Review

Does Radical Local Treatment in Oligometastatic Prostate Cancer Improve Overall Survival: A Systematic Review and Meta-analysis

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OBJECTIVE To determine the impact of radical local treatment (RLT) on overall survival (OS) and other survival outcomes in patients with OligoMetastatic Prostate Cancer (OMPC).

METHODS We performed a meta-analysis of randomized controlled trials (RCTs) published in the MEDLINE and CENTRAL databases until May 2023. We included RCTs that randomized patients to RLT (either radical prostatectomy [RP] or external beam radiotherapy [EBRT]) and standard of care and reported on OMPC. Our primary objective was to analyze OS with a minimum median follow-up of 4 years (PROSPERO-CRD42023422736).

RESULTS We analyzed 3 RCTs, presenting data across 5 papers. OS was significantly higher in the RLT group (HR - 0.643, 95%CI 0.514-0.8, *P*-value < .001). The data on EBRT was drawn from 520 patients and that of RP was from 85. The post-hoc power analysis showed 81% power to detect a difference of 10% with an alpha error of 0.01. Pooled prevalence of grade 3-4 bowel and bladder toxicity was 4.5%. Health-Related Quality of Life was similar in both groups (mean difference - 1.54, 95%CI − 0.625 − 3.705, *P*-value .163). The risk of bias as per the RoB2 tool was low for all domains and overall bias. As per GRADE criteria, the certainty of evidence was high.

CONCLUSION Our meta-analysis underscores the evidence-based significance of RLT, particularly emphasizing the benefits of EBRT in patients with OMPC. However, the findings should be interpreted with caution due to the limited number of studies and the relatively small sample sizes, especially in the RP subgroup. Future investigations in OMPC should consider incorporating EBRT in their standard treatment approach. UROLOGY 182: 5–13, 2023.

With the improvement in outcomes of patients being treated with systemic therapy for newly diagnosed metastatic hormone-sensitive prostate cancer, attention has now shifted to a combination of treatment of the primary tumor along with systemic therapy. The addition of local radical treatment (radiotherapy [RT] or radical prostatectomy [RP]) to systemic therapy has shown improvement in overall survival (OS) in patients with Oligo-Metastatic Prostate Cancer (OMPC) in 2 of the 3 randomized controlled trials (RCTs) including the STAMPEDE and HORRAD trials. The other trial was by Dai et al.[1-5] Several large-scale retrospective studies also reported similar outcomes.[6-9] Apart from this there are ongoing trials with results awaited, which are studying the role of RLT in patients with metastatic prostate cancer.[10-14]

The highest level of evidence on any proposed treatment modality is always obtained by randomized control trials comparing the modality against the standard of care (SOC). Keeping this in mind, we have done a systematic review and meta-analysis of RCTs comparing local therapy to the prostate plus systemic therapy vs the SOC in cases of newly diagnosed OMPC.

MATERIALS AND METHODS

Evidence Acquisition

We conducted a comprehensive search of the PubMed/MEDLINE database and the Cochrane Database of Systematic Reviews on May 1, 2023 for RCTs conducted over the last

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50 years. The search strategy applied was "randomized" OR "randomized" AND "radiation" OR "radiotherapy" OR "surgery" OR "local therapy" AND "metastatic" AND "prostate." No language restriction was placed. Our inclusion criteria were RCTs with[1] patients with prostate cancer with oligometastases (skeletal metastases < 5),[2] randomization to SOC including androgen deprivation therapy (ADT) with or without docetaxel or abiraterone with and without local treatment of prostate by RP or external beam radiotherapy (EBRT),[3] reporting of OS with a minimum median follow-up of 4 years, and[4] use of hazard ratio (HR) and confidence interval for reporting. References of review articles were identified in addition to finding any articles meeting our inclusion criteria. We also searched the ClinicalTrials.gov database for any ongoing RCTs. These authors were contacted for any data that could be included in our meta-analysis.

