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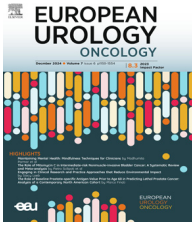

European Association of Urology

Review

A Systematic Review and Meta-analysis of the Impact of Local Therapies on Local Event Suppression in Metastatic Hormone-sensitive Prostate Cancer

Ichiro Tsuboi [a,b,c], *Akihiro Matsukawa* [a,d], *Mehdi Kardoust Parizi* [a,e], *Jakob Klemm* [a,f], *Stefano Mancon* [a,g], *Sever Chiujdea* [a,h], *Tamás Fazekas* [a,i], *Marcin Miszczyk* [a,j], *Ekaterina Laukhtina* [a,k], *Tatsushi Kawada* [a,c], *Satoshi Katayama* [a,c], *Takehiro Iwata* [a,c], *Kensuke Bekku* [a,c], *Pierre Karakiewicz* [l], *Koichiro Wada* [a,b], *Morgan Rouprêt* [m], *Motoo Araki* [c], *Shahrokh F. Shariat* [a,k,n,o,p,q,r,s,*]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Department of Urology, Shimane University Faculty of Medicine, Shimane, Japan;* [c] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;* [d] *Department of Urology, Jikei University School of Medicine, Tokyo, Japan;* [e] *Department of Urology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran;* [f] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [g] *Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Italy;* [h] *Department of Urology, Spitalul Clinic Judetean Murures, University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Mures, Romania;* [i] *Department of Urology, Semmelweis University, Budapest, Hungary;* [j] *Collegium Medicum - Faculty of Medicine, WSB University, Dąbrowa Górnicza, Poland;* [k] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia;* [l] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Quebec, Canada;* [m] *GRC 5 Predictive Onco-Uro, AP-HP, Urology, Pitie-Salpetriere Hospital, Sorbonne University, Paris, France;* [n] *Department of Urology, University of Texas Southwestern, Dallas, TX, USA;* [o] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [p] *Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan;* [q] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [r] *Research center of Evidence Medicine, Urology department Tabriz University of Medical Sciences, Tabriz, Iran;* [s] *Department of Urology, Weill Cornell Medical College, New York, NY, USA*

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Abstract

Context: It remains unclear to what extent the therapy of the primary local tumor, such as radical prostatectomy (RP) and radiation therapy (RT), improves overall survival in patients with low-volume metastatic hormone-sensitive prostate cancer (mHSPC). However, data suggest a benefit of these therapies in preventing local events secondary to local tumor progression.

Objective: To evaluate the efficacy of adding local therapy (RP or RT) to systemic therapies, including androgen deprivation therapy, docetaxel, and/or androgen receptor axis–targeted agents, in preventing local events in mHSPC patients compared with systemic therapy alone (ie, without RT of the prostate or RP).

Evidence acquisition: Three databases and meeting abstracts were queried in November 2023 for studies analyzing mHSPC patients treated with local therapy. The primary outcome of interest was the prevention of overall local events (urinary tract infection, urinary tract obstruction, and gross hematuria) due to local disease progression. Subgroup

* Corresponding author. Department of Urology, Comprehensive Cancer Center, Medical University Vienna, Vienna General Hospital, Währinger Gürtel 18-20 A-1090 Vienna, Austria. Tel. +43 1 40400 26150; Fax: +43 1 40400 23320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

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analyses were conducted to assess the differential outcomes according to the type of local therapy (RP or RT).

Evidence synthesis: Overall, six studies, comprising two randomized controlled trials, were included for a systematic review and meta-analysis. The overall incidence of local events was significantly lower in the local treatment plus systemic therapy group than in the systemic therapy only groups (relative risk [RR]: 0.50, 95% confidence interval [CI]: 0.28–0.88, $p = 0.016$). RP significantly reduced the incidence of overall local events (RR: 0.24, 95% CI: 0.11–0.52) and that of local events requiring surgical intervention (RR: 0.08, 95% CI: 0.03–0.25). Although there was no statistically significant difference between the RT plus systemic therapy and systemic therapy only groups in terms of overall local events, the incidence of local events requiring surgical intervention was significantly lower in the RT plus systemic therapy group (RR: 0.70, 95% CI: 0.49–0.99); local events requiring surgical intervention of the upper urinary tract was significantly lower in local treatment groups (RR: 0.60, 95% CI: 0.37–0.98, $p = 0.04$). However, a subgroup analysis revealed that neither RP nor RT significantly impacted the prevention of local events requiring surgical intervention of the upper urinary tract.

Conclusions: In some patients with mHSPC, RP or RT of primary tumor seems to reduce the incidence of local progression and events requiring surgical intervention. Identifying which patients are most likely to benefit from local therapy, and at what time point (eg, after response of metastases), will be necessary to set up a study assessing the risk, benefits, and alternatives to therapy of the primary tumor in the mHSPC setting.

Patient summary: Our study suggests that local therapy of the prostate, such as radical prostatectomy or radiotherapy, in patients with metastatic hormone-sensitive prostate cancer can prevent local events, such as urinary obstruction and gross hematuria.

