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Cytoreductive prostatectomy may improve oncological outcomes in patients with oligometastatic prostate cancer: An updated systematic review and meta-analysis

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The oncologic outcomes of cytoreductive prostatectomy (CRP) in oligometastatic prostate cancer (OmPCa) are still controversial. Therefore, we conducted a systematic review and meta-analysis on the oncologic outcome of CRP in OmPCa. OVID-Medline, OVID-Embase, and Cochrane Library databases were searched to identify eligible studies published before January 2023. A total of 11 studies (929 patients), 1 randomized controlled trial (RCT) and 10 non-RCT studies, were included in the final analysis. RCT and non-RCT were further analyzed separately. End points were progression-free-survival (PFS), time to castration-resistant prostate cancer (CRPCa), cancer-specific-survival (CSS) and overall-survival (OS). It was analyzed using hazard ratio (HR) and 95% confidence intervals (CIs). In PFS, in RCT, HR=0.43 (CIs=0.27–0.69) was shown statistically significant, but in non-RCTs, HR=0.50 (CIs=0.20–1.25), there was no statistical difference. And, in time to CRPCa was statistically significant in the CRP group in all analyses (RCT; HR=0.44; CIs=0.29–0.67) (non-RCTs; HR=0.64; CIs=0.47–0.88). Next, CSS was not statistically different between the two groups (HR=0.63; CIs=0.37–1.05). Finally, OS showed better results in the CRP group in all analyses (RCT; HR=0.44; CIs=0.26–0.76) (non-RCTs; HR=0.59; CIs=0.37–0.93). Patients who received CRP in OmPCa showed better oncologic outcomes compared to controls. Notably, time to CRPC and OS showed significantly improved compared with control. We recommend that experienced urologists who are capable of managing complications consider CRP as a strategy to achieve good oncological outcomes in OmPCa. However, since most of the included studies are non-RCT studies, caution should be exercised in interpreting the results.

Keywords: Cytoreduction surgical procedures; Neoplasm metastasis; Prostatectomy; Prostatic neoplasms; Radiotherapy

INTRODUCTION

The concept of oligometastatic cancer was first introduced by Hellman and Weichselbaum [1]. They defined it as a clinical stage between the simple localized state and the extensive metastasis state, that is, the oligometastasis stage.

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This stage may still be potentially curable. However, there is no formal distinction defined for "oligo" in the literature. Therefore, although the term oligometastasis is also used in prostate cancer (PCa), its precise definition remains unclear. At the Advanced Prostate Cancer Consensus Conference 2017, the most supported (approximately 61%) definition for oligometastatic PCa (OmPCa) was a limited number of bone and/or lymph node metastases [2].

Local therapy, such as surgery performed for the purpose of improving the oncological outcome rather than the palliative purpose in oligometastatic cancer, is still being studied continuously in various cancers, such as lung and breast cancers [3-5]. Similarly, research on local therapy for OmPCa is currently in progress. Currently, the standard treatment for *de novo* metastatic hormone-sensitive PCa (mHSPCa), suggested by guidelines such as the European Association of Urology and the National Comprehensive Cancer Network, is systematic therapy based on androgen deprivation therapy (ADT) and performing androgen receptor-targeted agents (ARTA) or chemotherapy together. GETUG-AFU15 [6], CHAARTED [7], and STAMPEDE [8] evaluated the clinical significance of docetaxel in patients with mHSPCa. The clinical effects of ARTA have been successfully reported in the LATITUDE [9] and ARCHES [10] trials. Based on these studies, compared to conventional ADT alone treatment, ADT combined ARTA or chemotherapy showed statistically better effects in oncological outcomes, including overall survival (OS) in mHSPCa. Therefore, this systemic therapy is regarded as a standard treatment for OmPCa as well. However, unlike high-burden metastatic PCa (mPCa) among mHSPCa, studies have shown better results when local therapy is added to OmPCa. In the STEMPEDE study [11], in contrast to high-burden patients with mPCa, patients with OmPCa who received external beam radiation therapy (EBRTx) showed better OS than those who did not. In contrast, the HORRAD study [12] with similar settings, did not show statistically significant results for radiotherapy, even in OmPCa. Although the results of these studies were conflicting, in the meta-analysis conducted based on these studies, EBRTx showed a good effect on OmPCa [13], and through this, evidence for EBRTx of the primary site in OmPCa was obtained. Therefore, even in the NCCN guideline, radiotherapy is suggested as one option that can be considered in OmPCa. However, controversy still exists regarding cytoreductive prostatectomy (CRP) among local therapies. Registry data analyzing the effect of CRP on mHSPCa through databases, such as SEER, NCDB, and the Munich Cancer Registry showed positive results [14-16]. This demonstrated that local tumor control resulted in good OS and cancer-specific survival (CSS) in men with newly diagnosed mHSPCa. However, huge bias exists in population databases because selective bias by clinicians can be large. Therefore, it is difficult to obtain high-quality evidence of CRP in OmPCa. Currently, the results of a phase 2 study on CRP have been announced and have shown good results [17]. Moreover, several case-control studies have been conducted [18-27]. However, the number included in each study was limited, and the results were also different. Large-scale clinical studies on CRP levels are still in progress. Therefore, as the evidence for CRP in OmPCa is still insufficient, we conducted a systematic review and meta-analysis to examine the effect of OmPCa on CRP by integrating the studies published to date. Therefore, we aimed to determine the effect of CRP in OmPCa.