Outcome Measures and Data Extraction

We used the Population, Intervention, Control, Outcomes, Study Design (PICOS) method to define inclusion and exclusion criteria. Our target population was patients with de novo synchronous metastatic prostate cancer with less than 5 skeletal metastases with an untreated primary tumor.[15] The intervention was radical treatment of the prostate by RP or RT with or without management of regional lymph node metastases in addition to SOC. The control was SOC without locoregional treatment. The study design was that only RCTs were included. The primary objective was OS, defined as death from any cause from time of randomization and secondary outcomes were progression fress survival (PFS), prostate cancer-specific survival (PCSS), toxicity (eg, Clavein-Dindo grade, Radiation Therapy Oncology Group [RTOG]/Common Terminology Criteria for Adverse Events [CTCAE] grade 3-4 acute toxicity) and patient-reported Health-Related Quality of Life (HRQoL).

Two authors (K.M. and R.J.) conducted the data extraction independently and this was reviewed by the third author (D.K.). We assigned Centre for Evidence-Based Medicine levels of evidence to each of the studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.[16] The study was registered with PROSPERO with registration number CRD42023422736.

Assessment of Bias

Risk of bias was assessed using the Cochrane RoB 2 tool and studies with high risk of bias were excluded.[17] Heterogeneity was assessed using the I^2 statistic (value > 50% suggestive significant heterogeneity), prediction interval, and the variance of the random effect (Tau-squared statistic). Publication bias was assessed using funnel plots and Egger's test. In case, the results were significant, failsafe N was used to assess publication bias and find the number of studies needed to render the results insignificant. Rosenthal's formula (5k + 10) was used as the threshold for failsafe N, where k is the number of studies included. Certainty of evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.

Statistical Analysis

Data were extracted from all included studies into standardized forms and then into Microsoft Excel 2007 for Windows (Microsoft Corporation, Redmond, WA) and Comprehensive Meta-Analysis version 3 (Biostat Inc, Englewood, NJ). Fixed effects model were used to synthesize results if there was no heterogeneity. Otherwise, random effects model was used. For survival rates, HR and 95%CI were used as the effect measure and measure of variance, respectively. For PCSS, odd's ratio (OR) and 95%CI were used. For HRQoL, mean difference and 95%CI were used. A *P*-value of less than .05 was considered significant for all comparisons.

The PRISMA checklist is given as Table S1 (online only).

RESULTS

Our search retrieved 3681 records initially, and we finally selected 5 papers (from 3 trials) for the meta-analysis as per the PRISMA diagram (Fig. 1). Of these only 1 trial included patients with solely oligometastatic prostate cancer. The STAMPEDE and HORRAD trials included patients with metastatic prostate cancer, irrespective of the number of metastasis but they reported separately on patients with oligometastatic disease. Both these trials reported OS for patients with oligometastatic disease, but only STAMPEDE reported cancer-specific survival, symptomatic local event-free survival (SLEFS), and local intervention-free survival (LIFS) for them. Neither trial reported side effects and quality of life separately for this subgroup. Data from the HORRAD trial were reported in 2 different papers, and we included both. All 3 trials had a low risk of bias on all parameters.

The baseline parameters of all 3 studies are shown in Table 1. STAMPEDE randomized 410 patients to SOC + RT and 409 patients to ADT. HORRAD randomized 89 patients to ADT + RT and 71 patients to ADT. Dai et al randomized 100 patients to each group. While STAMPEDE and HORRAD included only EBRT as a part of RLT, Dai et al included both RP and EBRT. Out of 100 patients randomized to RLT + ADT by Dai et al, 85 received RP and 11 received EBRT. For the analysis of OS, we had a total of 599 patients in the SOC + RT group and 580 patients in the ADT group. This gives us 81% power to detect a difference of 10% between the two groups while keeping the alpha error at 0.01.

All patients were diagnosed with de novo hormone-sensitive metastatic prostate cancer. STAMPEDE defined oligometastatic disease using the CHAARTED definition and included patients with nodal metastasis or fewer than 4 skeletal metastases. The HORRAD trial defined oligo-metastatic disease as less than 5 skeletal lesions. Dai et al included patients with 5 or fewer skeletal metastasis.