1. Introduction

The treatment landscape of mHSPC has been evolving rapidly in the past decade. While improving overall survival (OS) is of utmost importance, other factors and patients may be of high value for patients with metastatic hormone-sensitive prostate cancer (mHSPC) in an era when combination systematic therapy can achieve durable metastatic disease control. For example, time to castration resistance and local (vs distant) disease progression with local symptoms may affect each mHSPC patient's quality of life (QoL). Clinical practice guidelines recommend the combination of androgen deprivation therapy (ADT) with a novel antiandrogen, such as abiraterone acetate, enzalutamide, apalutamide, or darolutamide, with the addition of docetaxel in selected patients for the treatment of mHSPC [1–5]. Additionally, local therapy for the primary tumor in mHSPC has been shown to improve OS and delay prostate-specific antigen progression [6]. In contrast to the HORRAD trial that did not demonstrate a significant benefit of local radiotherapy (RT) in improving OS for newly diagnosed mHSPC, the STAMPEDE trial demonstrated a significant benefit of local RT in improving OS for newly diagnosed low-volume mHSPC patients [5,7,8]. Furthermore, population-based and cohort studies have shown a survival benefit of local treatment of the prostate with cytoreductive radical prostatectomy (RP) [9–13].

Complications in the upper and lower urinary tracts, including urinary tract infections, urinary obstructions, and gross hematuria, can occur occasionally secondary to disease progression of the primary site. These local events may require palliative surgical interventions such as transurethral resection of the prostate (TURP), suprapubic catheterization, ureteral stent insertion, and percutaneous nephrostomy (PCN). Significantly reducing these occurrences is crucial, as these greatly diminish a patient's QoL. Therefore, preventing these more frequent local events in high-risk patients represents an important unmet need.

While treatment of the primary tumor might help avoid local events, their true effectiveness in mHSPC patients remains poorly investigated. Therefore, we conducted this systematic review and meta-analysis to evaluate and clarify the true efficacy of adding RP and RT as local treatment to systemic therapy in mHSPC patients focusing on the prevention of local complications compared with systematic therapy without local treatment.

2. Evidence acquisition

We registered the study with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42023482034). This systematic review and meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see the PRISMA 2020 checklist in Supplementary Table 1).

2.1. Search strategy

On November 11, 2023, the PubMed, Scopus, and Web of Science databases were searched to identify studies investigating the effectiveness of local treatment of primary tumor for mHSPC to reduce local events. The search terms included the following: "metastatic", "castration sensitive", "castration naive", "hormone sensitive", "hormone naive", "local treatment", "prostatectomy", "radiotherapy", and

"cytoreductive". The detailed search strategy for each database is shown in the Supplementary material. Furthermore, we also reviewed meeting abstracts presented at recent major congresses, such as those of the American Society of Clinical Oncology and the European Society for Medical Oncology, to include trial updates. Two investigators independently performed an initial screening based on the titles and abstracts, and noted the cause of the exclusion of ineligible reports. Full texts were retrieved and evaluated for eligibility. In addition, hand searches of reference lists were performed to identify additional studies of interest. In the case of discrepancies, the disagreements were solved by consensus among the authors.

2.2. Inclusion and exclusion criteria

We incorporated studies that evaluated mHSPC patients who underwent RP or RT with systemic therapies including ADT, docetaxel, and/or androgen receptor axis–targeted agents compared with patients who received systemic therapy (ADT with or without other systemic therapy), without local treatment of the primary tumor. The studies were required to report the incidence of pooled complications related to local prostate cancer. These complications include urinary tract infection, urinary tract obstruction, and gross hematuria, among progressive others. We excluded studies that lacked original patient data, along with reviews, letters, editorial remarks, responses from authors, case reports, and articles not written in English. When encountering duplicate studies from the same cohorts, we selected either the more recent or the higher-quality publication. We scanned references of included manuscripts for additional studies of interest.

2.3. Data extraction

Two reviewers independently extracted data on the baseline study and patients' characteristics. From each study, we gathered essential details: the first author's name, publication year, country, design of the study, methods used for local treatment of primary cancer, criteria for both inclusion and exclusion, the main endpoint, the number of participants and their ages, events occurring locally due to the primary tumor, and the types of procedures employed for these local events, such as TURP, urethral catheterization, ureteral stent, clean intermittent catheterization, and PCN. We also recorded the median duration of follow-up. All discrepancies were resolved by consensus with coauthors.

2.4. Quality assessment and risk of bias

Study quality and risk of bias were evaluated using the Risk-of-Bias version 2 (RoB2) tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [14]. We used the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool to evaluate the bias in nonrandomized studies, covering aspects such as confounding and intervention classification, to determine each study's bias risk as low, moderate, or serious [15]. The RoB2 and ROBINS-I assessments of each study were performed by two authors independently, and any disagreements were resolved by a third author.

2.5. Statistical analysis

All statistical analyses were performed using R version 4.2.2 (meta, 2023; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$. To evaluate the effectiveness of local therapy in preventing local events in mHSPC patients, we generated and analyzed forest plots with relative risks (RRs) and 95% confidence intervals (CIs). Subgroup analyses were performed to investigate the effectiveness of specific procedures, including RT and RP. Additionally, we assessed the impact of local treatment on reducing the need for surgical intervention due to the progression of the primary tumor. Moreover, we divided these surgical interventions into upper and lower urinary tract categories for further detailed analysis. Cochrane's Q test and the I^2 test were used to evaluate the heterogeneity. Significant heterogeneity was indicated by $p < 0.05$ in the Cochrane's Q tests and I^2 statistics >50%. When significant heterogeneity was observed, we attempted to investigate the causes of heterogeneity [16]. We performed sensitivity analyses to increase homogeneity and confirm the reliability of our results.