MATERIALS AND METHODS

1. Evidence acquisition

This systematic review was registered in PROSPERO (CRD42022349725).

The study was exempt from the approval of an ethics committee or institutional review board because it was a systematic review and meta-analysis.

1) Search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (http://www.prisma-statement.org/) [28].

A literature search of all publications up to January 2023 was conducted using the Ovid-Medline, Ovid-Embase, and Cochrane Library databases. In addition, a cross-reference search of eligible articles was performed to identify studies that were not found in the computerized search. We used a combination of the following MeSH terms and keywords: "prostate cancer," "prostate carcinoma," "cytoreduct," "oligo," and relevant variants. Relevant articles were included in the search. Two authors (D.Y.C. and D.H.K.) independently reviewed titles and abstracts according to the inclusion criteria. Subsequently, they conducted a full-text evaluation of the identified papers. Any disagreement regarding the inclusion of an article was discussed with the third author (K.S.C.). The search strategies for the systematic review are included in the Supplementary material, Supplementary Fig. 1, Supplementary Table 1.

2) Inclusion criteria and study eligibility

The eligibility of each study was assessed by considering

the participants, interventions, comparators, outcomes, and study design [29].

First, we defined OmPCa as a limited number of bone and/or lymph node metastases:

(1) Interventions: Patients who underwent CRP for OmPCa.
(2) Comparators: Patients who did not undergo CRP for OmPCa.
(3) Outcomes: Follow-up progression-free survival (PFS), time to castration-resistant prostate cancer (CRPCa), CSS, and OS.
(4) Study design: We did not place any restrictions on the study design so that both randomized controlled trials (RCTs) and observational studies could be included.

In addition, (1) non-human studies; (2) documents not written in English; (3) case reports, reviews, guidelines, and editorial comments; and (4) conference abstracts were excluded from the analysis.

3) Study quality assessments

Quality assessments were conducted independently by two reviewers (D.Y.C. and H.D.J.) and were divided into RCTs and observational studies. The Cochrane Bias Risk Tool for Quality Assessment, recommended by the Cochrane Handbook for Systematic Reviews of Interventions, was used in the RCTs [30]. It included the following risk areas for bias: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other potential biases. Each item was evaluated using the following three categories based on the risk of bias: low, unclear, high. The Newcastle–Ottawa scale was used for observational studies [31]. The three major assessment categories were selection, comparability, and exposure. Each piece of research received up to nine stars. A study score of 7–9 indicated high quality; 4–6, high risk; and 0–3, very high risk of bias.

4) Statistical analysis

The effects of CRP on OmPCa were measured using hazard ratio (HR). Log HR values were obtained directly from trials reporting HR point estimates and confidence intervals (CIs), and the standard errors of log HR were calculated using published CIs [32]. Some studies reported Kaplan–Meier log-rank p-values but omitted HR, 95% CI, or both. In these cases, we estimated HR and 95% CI using p-values, the number of total events, and the number of participants randomized to each arm [33]. The effects of CRP on PFS, time to CRPCa, CSS, and OS were assessed using pooled HRs and 95% CIs. Each analysis was performed by separating the RCT and non-RCT. In addition, complications reported in each study were tabulated according to Clavien-Dindo grade instead of statistical analysis because there was no comparative data between the two groups.

Heterogeneity was assessed using the chi-square and I^2 tests. A Cochran Q statistic p-value <0.05 or an I^2 statistic >50% was used to indicate statistically significant heterogeneity between studies [34]. When there was evidence of heterogeneity, analyses were performed using a random-effects model. In addition, we tried to reduce the heterogeneity of the final results by analyzing characteristics such as the age, cancer burden, and EBRTx of the patients included between each study.

The meta-analysis was conducted using Review Manager Version 5.3 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2013). Statistical significance was set at p <0.05 [35]. Although each analysis was an analysis of fewer than 10 studies, we also added funnel plots to the supplementary data to assess publication bias [36].

RESULTS

1. Evidence synthesis

1) Systematic review process and study characteristics

The PRISMA guidelines were followed, and a flowchart of the study selection process is shown in Fig. 1. The initial international database search identified 1,206 studies (348 from Ovid-MEDLINE, 606 from OVID-EMBASE, and 252 from the Cochrane Library), of which 493 remained after the removal of duplicates. After screening titles and abstracts, 438 articles were excluded. Subsequently, 55 full-text articles were evaluated based on pre-established inclusion criteria. As a result, a total of 11 papers (929 patients) were included in the final analysis (Table 1) [17-27]. There was one RCT [17] and 10 non-RCT case-control studies (one prospective [26] and nine retrospective [18-25,27]). All trials enrolled patients with OmPCa treated with or without CRP.

