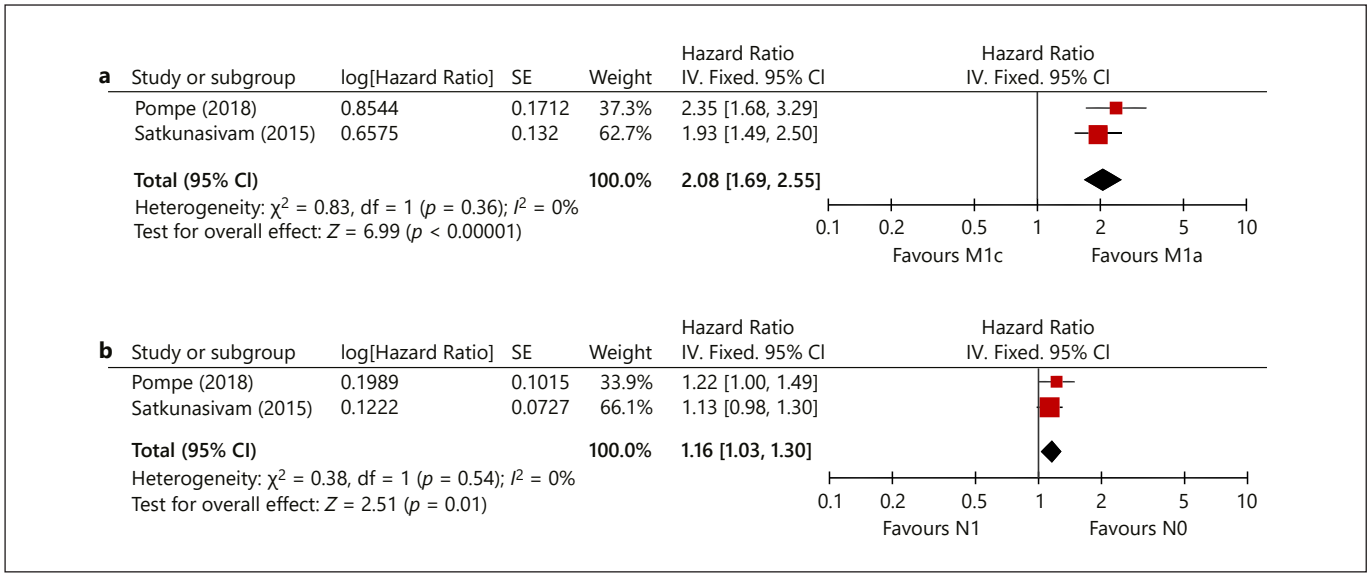

Fig. 4. Meta-analysis of CSM with different levels of M-stage or N-stage in enrolled studies. M1c versus M1a (**a**); N1 versus N0 (**b**). CSM, cancer-specific mortality.

groups. Pompe's study only selected patients who underwent BT, due to lack of EBRT organ site-specific codes. It is difficult to acquire specific method of local treatment in each patient; therefore, we failed to draw definite conclusions from this study. The CRS and RCTs had a different level of evidence though propensity score analysis was used by Rusthoven et al. [27] and Leyh-Bannurah et al. [21] to match the baseline characteristics of the LT versus the NLT group. Generally, patients submitted to LT were younger, with better general health and more favorable disease feature in relation to Gleason score, M-stage, or N-stage and PSA at diagnosis. These factors may distort the results of the real differences between CSM and OS in each study. Also, the treatment of mPCa was difficult to be randomized, let alone blind, which might affect the quality of RCTs. In addition, the dominant ethnicity was Caucasian or White; therefore, this might result in some bias.

Conclusions

In short, mPCa is an extremely heterogeneous disease and the advantage of RT in patients with mPCa was controversial. In light of the above considerations, our study preliminarily draws a conclusion that RT at least does not appear to be harmful and may be beneficial for low-metastatic burden patients and better condition patients. The

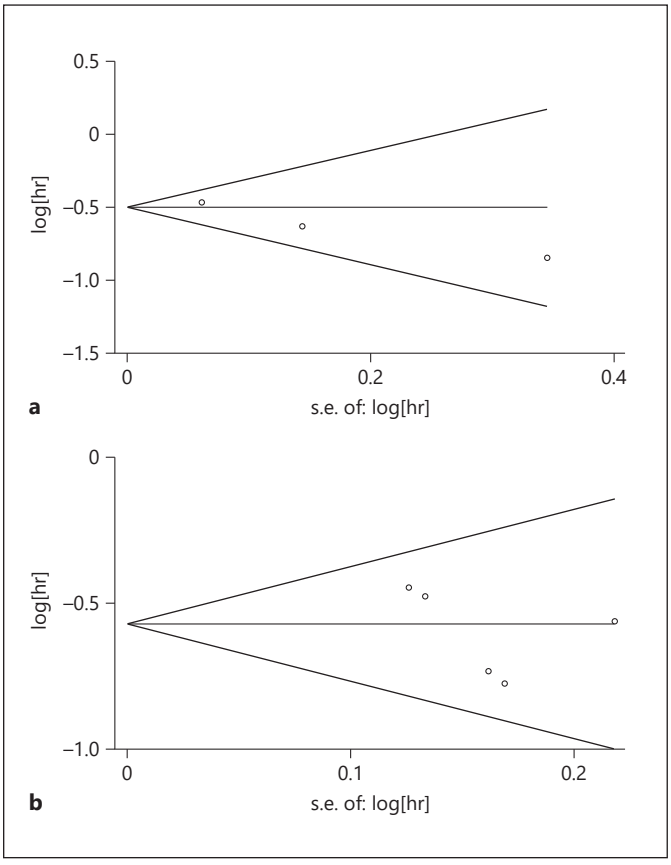

Fig. 5. a, **b** Begg's funnel plots of the publication bias among the OS in CRS. OS, overall survival; CRS, cohort retrospective studies.

absence of proof is not proof of absence, aggressive LT in the setting of mPCa needs to be studied carefully about different states, local symptoms [39], treatment costs, and the risk of toxicity before clinical decision. In addition, it is important to consider our study limitations until more prospective and randomized studies confirm our results.

Acknowledgements

The authors would like to thank the researchers and study participants for their contributions.

Statement of Ethics

RCTs were evaluated using the Cochrane Risk of Bias Tool, and the CRS were analyzed using the Newcastle-Ottawa Scale.

Conflict of Interest Statement

The authors declare that they have no possible conflicts of interest.

Funding Sources

This study was funded by the Jiangsu Province Medical and Health Research Project (No. H2017060).

Author Contributions

S.L. and G.-C.Z. conceived and designed this study. S.L., T.-B.H., X.-Y.W., Z.-Z.X., and L.-B.T. accomplished the selection of articles. X.-Y.W. and X.-X.M. extracted the data. S.L., T.-B.H., X.-Y.W., and T.-S.Z. performed quality assessment, analyzed the data, and wrote the paper. All authors reviewed the paper and approved the final manuscript.

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