3. Evidence synthesis

3.1. Study selection and characteristics

Our initial search identified 1194 records. As a result of removing duplicates, 694 records were left for title and abstract screening, and subsequently, 664 articles were excluded (Fig. 1). According to our inclusion criteria, we identified two randomized controlled trials (RCTs), two prospective studies, and two retrospective studies with 3565 patients eligible for meta-analyses [17–22]. The inclusion criteria of patients were different among the studies. Four studies involved mHSPC patients with low-volume metastasis, although the definition of "low volume" varied among these studies. In these four studies, bone metastases were identified using modalities such as computed tomography, magnetic resonance imaging, or bone scintigraphy. Low-volume metastasis was defined as having a lesion count ranging from <3 to 5 [17–19,21]. The LoMP, STAMPEDE, and PEACE-1 trials described the metastatic volume of mHSPC according to CHAARTED [20–22]. The detailed characteristics of the included studies are summarized in Table 1.

Among the six studies included, three assessed RP as local treatment, the STAMPEDE and PEACE-1 trials utilized RT, and the LoMP trial allowed both RP and RT. The RP procedures included both robot-assisted and open RP. Detailed information regarding the intensity, fraction and duration of radiation can be found in Table 1. Additionally, we compiled information about the surgical procedures that were employed as palliative local treatments for managing local events associated with the progression of primary cancer (Table 2). Regarding the PEACE-1 trial, no detailed information about surgical procedures was found in the overall patient group. However, we found data on the types and numbers of surgical interventions in patients with low-volume metastasis. The median follow-up duration among included studies ranged from 32.7 to 73 mo.

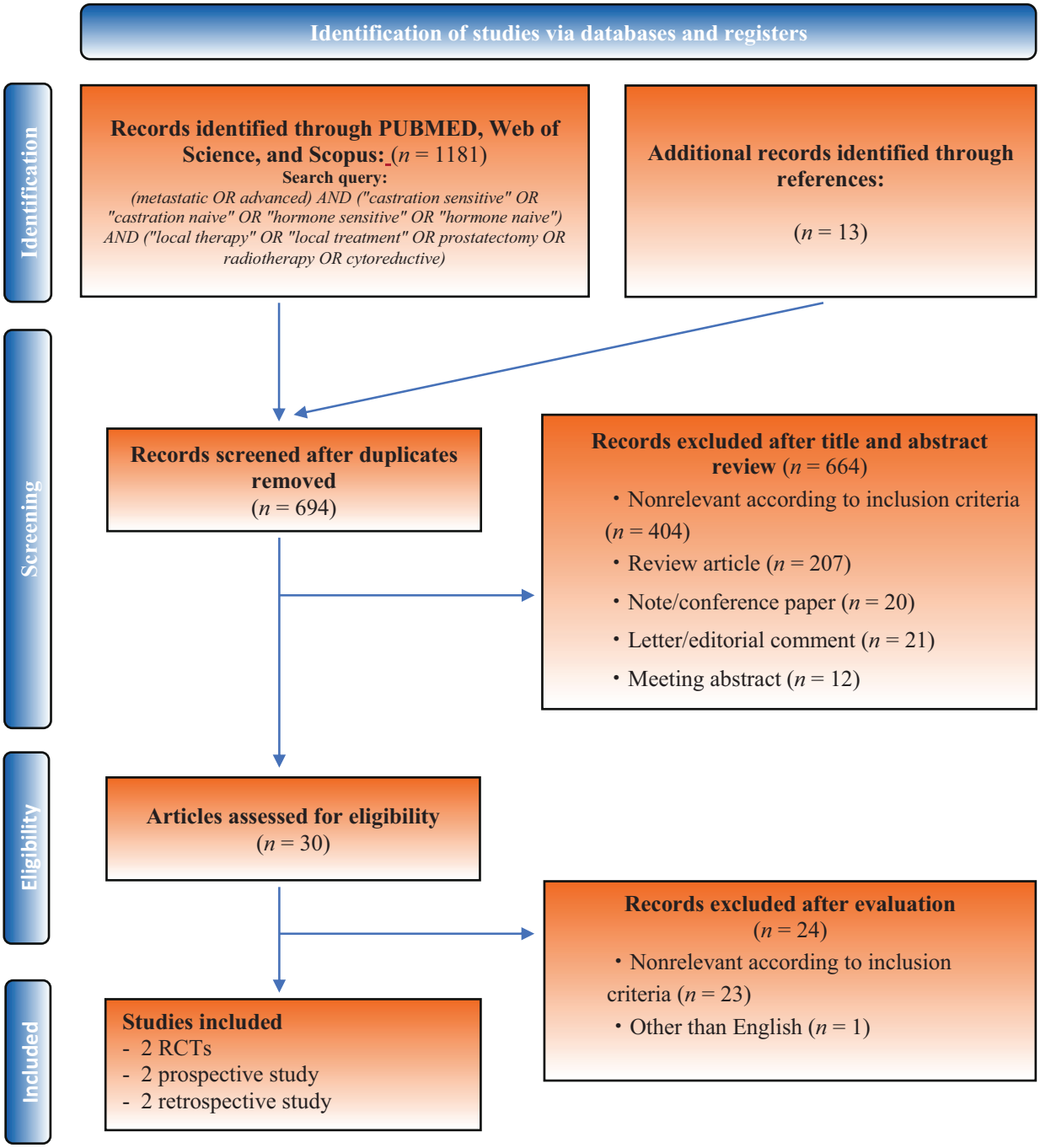

Fig. 1 – PRISMA flowchart detailing the article selection process. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomized controlled trial.