STAMPEDE allowed docetaxel in addition to ADT in both groups but this was not the case with HORRAD and Dai et al. In the intervention arm, STAMPEDE used EBRT to the prostate with a total dose of 36 Gy in 6 consecutive fractions of 6 Gy every week or 55 Gy in 20 daily fractions of 2.75 Gy over a period of 4 weeks. HORRAD also used EBRT to the prostate given within 3 months of starting ADT at a dose of 70 Gy in 35 fractions of 2 Gy or 57.76 Gy in 19 fractions of 3.04 Gy, three times a week for 6 weeks. Dai et al performed either cytoreductive open or laparoscopic RP in patients with resectable disease with or without lymph node dissection or gave intensity-modulated radiotherapy at a dose of 74 Gy (37 fractions) for all patients and 45 Gy (18 fractions) to the draining lymph node for those with pelvic lymph node metastases.

Median age was similar across the three trials (67-69 years) but this was not reported separately for oligometastatic disease by STAMPEDE and HORRAD. Dai et al only included patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. Similarly, most

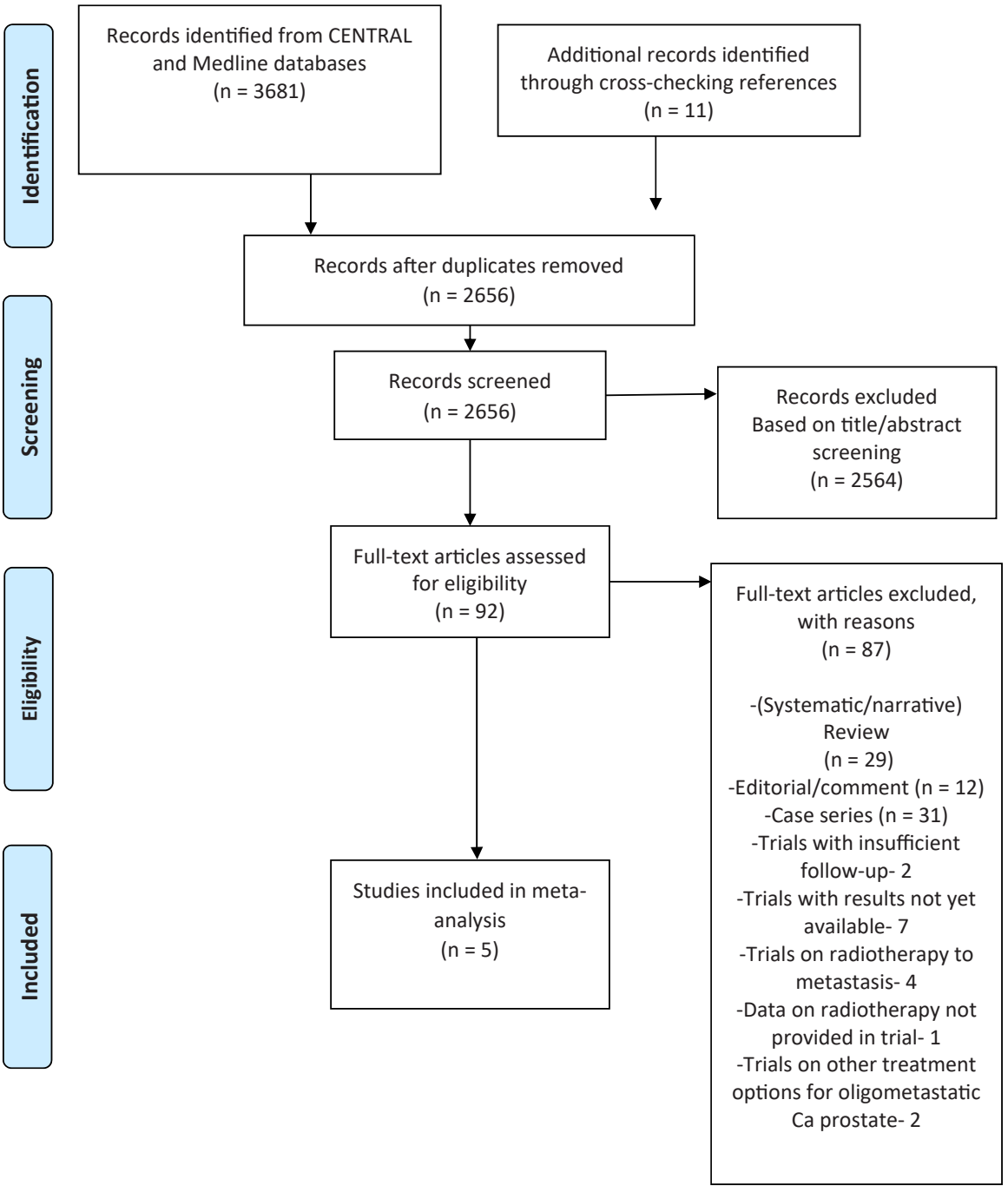