2) Quality assessment

The quality assessment results based on the Cochrane risk-of-bias tool or the Newcastle–Ottawa are shown in Tables 2, 3 [17-27]. In one RCT, there was a risk of blinding (detection bias) and allocation concealment (selection bias) as an open label study. All non-RCT studies received a score of six to seven points. In the three studies [19,21,27], there was

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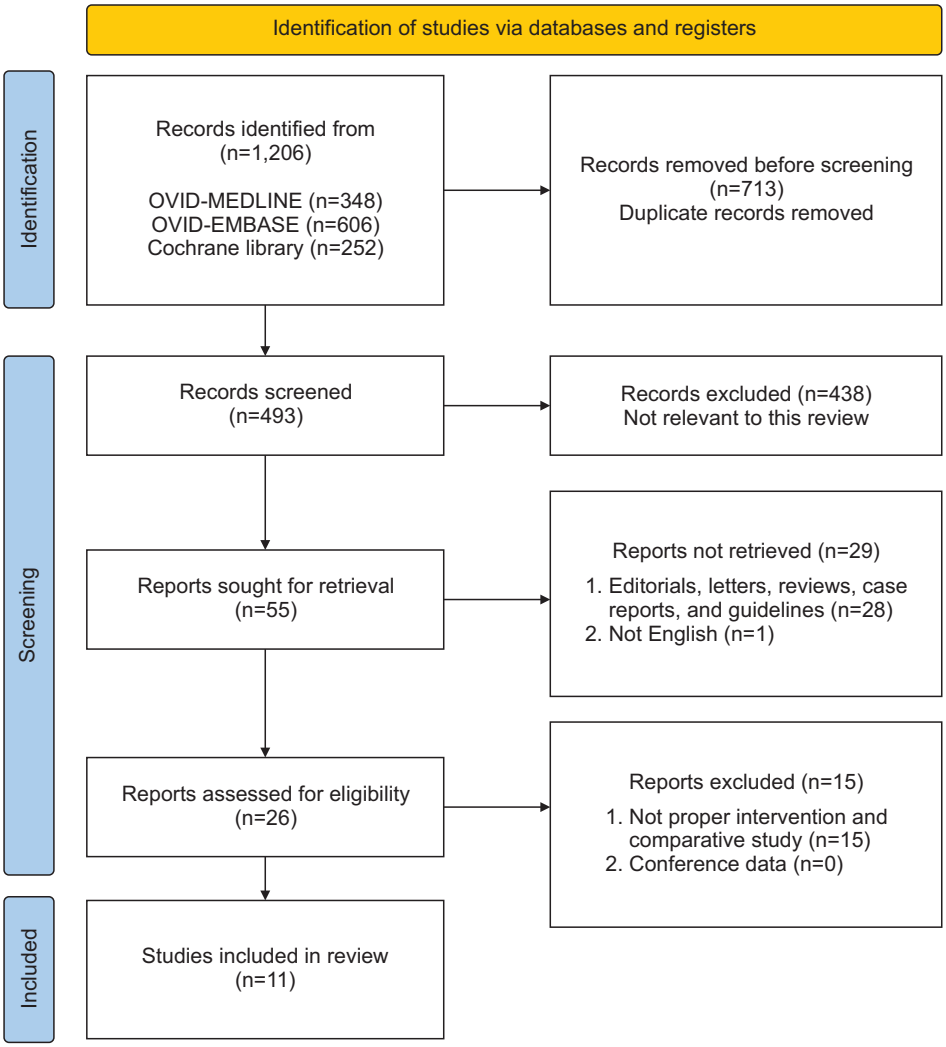

Fig. 1. Study selection flowchart according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

a difference in treatment modality between the two groups according to the needs of the clinician. Otherwise, no major problems were noted except for the selection of control and non-response rates.

3) Progression-free survival

Four studies [17,19,21,22] (421 patients) were included in the comparison of PFS according to CRP for OmPCa. First, in one RCT [17], PFS was better in the CRP group (HR, 0.43; 95% CIs, 0.27–0.69; p<0.001). Next, the meta-analysis results, including three observational studies [19,21,22] no show statistically significant results were observed (random effects HR, 0.50; 95% CIs, 0.20–1.25; p=0.14). Heterogeneity was also identified across studies (Cochran's Q statistic, p=0.009; I^2 statistic, 79%). Finally, in a meta-analysis that included all four studies [17,19,21,22], there was a significant difference in PFS (random effects HR, 0.49; 95% CIs, 0.27–0.88; p=0.02). In this analysis as well, heterogeneity was identified across studies (Cochran's Q statistic, p=0.02; I^2 statistic, 70%). Fig. 2 shows the forest plots of the PFS.

4) Time to castration-resistant prostate cancer

A total of seven studies [17,18,20,22,24,26,27] (671 patients were included) were included in a comparison of time to CRPCa according to CRP for OmPCa. First, in one RCT [17], time to CRPCa showed a better result in the CRP group (HR, 0.44; 95% CIs, 0.29–0.67; p<0.001). Next, in a meta-analysis of six observational studies [18,20,22,24,26,27], the CRP group showed significantly better results (random effects HR, 0.64; 95% CIs, 0.47–0.88; p=0.006). In this analysis, no heterogeneity was identified across the studies (Cochran's Q statistic, p=0.29; I^2 statistic, 18%). Finally, in the meta-analysis that included all seven studies, a significantly better result was reported in the CRP group (random effects HR, 0.58; 95% CIs, 0.44–0.78; p=0.0003), and no heterogeneity was identified across studies (Cochran's Q statistic, p=0.21; I^2 statistic, 29%). Fig. 3 shows forest plots of time to CRPCa.