3.1.1. *Overall local events*

Six studies, comprising 3565 patients, reported the incidence of symptomatic local events due to primary cancer progression [17–23]. Jang et al [19] and Heidenreich et al [17] described lymphoceles, deep venous thrombosis, and incontinence as peri- and postoperative complications. Thus, we excluded these complications as overall local events. Conversely, Steuber et al [18] and Lumen et al (LoMP trial) [21] reported severe incontinence, which required surgery. We included this complication as overall local events. Our analyses included 1794 patients in the local treatment group (encompassing RP and RT) and 1771 patients in the nonlocal treatment control group. In the intervention group, 275 patients (15.3%) experienced local complications related to disease progression compared with 343 patients (19.4%) in the control group.

3.1.2. *Surgical intervention required for local events*

In our analysis of six studies with a total of 3565 patients, we focused on the efficacy of local treatments in averting the need for surgical intervention for local events [17–22]. Steuber et al [18] and Lumen et al (LoMP trial) [21] reported severe incontinence, which required surgery. We excluded these complications from the analysis of local events requir-

Table 1 – Characteristics of the included studies

Author (year published), trial	Study design	Period (year)	Inclusion criteria of metastasis	No. of patients Overall (low/high)	Detail of procedure	Time to local treatment	Treatment of control group	Median follow-up
cRP + systemic therapy vs systemic therapy alone								
Heidenreich et al, 2015	Retrospective	NA	One to three bone metastases	61 (61/0)	Open retropubic RP with extended pelvic lymphadenectomy	At least 6 mo after ADT	ADT	34.5 mo (RP), 47 mo (control)
Steuber et al, 2017	Prospective	2012–2015	One to three bone metastases	83 (83/0)	NA	NA	NA	32.7 mo (RP), 82.2 mo (control)
Jang et al, 2018	Retrospective	2005–2015	One to five bone metastases	79 (79/0)	RARP with extended pelvic lymphadenectomy	NA	ADT + bicalutamide 50 mg once daily	40 mo
Lumen et al, LoMP, 2021	Prospective	2014–2020	Low-volume mHSPC *	48 (48/0)	Open RP or RARP with extended pelvic lymphadenectomy	within 3 mo	ADT ± DTX ± Abi	32 mo
Radiotherapy + systemic therapy vs systemic therapy alone								
Parker et al, STAMPEDE, 2018	RCT, phase 3 trial	2013–2016	All mHSPC *	2061 (819/1120)	55 Gy in 20 fractions over 4 wk or 36 Gy in six fractions over 6 wk	95 (74–120) d from starting hormone therapy	ADT ± DTX (75 mg/m^2 every 3 wk for 6 cycles)	37 mo
Lumen et al, LoMP, 2021	Prospective	2014–2020	Low-volume mHSPC *	26 (26/0)	In accordance with ESTRO-ACROP guidelines	NA	ADT ± DTX ± Abi	32 mo
Fizazi et al.(Bossi et al.) PEACE-I, 2022	RCT, phase 3 trial	2013–2018	All mHSPC *	1172 (505/667)	74 Gy in 37 fractions over 7–8 wk	NA	ADT ± DTX ± Abi	52 mo **

Abi: Abiraterone acetate, ADT: androgen deprivation therapy, DTX: docetaxel, mHSPC: metastatic hormon-sensitive prostate cancer
* Metastatic volume was defined by the CHAARTED trial.
** Overall population for overall survival.

ing surgical intervention. RP groups had only two surgical intervention cases (Table 2). The local treatment group comprised 1794 patients, and the control group had 1771 patients. Of these patients, 137 (7.6%) in the intervention group and 247 (13.9%) in the control group required surgical intervention for local events.

3.1.3. *Lower urinary tract events (surgical intervention required)*

Six studies, comprising 2933 patients, were analyzed to compare the incidence of lower urinary tract events requiring surgical intervention between the local treatment group (1462 patients) and the control group (1471 patients) [17–22]. Overall, 77 patients (5.3%) in the intervention group and 147 (9.9%) in the control group experienced lower urinary tract events requiring surgical intervention.

3.1.4. *Upper urinary tract events (surgical intervention required)*

An analysis of six studies, comprising 2933 patients, was conducted to compare the incidence of upper urinary tract events requiring surgical intervention between the local treatment and control groups [17–22]. The local treatment group included 1462 patients, while the control group had 1471 patients. Among these patients, 26 (1.8%) in the local treatment group and 47 (3.2%) in the control group experienced upper urinary tract events requiring surgical intervention.

3.2. *Risk of bias assessment*

Authors' judgments about each domain for each included study are graphed in Supplementary Figure 1 and Supplementary Table 2. Although there was no concern in two RCTs, the other four nonrandomized studies presented concerns in certain domains. Funnel plots of each analysis are depicted in Supplementary Figure 2.

3.3. *Meta-analysis*

The results of the meta-analysis are described in Figures 2–5.