Figure 1. Flowchart assessing evidence following PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis). (Color version available online.)

patients in STAMPEDE and HORRAD were ECOG 0 (HORRAD, 84%; STAMPEDE, 71%). All 3 trials were judged to be at a low risk of bias based on randomization sequence generation, allocation concealment, completeness of outcome data, and selective outcome reporting.

Overall Survival

All 3 trials reported on OS and the OS was significantly improved in the intervention group (HR - 0.643, 95%CI 0.514-0.8, *P*-value < .001) (Fig. 2). There was no statistical heterogeneity with an I^2 statistic of 0. Egger's test was not significant suggesting no publication bias with a *P*-value of .45. Funnel plots were not drawn as there were only 3 studies. Orwin's Failsafe-N was 10 considering 0.9 an insignificant HR.

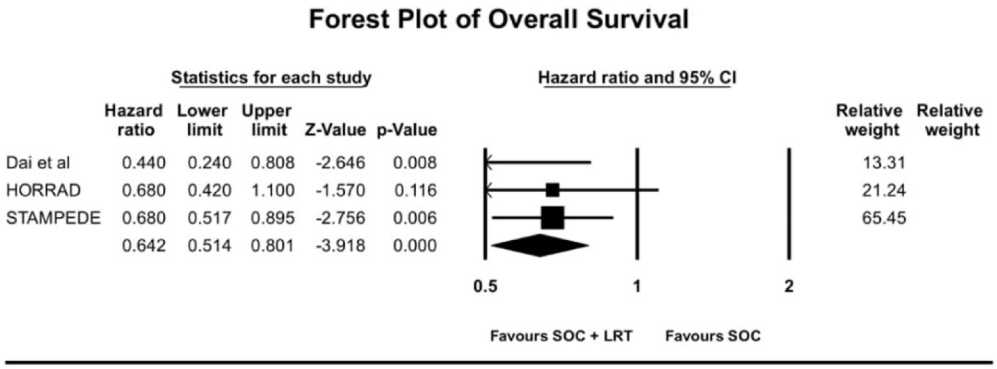
Prostate Cancer-specific Survival

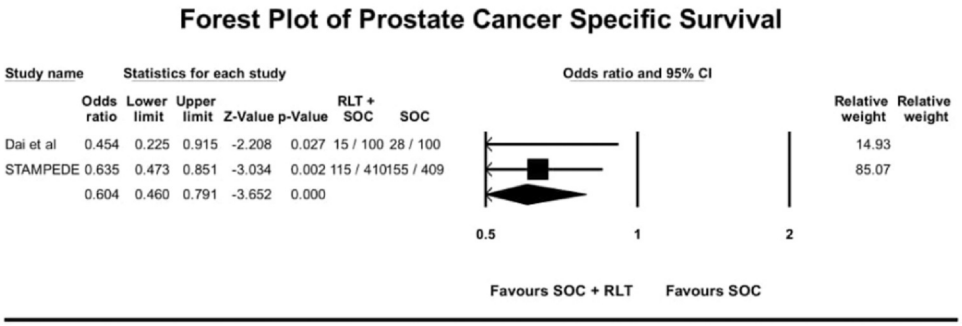
PCCS was reported by STAMPEDE and Dai et al for OMPC and this was significantly higher in the SOC + RT arm (OR - 0.604, 95%CI 0.46-0.791, *P*-value < .0001) (Fig. 2). There was no statistical heterogeneity with an I^2 statistic of 0. Publication bias could not be assessed as there were only 2 studies.