Table 1. Characteristics of eligible studies

Study, country	Study design	Metastasic lesions[a]	Additional therapy other than ADT	Group	No	Follow up (mo)	Age (yr)	Initial PSA (ng/mL)	PFS (mo)		Time to CRPCa (mo)		CSS (mo)		OS (mo)	
Dai et al. [17], China	Randomized clinical trial	Minimal osseous metastases (5 or fewer on bone scan)	No consolidation therapy	Control	100	48 (43–50)	69 (64–73)	102 (49–254)	3 yr: 56%	0.43 (0.27–0.70)[b]	3 yr: 45%	0.44 (0.29–0.67)[b]	NR		3 yr: 70%	0.44 (0.24–0.81)[b]
				CRP 85 RTx 11 Exclusion 4	100		67 (62-71)	90 (35–236)	3 yr: 79%		3 yr: 71%				3 yr: 88%	
Heidenreich et al. [18], Germany	Retrospective case-control	Minimal osseous metastases (3 or fewer on bone scan)	Adjuvant RTx (66.6 Gy) on prostate bed, if positive surgical margins	Control	38	44.0 (24–96)	63.9 (47–83)	135.2 (3.5–150.4)	26.5 (12–48)	NR	29 (16–54)	0.63 (0.35–1.10)[c]	40.5 (19–75)	1.15 (0.65–2.03)[c]	NR	NR
				CRP	23	40.6 (3–71)	61 (42–69)	105.9 (45–195)	38.6 (42–52)		40 (9–65)		47 (9–71)		NR	
Jang et al. [19], South Korea	Retrospective case-control	Minimal osseous metastases (5 or fewer on bone scan)	Twenty-two patients (57.9%) determined to be necessary by the clinician received RTx	Control	41	40 (28–58)	71 (67–76)	50.0 (23.8–162.8)	28 (NR)	0.388 (0.206–0.731)	NR		40 (NR)	0.264 (0.107–0.650)	NR	
				CRP	38		65 (62–69)	39.0 (15.0–84.5)	75 (NR)				Not reached			
Lan et al. [20], China	Retrospective case-control	Minimal osseous metastases (5 or fewer on bone scan)	NR	Control	76	39.21±20.62	67.83±7.19	90.4±52.8	NR		35 (18–59)	0.84 (0.53–1.35)[c]	3 yr: 87.9% 5 yr: 74.9%	1.11 (0.56–2.19)[c]	NR	
				CRP	35	36.86±16.55	71.17±7.73	502.9±806.0			21 (10–49)		3 yr: 90.8% 5 yr: 63.6%			
Lumen et al. [21], Belgium	Retrospective case-control	Low-volume metastasis without visceral metastasis and four or more bone lesions	In some case (17.4%), using chemotherapy or apalutamide other than ADT	Control	35	24 (12–44)	74 (69–84)	47 (17–156)	2 yr: 60±9%	0.25 (0.10–0.64)	NR		2 yr: 75±8%	0.36 (0.14–0.94)	2 yr: 69±9%	0.28 (0.11–0.71)
				CRP	48	42 (24–57)	64 (59–72)	19 (11–42)	2 yr: 92±4%				2 yr: 93±4%		2 yr: 93±4%	
Mistretta et al. [22], Italy	Retrospective case-control	Minimal osseous metastases (5 or fewer on bone scan)	Adjuvant RTx on prostate bed and directed RTx on metastasis lesions	Control	34	50 (NR)	64 (60–74)	87 (35–186)	NR	1.19 (0.62–2.28)	NR	0.40 (0.19–0.84)	NR	0.21 (0.07–0.59)[c]	NR	
				CRP	40	55 (NR)	67 (58–68)	14 (9–29)								
Moschini et al. [23], United States	Retrospective case-control	Only M1a and M1b (M1a 53% and M1b 47%)	Directed RTx on metastasis lesions in M1b patients	Control	16	38.8 (NR)	59 (54–59)	76.5 (2.7–218)	NR		NR		3 yr: 76.9% 5 yr: 46.2%	1.89 (0.59–6.00)	NR	
				CRP	31		62 (56–66)	24.4 (12.4–107.0)					3 yr: 91.3% 5 yr: 61.9%			
Si et al. [24], China	Retrospective case-control	Minimal osseous metastases (5 or fewer on bone scan)	NR	Control	57	73.0 (56.0–85.4)	76.42±9.69	70.83 (26.08–100)	NR		25.35 (18.43–31.23)	0.587 (0.251–1.376)	NR		80.7 (72.3–89.1)	0.659 (0.352–1.233)
				CRP	27	64.2 (56.4–81.6)	76.67±9.66	28.93 (10.76–100)			35.30 (23.60–48.20)				78.6 (58.8–98.4)	
Simforoosh et al. [25], Iran	Retrospective case-control	M1b patients Oligo 19 Poly 30	Include total orchiectomy, bilateral	Control	23	21 (14–43)	64.6±6.18	84±61	NR		NR		NR	0.66 (0.31–1.41)[c]	NR	
				CRP	26	18 (9–42)	61.5±7.67	108±73								