3.3.1. *Overall local events*

The incidence of overall local events was significantly lower in the local treatment group than in the control group (RR: 0.50, 95% CI: 0.28–0.88, $p = 0.016$; Fig. 2). A subgroup analysis further indicated that RP reduced local event incidence significantly (RR: 0.24, 95% CI: 0.11–0.52; Fig. 2), whereas RT did not show a significant difference in preventing overall local events (RR: 0.77, 95% CI: 0.47–1.25; Fig. 2). There was statistical difference in RR for overall local events between RP and RT as local therapy for primary cancer ($p = 0.012$; Fig. 2). The Cochrane's Q tests and I^2 statistic revealed the significant heterogeneity in the subgroup analysis of RT ($p < 0.001$, $I^2 = 74\%$). Although a sensitivity analysis was conducted, the cause of heterogeneity could not be detected (Supplementary Fig. 3).

3.3.2. *Surgical intervention required for local events.*

The incidence of surgical interventions for local events was notably lower in the local treatment group than in the control group (RR: 0.33, 95% CI: 0.14–0.78; Fig. 3). Further, sub-

Table 2 – Type and number of local treatment due to local event of primary tumor requiring surgical intervention

Author, trial	Local radical treatment		TURP or suprapubic cystostomy or urethral catheter or CIC or RT	PCN or ureteral stent	Total
Heidenreich et al.	RP	LT	0	0	0
		NLT	9	2	11
Steuber et al.	RP	LT	0	0	0
		NLT	14	0	14
Jang et al.	RP	LT	0	0	0
		NLT	8	2	10
Lumen et al., LoMP	RP	LT (RP)	2	1	2 *
	or	LT (RT)	5	2	7
	RT	NLT	11	2	12 *
Parker et al., STAMPEDE	RT	LT	60	10	70
		NLT	58	24	82
Fizazi et al., (Bossi et al.), PEACE-I	RT	LT (O/L **)	NA/10	NA/13	58/23
		NLT (O/L **)	NA/36 ***	NA/15	106/51

LT: local treatment NLT: non-local treatment PCN: percutaneous nephrostomy RP: radical prostatectomy RT: radiotherapy TURP: transurethral resection of the prostate
* Including duplicate.
** Division of **O**verall patients by a **L**ow-volume metastasis patient.
*** Including RT.

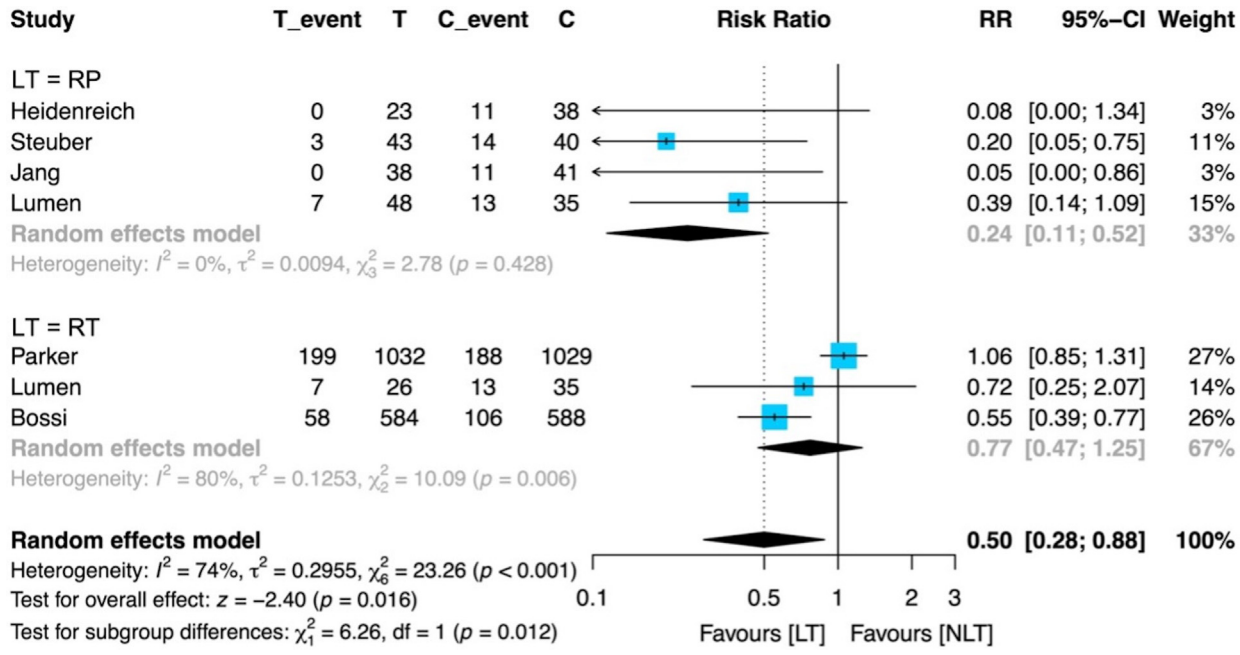

Fig. 2 – Forest plots showing the effect of radical prostatectomy and radiotherapy in preventing overall local events for patients with mHSPC. CI = confidence interval; LT = local treatment; mHSPC = metastatic hormone-sensitive prostate cancer; NLT = nonlocal treatment; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy.

group analyses indicated a significant reduction in local events requiring surgical intervention with RP (RR: 0.08, 95% CI: 0.03–0.25; Fig. 3) as well as with RT (RR: 0.70, 95% CI: 0.49–0.99; Fig. 3). There was a significant statistical difference in the RRs for local events requiring surgical intervention between RP and RT (p = 0.01; Fig. 3). The Cochrane's Q tests and I^2 statistic revealed no significant heterogeneity among these analyses.