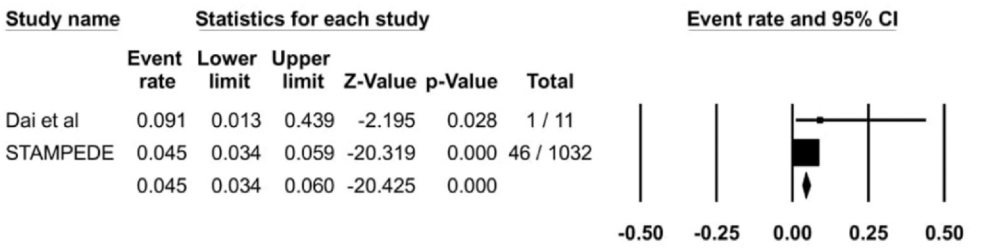
Table 1. Parameters of included studies.

Study/ Parameters	Country	Year	Intervention	Control	N- LRT + ADT	N- ADT	Median Age in Years	Median PSA in ng/mL at Recruitment	Median Follow-up in Months	Nadir PSA in ng/mL	OS (HR and 95%CI)	Cancer-specific Survival (HR and 95%CI)	PFS (HR and 95%CI)	Metastatic PFS (HR and 95%CI)	Failure Free Survival (HR and 95%CI)	Symptom-atic Local Event Free Survival
Stampede Arm H	UK and Switzerland	2018	EBRT - 36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2·75 Gy over 4 wk	SOC (ADT +/− docetaxel)	410	409	68 (63-73)		61.9		0.68 (0.52-0.90)	0.62 (0.49-0.79)			0.59 (0.49-0.72)	0.72 (0.59-0.88)
HORRAD	Netherlands	2018	70 Gy in 35 fractions of 2 Gy, during an overall treatment time of 7 wk	SOC	89	71	67 (62-71)		47		0.68 (0.42-1.1)					
Dai et al	China	2022	RT - 74 Gy (37 fractions) for all patients and 45 Gy (18 fractions) to the draining lymph node for those with pelvic lymph node metastases or cytoreductive RP	ADT	100	100	68 (62-73)	99	48		0.44 (95% CI 0.24-0.81)		(HR 0.43, 95% CI 0.27-0.70)			

ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; HR, hazard ratio; LRT, local radical therapy; OS, overall survival; PFS, progression fress survival; PSA, prostate specific antigen; RP, radical prostatectomy; RT, radiotherapy; SOC, standard of care.







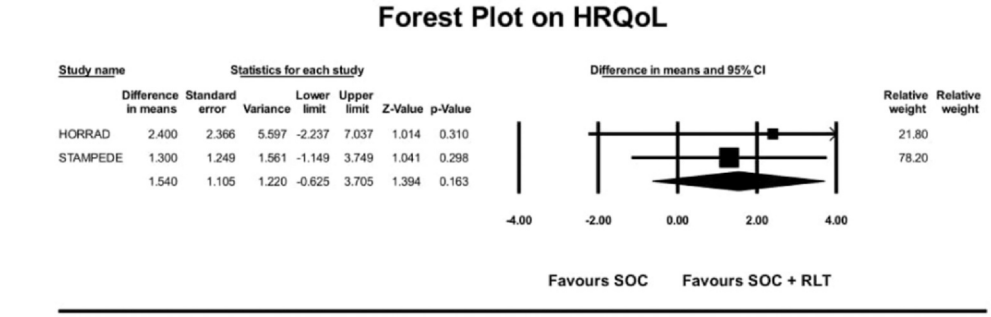


Figure 2. Forest plots of overall survival, prostate cancer-specific survival and HRQoL and pooled incidence of grade 3-4 bowel or bladder toxicity. HRQoL, Health-Related Quality of Life.