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Table 1. Continued

Study, country	Study design	Metastasic lesions[a]	Additional therapy other than ADT	Group	No	Follow up (mo)	Age (yr)	Initial PSA (ng/mL)	PFS (mo)	Time to CRPCa (mo)		CSS (mo)		OS (mo)	
Steuber et al. [26], Germany	Prospective case-control	Minimal osseous metastases (3 or fewer on bone scan)	No consolidation therapy	Control	40	82.2 (37.1–121.2)	70 (NR)	42.5 (NR)	NR	NR	1.49 (0.58–3.83)[c]	NR		NR	1.01 (0.39–2.64)[c]
				CRP	43	32.7 (23.5–84.6)	65 (NR)	29 (NR)							
Xue et al. [27], China	Retrospective case-control	Minimal osseous metastases (5 or fewer on bone scan)	Directed RTx on metastasis lesions (45%)	Control	32	47.6 (18–65)	67.5 (54–78)	36.4 (9.7–756.3)	NR	3 yr: 75.9%	0.411 (0.178–0.950)	3 yr: 91.4%	0.5855 (0.116–2.949)	NR	
				CRP	26	43.1 (15–61)	65.5 (51–79)	35.3 (8.9–213.5)							

Values are presented as median (interquartitle range), mean±standard deviation, or hazard ratio (95% confidence interval).
ADT, androgen deprivation therapy; CRP, cytoreductive prostatectomy; CRPCa, castration-resistant prostate cancer; CSS, cancer specific survival; NR, not reported; OS, overall survival; PFS, progression free survival; PSA, prostate specific antigen; RTx, radiation therapy.
[a]:Patients included in all studies had no visceral and extra-pelvic nodal metastasis.
[b]:Compared only CRP and Control excluding RTx patients.
[c]:Values were estimated from the Kaplan-Meier curves.

Table 2. Results of quality assessment of randomized control trial study by the Cochrane risk of bias tool

Study, country	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other bias
Dai et al. [17], China	Low risk	High risk	High risk	High risk	Low risk	Low risk	Unclear

Table 3. Results of quality assessment of nonrandomized studies by the Newcastle–Ottawa Scale

Study, country	Selection (4)				Comparability (2)	Exposure (3)			Total score
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Heidenreich et al. [18], Germany	1	1	0	1	2	1	1	0	7
Jang et al. [19], South Korea	1	1	0	1	2	1	0	0	6
Lan et al. [20], China	1	1	0	1	2	1	1	0	7
Lumen et al. [21], Belgium	1	1	0	1	2	1	0	0	6
Mistretta et al. [22], Italy	1	1	0	1	2	1	1	0	7
Moschini et al. [23], United States	1	1	0	1	2	1	1	0	7
Si et al. [24], China	1	1	0	1	2	1	1	0	7
Simforoosh et al. [25], Iran	1	1	0	1	2	1	1	0	7
Steuber et al. [26], Germany	1	1	0	1	2	1	1	0	7
Xue et al. [27], China	1	1	0	1	2	1	0	0	6

5) Cancer-specific survival

A total of eight studies (562 patients) were included in the comparison of CSS according to CRP for OmPCa. All included studies were observational. This analysis did not show any statistically significant differences (random effects HR, 0.63; 95% CIs, 0.37–1.05; p=0.08). In this analysis, heterogeneity was identified across studies (Cochran's Q statistic, p=0.008; I^2 statistic, 63%). Fig. 4 shows the forest plot of the CSS.

6) Overall survival

A total of four studies [17,21,24,26] (450 patients) were included in the comparison of OS according to CRP for OmPCa. First, in one RCT [17], OS was better in the CRP group (HR, 0.44; 95% CIs, 0.26–0.76; p=0.003). Next, in a meta-analysis of three observational studies [21,24,26], the CRP group showed significantly better results (fixed effects HR, 0.59; 95% CIs, 0.37–0.93; p=0.02). In this analysis, no heterogeneity was identified across the studies (Cochran's Q statistic, p=0.15; I^2 statistic, 47%). Finally, in the meta-analysis that included all four studies, there was also a significantly better result in the CRP group (fixed effects HR, 0.52; 95% CIs, 0.37–0.74; p=0.0003), and no heterogeneity was identified across studies (Cochran's Q statistic, p=0.22; I^2 statistic, 32%). Fig. 5 shows the forest plots of the OS.

DISCUSSION

Prostate cancer is the most common cancer among men in the United States, with an estimated 191,000 new cases diagnosed in 2020 [37]. Despite a 5-year relative survival rate of >99% for localized disease, mPCa remains the second leading cause of cancer-related deaths in men, with a 5-year relative survival rate of 30.2%. Prior studies have demonstrated an increase in the diagnosis of *de novo* mPCa in recent years, perhaps related to the United States [38]. Therefore, although the birth of ARTA has opened a new horizon for mPCa treatment, it is still an incurable disease and requires continuous research. Among them, *de novo* OmPCa is a pioneering field. In the "seed and soil" theory, tumors can have limited metastases in their number and location if facilities for metastatic growth of cancer cells are not sufficiently developed and the quality of sites for growth is limited. Based on this theory, treatment of the primary lesion is considered for OmPCa [39]. Among the local therapies for OmPCa, EBRTx currently has the highest evidence. Burdett et al. [13] reported a 7% improvement in the 3-year survival rate when EBRTx was performed in patients with OmPCa with not more than five bone metastases. In addi-