3.3.3. Lower urinary tract events (surgical intervention required).

The incidence of lower urinary tract events was significantly lower in the local treatment group (RR: 0.29, 95% CI: 0.12–0.70, p = 0.006; Fig. 4). A subgroup analysis showed that RP reduced the incidence of these events significantly (RR: 0.09, 95% CI: 0.03–0.28; Fig. 4), while RT did not demonstrate a significant effect (RR: 0.58, 95% CI: 0.25–1.35;

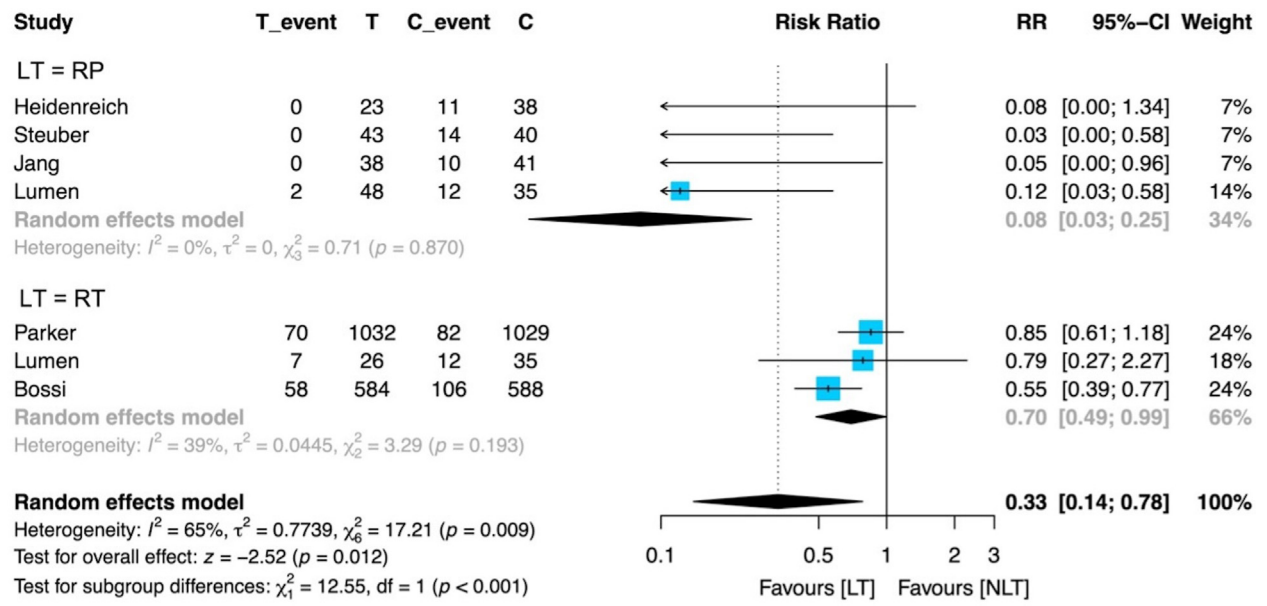

Fig. 3 – Forest plots showing the effect of radical prostatectomy and radiotherapy in preventing local events requiring surgical intervention in patients with mHSPC. CI = confidence interval; LT = local treatment; mHSPC = metastatic hormone-sensitive prostate cancer; NLT = nonlocal treatment; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy.