Symptomatic Local Event Free Survival (SLEFS) and Local Intervention Free Survival (LIFS)

SLEFS was also reported by STAMPEDE for OMPC and this was significantly higher in the SOC + RT arm (HR - 0.72, 95%CI 0.59-0.88). Similarly, LIFS was significantly higher in the SOC + RT arm (HR - 0.62, 95%CI 0.49-0.77).

Progression-free survival - Dai et al provided data on PFS for patients with oligometastatic disease. Radiological PFS was significantly lower in the RLT arm (HR 0.43, 95% CI 0.27-0.70, *P*-value .001). Radiological progression was noted in 23 patients in the RLT + ADT arm compared to 47 patients in the ADT alone arm. Median radiological PFS was 40 months in the ADT arm and was not reached in the RLT + ADT arm.

Adverse Events

The side effects related to RLT were described by all 3 studies, but only Dai et al reported them separately for patients with OMPC, while STAMPEDE and HORRAD reported them for metastatic prostate cancer patients as a group. Out of 85 patients who underwent RP, 24 had early postoperative complications, of which 7 were Clavien-Dindo grade 3 and above. There were no deaths, and only 4 patients were incontinent at the end of 2 years. One patient had a vesico-urethral anastomotic site recurrence leading to a urethral stricture. Among patient that underwent EBRT, STAMPEDE and Dai et al reported adverse events. Pooled prevalence of grade 3-4 bowel and urinary-related adverse events was 4.5% (Fig. 2).

Health-related Quality of Life

HORRAD and STAMPEDE trials reported on 2-year QOL. Global HRQoL at 2 years was not different between the 2 groups (mean difference - 1.54, 95%CI − 0.625 – 3.705, *P*-value .163) (Fig. 2). There was no heterogeneity with an I^2 statistic of 0.

The risk of bias as per the RoB2 tool was low for all outcomes for all domains including overall bias (Fig. S1). Based on the GRADE criteria, evidence certainty was not downgraded. There was some concern about unpublished data and randomization, but this did not downgrade the certainty from high (Table 2).

DISCUSSION

The management of metastatic prostate cancer has seen significant changes in the last 2 decades with the general trend being that the addition of new modalities of treatment has led to modest increases in OS. The addition of RLT to SOC in the management of OMPC seems to follow in this general direction. This is not without biological rationale. There is evidence that the development of new metastases requires the development of a premetastatic niche by the primary tumor. The primary tumor secretes cytokines and exosomes, and this molecular communication between the tumor and metastases allows evasion from cytotoxic T cells and natural killer cells. This also stimulates angiogenesis in hypoxic environments. In addition, circulating tumor cells may recolonize the primary tumor and promote the process of development of further metastases. Thus, RLT could break this communication chain by removing (surgery) or destroying (RT) the primary tumor.[18-21]

Our meta-analysis demonstrates that RLT can improve OS and PCSS in patients with OMPC without negative impact on patients. The first two studies that reported on this included EBRT as the modality of RLT. While STAMPEDE documented a clear benefit in terms of OS, there was a trend toward improved survival in the HORRAD trial. The STOPCAP meta-analysis also reported a 7% improvement in 3-year survival in patients with OMPC, who received EBRT.[22] In the trial by Dai et al, both RP and EBRT were used but most patients underwent RP. While EAU guidelines have already incorporated EBRT as a treatment modality for OMPC, the same has not been done for RP.[23] Although there may be some additional role of EBRT via the mechanism of radiosensitization, the success of EBRT may also be replicated by RP as shown by Dai et al. The feasibility and safety of RP in OMPC has been confirmed by the TROMBONE RCT and a further large full RCT is being planned.[24] Certain patient-related factors may also favor the choice of one RLT over the other. For instance, older and more comorbid patients may be less fit for RP than EBRT, whereas those with lower urinary tract symptoms and large prostates may benefit more from RP.[23] RP may also have a greater impact on local progressive symptoms with less pelvic pain, lower rates of ureteric obstruction and renal failure, and less hematuria than RT due to the primary tumor being removed rather than remaining in situ. The follow-on full trial to TROMBONE will interrogate these endpoints as well as oncological differences between RLT modalities, unlike current trials in this space which[1] do not separate OMPC from polymetastatic patients and[2] do not randomize between RLT modalities but rather offer patient/clinician choice and thus may lead to unbalanced groups and confounding by indication.