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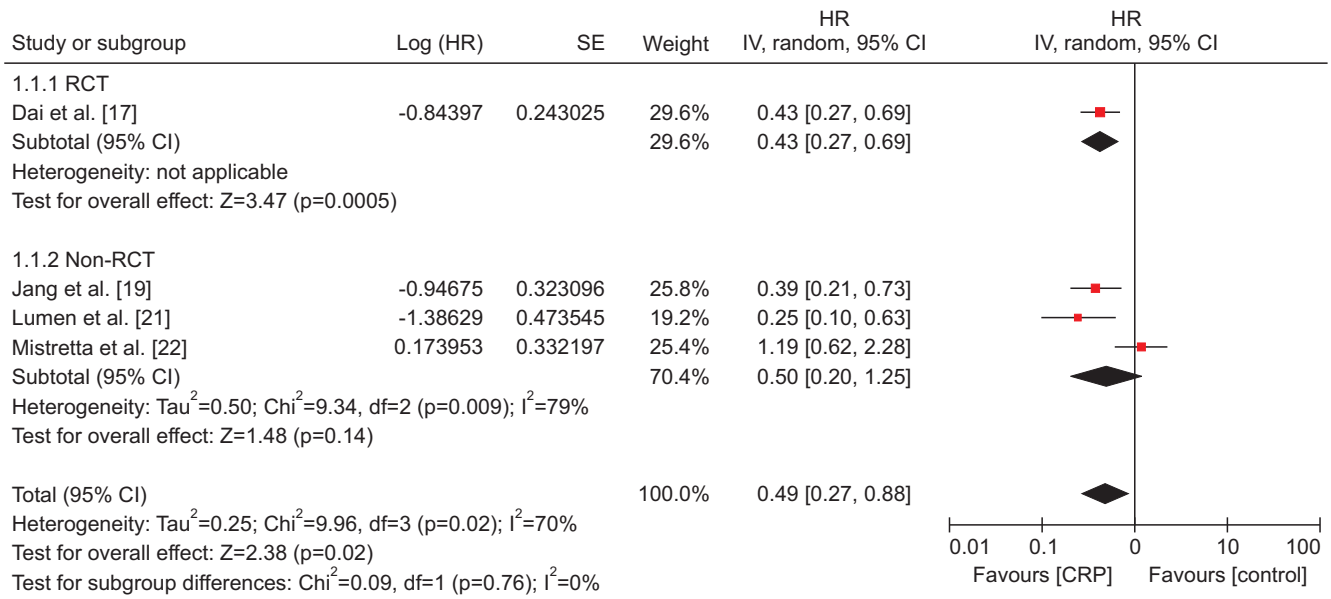

Fig. 2. Forest plots of progression-free survival. HR, hazard ratio; CI, confidence interval; RCT, randomized controlled trial; CRP, cytoreductive prostatectomy; SE, standard error.

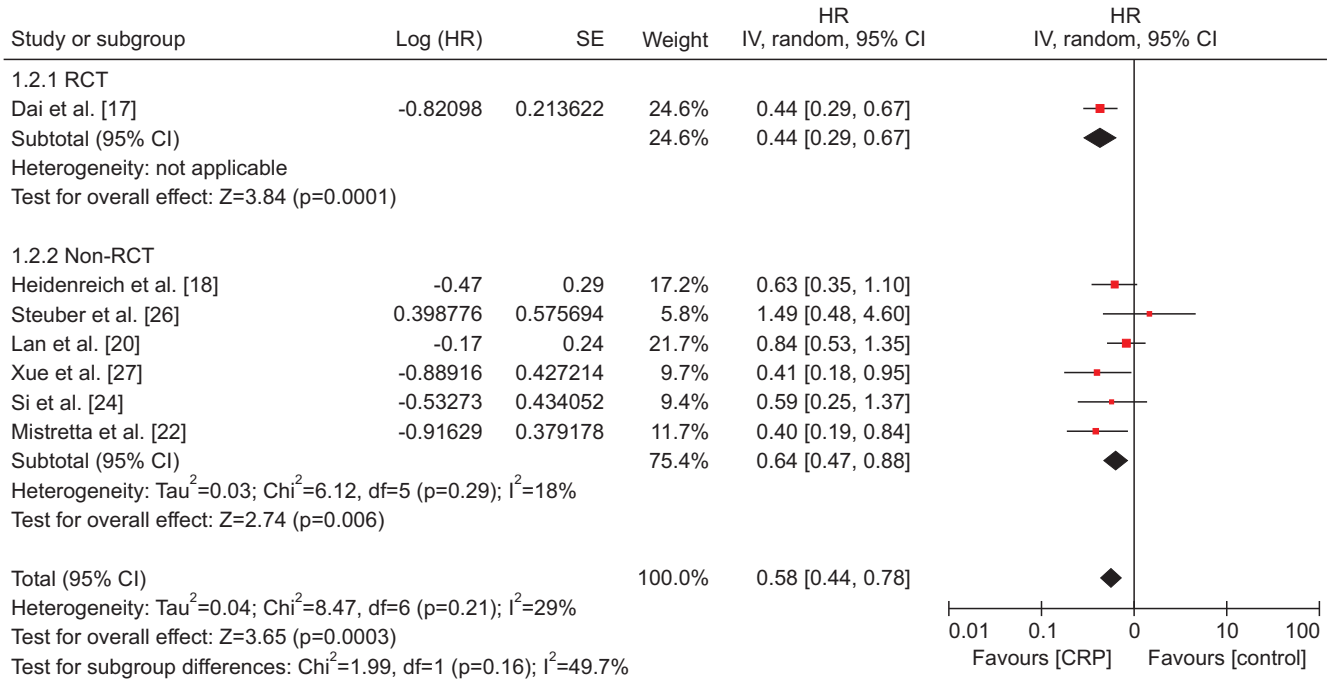

Fig. 3. Forest plots of time to castration-resistant prostate cancer. HR, hazard ratio; CI, confidence interval; RCT, randomized controlled trial; CRP, cytoreductive prostatectomy; SE, standard error.