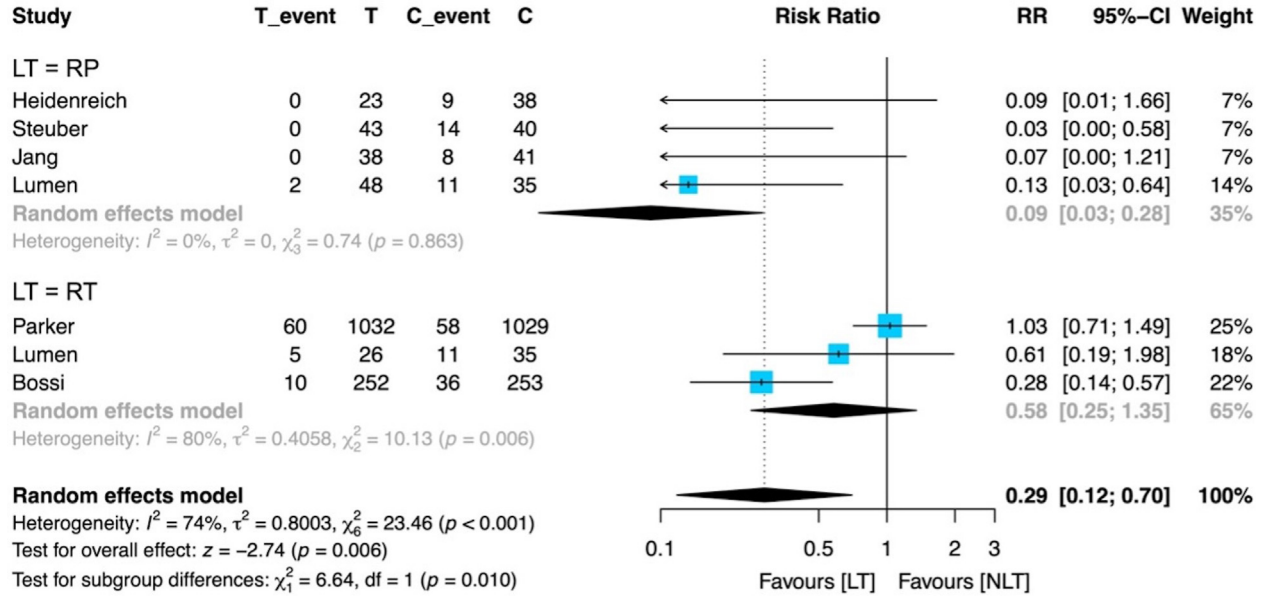

Fig. 4 – Forest plots showing the effect of radical prostatectomy and radiotherapy in preventing local events requiring surgical intervention of the lower urinary tract in patients with mHSPC. CI = confidence interval; LT = local treatment; mHSPC = metastatic hormone-sensitive prostate cancer; NLT = nonlocal treatment; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy.

Fig. 4). A significant difference in RR for lower urinary tract complications was observed between RP and RT as local therapies for primary cancer (p = 0.01; Fig. 4). The Cochrane's Q tests and I^2 statistic indicated significant heterogeneity in the RT subgroup analysis (p < 0.001, I^2 = 80%). Despite conducting a sensitivity analysis, the cause of heterogeneity remained undetected (Supplementary Fig. 3).

3.3.4. Upper urinary tract events (surgical intervention required).

The incidence of upper urinary tract events was significantly lower in the local treatment group (RR: 0.60, 95% CI: 0.37–0.98, p = 0.04; Fig. 5). A subgroup analysis indicated that neither RP (RR: 0.40, 95% CI: 0.09–1.83; Fig. 5) nor RT (RR: 0.65, 95% CI: 0.34–1.23; Fig. 5) showed a significant effect on reduction of the incidence of upper urinary tract

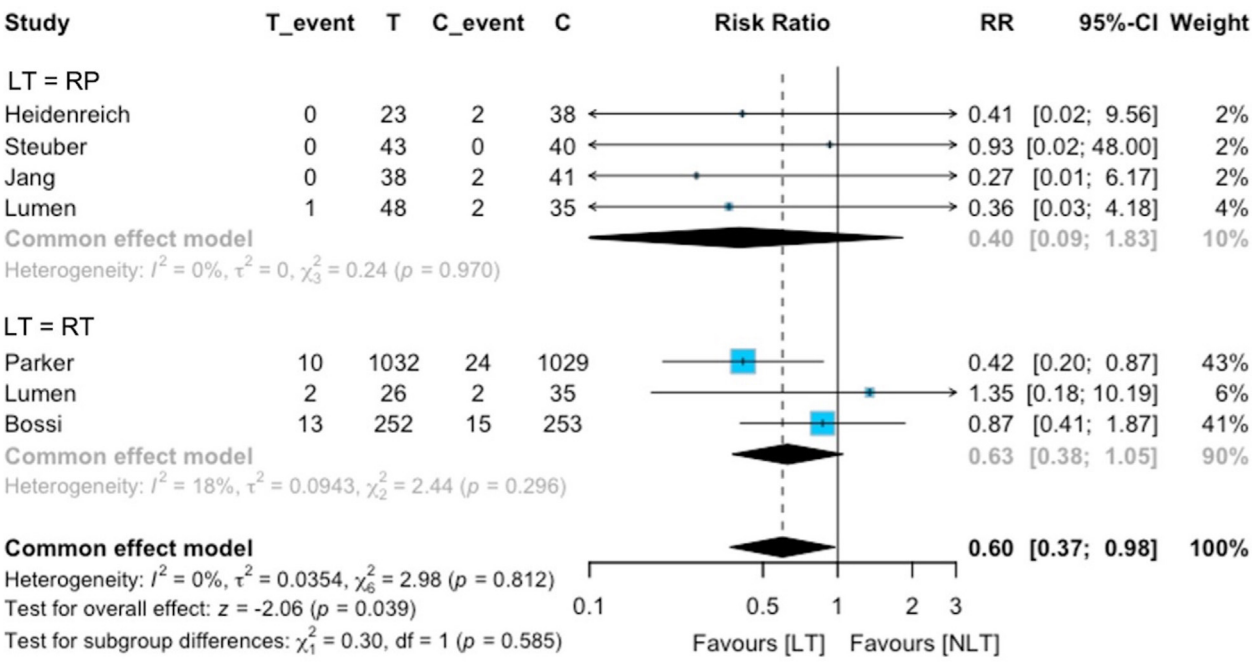

Fig. 5 – Forest plots showing the effect of radical prostatectomy and radiotherapy in preventing local events requiring surgical intervention of the upper urinary tract in patients with mHSPC. CI = confidence interval; LT = local treatment; mHSPC = metastatic hormone-sensitive prostate cancer; NLT = nonlocal treatment; RP = radical prostatectomy; RR = relative risk; RT = radiotherapy.

complications. No significant difference in the RR for upper urinary tract complications was observed between RP and RT as local therapies for primary cancer (p = 0.58; Fig. 5). Cochrane's Q tests and the I^2 statistic showed no significant heterogeneity in these analyses (p = 0.8, I^2 = 0%).