Considering these findings, an ethical question arises over further randomization of patients to groups that do not offer any RLT. The data on EBRT is more robust than RP. Since we have shown more than 80% post-hoc power in our meta-analysis to detect a difference of 10% with an alpha-error of 0.01, future trials on OMPC may consider including RLT, especially EBRT as SOC. In fact, of the recent trials, the g-RAMPP trial stopped randomization patients after the findings of the STAMPEDE trial for this reason.[25,26] Further most guidelines have also included EBRT as SOC in the management of OMPC.[23] The results of other similar trials such as best systemic therapy or best systemic therapy (BST) Plus Definitive Treatment (Radiation or Surgery) trial and the Peace-1 trial (with respect to RLT vs SOC) are awaited.[10,27] Some other similar trials, which are continuing recruitment include the Surgery in Metastatic Carcinoma of Prostate (SIMCAP) trial, SWOG1802 and the LOMP II trial.[13,14,28] The Adjuvant Treatments to the Local Tumour for Metastatic Prostate Cancer: Assessment of Novel Treatment Algorithms (IP2-ATLANTA) trial (NCT03763253) is a triple

Table 2. Summary of findings table as per GRADE approach.

Certainty Assessment							№ of Patients		Effect			
№ of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	RLT +SOC	SOC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Overall survival (follow-up: median 4 yr; assessed with HR and 95%CI)												
3	Randomized trials	Serious	Not serious	Not serious	Not serious	Strong association	599 participants	580 participants	**HR 0.643** (0.514-0.800) [Death]	**140 more per 1000** (from 74 more to 200 more)	⊕⊕⊕⊕ High	CRITICAL
							-	50.0%		**140 more per 1000** (from 74 more to 200 more)		
Prostate cancer-specific survival (follow-up: median 4 yr; assessed with HR and 95%CI)												
2	Randomized trials	Serious	Not serious	Not serious	Not serious	Strong association	510 participants	509 participants	**HR 0.604** (0.460-0.791) [Prostate cancer-specific mortality]	**158 more per 1000** (from 78 more to 227 more)	⊕⊕⊕⊕ High	CRITICAL
							-	50.0%		**158 more per 1000** (from 78 more to 227 more)		
Heath-related Quality of Life (follow-up: median 2 yr; assessed with mean difference and 95%CI; Scale from 0-100)												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	499	480	-	MD **1.54 higher** (0.625 lower to 3.705 higher)	⊕⊕⊕⊕ High	IMPORTANT

CI, confidence interval; HR, hazard ratio; MD, mean difference.
GRADE 1 assessment of certainty is done by consideration of 5 important domains. It is used to assess the outcome specific certainty of evidence in systematic reviews.

arm RCT, with systemic therapy as SOC in one arm. The other 2 arms contained minimally invasive ablative therapy (Intervention Arm 1) or local RT or RP (Intervention Arm 2).[29]

LIMITATIONS

While our meta-analysis generates enough power to suggest a benefit of RLT, it does not do so separately for EBRT and RP and the follow-on RCT to TROMBONE is widely anticipated. There is some amount of inherent heterogeneity in our meta-analysis, as evidenced by the fact that the RLT group included both EBRT and RP. Additionally, the definition of OMPC was different in all three trials. The dose of radiation was also different among the 3 trials. An additional limitation of our meta-analysis is the unavailability of patient-level data for combining across studies. While this would offer more comprehensive insights, the logistical complexities of harmonizing diverse datasets prevented its inclusion in this analysis.

CONCLUSION

Our meta-analysis underscores the evidence-based significance of RLT, particularly emphasizing the benefits of EBRT in patients with OMPC. However, the findings should be interpreted with caution due to the limited number of studies available and the relatively small sample sizes, especially in the RP subgroup. While our analysis indicates improved OS and PCSS in the RLT group, the certainty of evidence remains tempered by the limitations inherent in interpreting pooled results from diverse studies. Future investigations in OMPC should consider the incorporation of EBRT in their standard treatment approach.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2023.09.014.

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