tion, the European Society for Radiotherapy and Oncology Guidelines Committee has recently recommended EBRTx in OmPCa [40]. In contrast, CRP still lacks evidence. Previously, PCa with regional lymph node metastases (LNM) was considered to have a poor prognosis and systemic treatment without local therapy was chosen [41]. However, recently, radical prostatectomy (RP), including pelvic node dissection, as well as EBRTx in selective patients with regional LNM have been considered as treatments to improve oncological outcomes. Engel et al. [42] reported that those with LNM who did not undergo radical prostatectomy had an increased risk of death compared to men who underwent RP. Multivariate analysis demonstrated radical prostatectomy as an independent predictor of survival (HR, 2.04; 95% CI, 1.59–2.63; p<0.0001). Several studies have reported positive results [43,44]. Based on these results, studies were conducted on

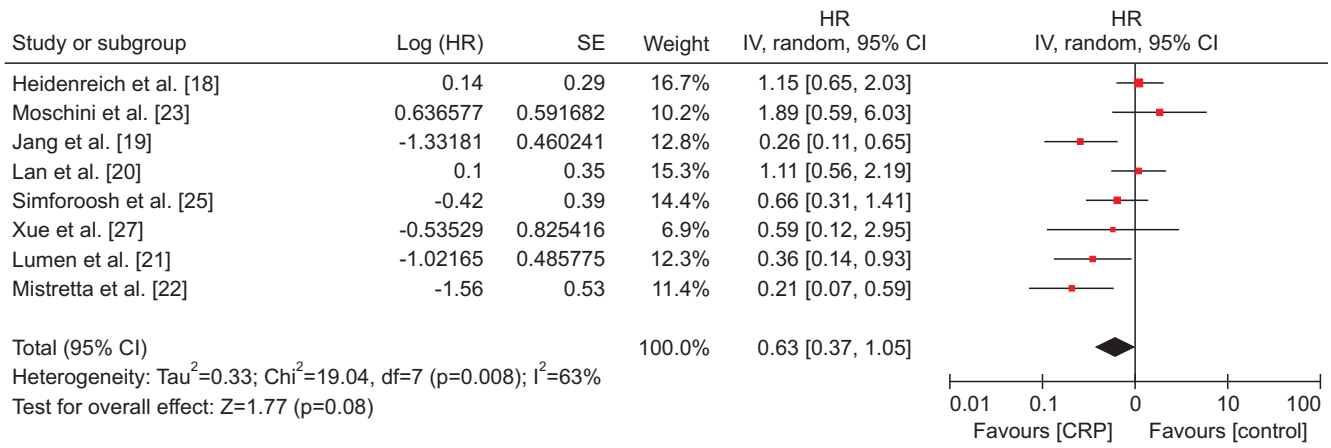

Fig. 4. Forest plots of cancer-specific survival. HR, hazard ratio; CI, confidence interval; CRP, cytoreductive prostatectomy; SE, standard error.

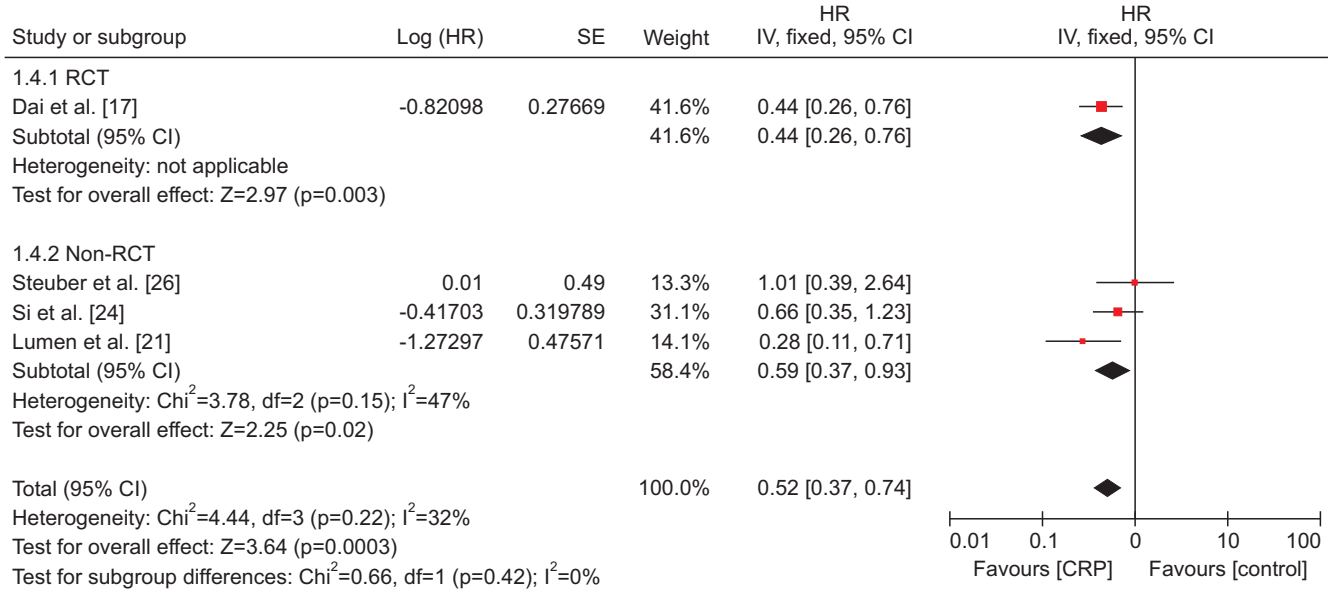

Fig. 5. Forest plots of overall survival. HR, hazard ratio; CI, confidence interval; RCT, randomized controlled trial; CRP, cytoreductive prostatectomy; SE, standard error.

the benefits of CRP in OmPCa as a small number of bone metastasis developed. Currently, several RCTs on CRP, such as NCT03456843, are being conducted in OmPCa, but only one phase 2 study in China [17] has been published to date. In this study, the CRP group showed a positive effect on the 3-year OS by 56% compared to the control group. However, the sample size of this study was relatively small, and the results require validation through large multicenter RCTs.

Meta-analyses of CRP for OmPCa have been published only recently [45,46]. These studies, similar to the results of our study, show good effects in CRP. However, these two studies differed from our study. First, Cheng et al. [45] analyzed the range of OmPCa, including patients with only regional LNM and not patients with distant metastasis. A recently published study by Mao et al. [46] was conducted in a setting similar to our study. They reported significant improvements in CSS and PFS, but not OS, in the CRP group. However, they did not report HR through survival analysis but performed a meta-analysis using odds ratios according to the number of events. Therefore, these analyses may introduce a time-dependent bias. In this regard, we added the latest study, secured the largest number of patients, and performed an updated meta-analysis using the HR for each oncological outcome. Therefore, our study is the first meta-analysis to analyze the HR for the oncological outcome of CRP by integrating the studies published to date to redeem the lack of evidence for CRP in OmPCa. Although most of the included studies were non-randomized case-control studies, our results showed positive oncological results for CRP in OmPCa.

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First, the time to CRPCa showed good results. The time to CRPCa is an important factor in the prognosis of mHSPCa [47-49]. In these studies, prolongation of time to CRPCa was explained as a prognostic factor for survival rate. In addition, although statistically significant values were not shown for CSS, CRP showed a very good effect on OS. When looking at the OS in our study, the CRP group showed a positive result of 47% compared to the control group. Although direct comparison is difficult, our results were also good when compared with the results of the STAMPEDE studies (HR, 0.68; 95% CI, 0.52–0.90; p=0.007) on EBRTx for OmPCa. Although it is difficult to conclude that CRP is still better than EBRTx in OmPCa, in the Local Treatment of Metastatic Prostate Cancer Registry study, CRP also showed better results than EBRTx in PFS (HR, 0.3; CI, 0.11–0.86; p=0.024) [21]. To support these findings, it is thought that additional large-scale RCTs for direct comparison of EBRTx and CRP in OMPCa are needed.

Regardless of how good the oncological outcome of CRP is, it will be difficult to proceed if the complication that can deteriorate the patient's quality of life is high. The complication rates in the studies included in the analysis are summarized. (Supplementary Table 1) In each study, complications of Clavien–Dindo grade III or higher were reported in 5.2%–16%, but most studies did not report high complications compared to conventional RP. However, rectal injury among the complications in the included studies was higher than that reported in previous reports (approximately 0.1%) [50,51]. This is considered a complication to be aware of when implementing CRP. In addition, the prevalence of complications associated with CRP remains controversial. Preisser et al. [52] published a study comparing the complications of CRP and RP in non-metastatic PCa. They reported that in CRP, the overall complications were significantly higher, but there was no difference in major complications related to mortality. In addition, Yuh et al. [53] conducted a phase 1 study on CRP, including 36 patients. They evaluated that CRP were mostly safe and feasible. However, it cautioned that there may be a small group of patients that could cause serious harm. However, several studies have reported the feasibility and safety of CRP. They reported no significant difference in complication rates or functional outcomes, such as incontinence [54-56]. In addition, according to several reports, CRP reduces locoregional complications, such as bladder outlet obstruction, that can occur in mPCa and improve quality of life [57,58]. Although, CRP complication rates appear to be manageable, explicit discussion might be required during patient consultation.

Our study has some limitations. First, most of the included studies were case-control studies with a non-randomized design, which may inevitably include selection bias. Second, although most studies used a similar ADT schedule, there were differences in the treatment with adjuvant therapy and EBRTx for metastatic lesions. Finally, some studies did not provide accurate HR and 95% CI. Therefore, the estimates obtained using the Kaplan–Meier curve may include some errors. To overcome these limitations, well-designed randomized trials should be performed in the future. Despite these limitations, our study provides high-quality information by integrating the studies reported to date to clinicians considering CRP in OmPCa.

CONCLUSIONS

Our results shows that patients with OmPCa who were treated with CRP had better oncological outcomes. In particular, patients who had undergone CRP showed significantly improved time to CRPC and OS compared with those who had not undergone CRP. Therefore, we recommend that experienced urologists who are capable of managing complications consider CRP as a strategy to achieve good oncological outcomes in patients with *de novo* OmPCa. However, since most of the included studies are non-RCT studies, caution should be exercised in interpreting the results.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20230058.

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