3.4. Discussion

This is the first systematic review and meta-analysis that analyzed the effectiveness of RP and RT as local treatments in preventing local events in patients with mHSPC. Our study reveals several critical findings. First, RP was effective in reducing overall local events, whereas RT did not show a similar reduction in these events. Second, both RP and RT were successful in decreasing the incidence of events requiring surgical intervention. Third, neither RP nor RT demonstrated efficacy in reducing upper urinary tract complications that necessitate surgical intervention.

Our study indicated that RP as a local treatment in patients with mHSPC led to a 76% reduction in the overall local events caused by the progression of the primary tumor [17–19,21]. We also indicated that RP led to a 92% reduction in the local events requiring surgical intervention. Similar to this, although our study showed successfully that RP can significantly reduce local events in cases where surgery is feasible, in RP groups, we could not find and include RCTs in our analysis. As several studies (SWOGS1802: NCT03678025; TRoMbone: ISRCTN15704862, NCT02971358) are currently underway, the results are awaited eagerly.

We found no significant difference in RT in terms of the reduction of overall local events [20–22]. The local events observed in these groups include urinary tract infections and urinary obstructions, which could not distinguish cancer progression from the toxicity of RT. Therefore, we focused our analysis only on cases that required surgical intervention, which are more likely to be symptomatic due to the progression of the tumor. As a result, it was shown that RT had an effect on local events that require intervention (RR: 0.70, 95% CI: 0.49–0.99; Fig. 3). Recently, a STOPCAP systematic review and meta-analysis revealed that RT as local therapy in patients with low-volume mHSPC provides an OS benefit, although it does not improve OS and progression-free survival in patients with mHSPC in general [6]. Given that local therapy with RT does not improve the OS in patients with high-volume mHSPC, these patients seem not to undergo RT. However, our study may indicate that mHSPC patients, including both low- and high-volume patients, derive benefits from RT in terms of preventing the local events requiring surgical intervention. Therefore, RT might be considered for patients at a high risk of local events. We believe that further research is necessary to determine which patients have a high risk of local events secondary to primary tumor progression.

Regarding the upper urinary tract events requiring surgical intervention, neither RP not RT showed a benefit in preventing these events. RT could significantly reduce these events from the STAMPEDE data (RR: 0.42, 95% CI: 0.20–0.87), although RT did not reduce these events from the PEACE-1 data (RR: 0.87, 95% CI: 0.41–1.87) [20,22]. The differences in these results are believed to stem from variations in the systematic therapy and patient backgrounds. Given the limited number of events and limited number of studies, we believe that accumulation of more research findings may yield results indicating that RP and RT are effective in suppressing these events as well.

Regarding the efficacy of RP and RT in reducing overall local events and those requiring surgical intervention, a

comparison between these two treatments reveals significant findings. Our study obtained results indicating that in both these local events, RP reduced local events more effectively than RT by a statistically and clinically significant margin. It is conceivable that RT groups may include patients at a higher risk of local events than those who cannot undergo RP. However, Lumen et al (LoMP trial) [21] reported that RP is significantly more effective in preventing local events than RT (hazard ratio [HR]: 0.31, 95% CI: 0.11–0.86, $p = 0.024$), even though there were no significant differences in grade group and tumor stage between the RP and RT groups ($p = 0.18$). Moreover, this trial revealed that there was no significant difference in 2-yr OS and cancer-specific survival between the RP and RT groups (HR: 1.08, 95% CI: 0.27–4.29, $p = 0.9$ and HR: 1.08, 95% CI: 0.27–4.29, $p = 0.9$, respectively). Considering the latter trial and our meta-analysis data, RP potentially results in a significant reduction of local events and favorable OS compared with RT in selected patients.

3.4.1. Limitations

There are some limitations of our study. First, a major limitation in our research is that we were comparing small-scale retrospective or prospective cohorts of RP against two extensive multicentric RCTs of RT. Second, we intend not to include the perioperative complications of RP, such as incontinence, and toxicity of RT. However, differentiating perfectly between urinary tract infections caused by RT toxicity and those resulting from the progression of primary prostate cancer was difficult and challenging. Third, regarding the STAMPEDE trial, it was not possible to distinguish between low- and high-volume mHSPC in terms of local events. Consequently, this limitation precluded the analysis of the effectiveness of RT in preventing local events in patients with high-volume mHSPC.

4. Conclusions

We found that RP reduces both the overall local events and those requiring surgical intervention secondary to the progression of the primary tumor in patients with mHSPC compared with those treated with systemic therapy alone. Although RT similarly reduced local events requiring surgical intervention, no significant preventive effect of RT was observed separately on the overall local events. Neither RP nor RT showed a significant effect in preventing local events of the upper urinary tract requiring surgical intervention. We believe this research to be of importance as cytoreductive strategies such as RP and RT are more likely to be measured according to their local treatment–suggested complications versus their ability to prevent local debilitating events.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Araki, Shariat.
Acquisition of data: Tsuboi, Matsukawa.
Analysis and interpretation of data: Tsuboi, Matsukawa.
Drafting of the manuscript: Tsuboi, Matsukawa.
Critical revision of the manuscript for important intellectual content: Parizi, Klemm, Mancon, Chiujdea, Fazekas, Miszczyk, Laukhtina, Kawada, Katayama, Iwata, Bekku.
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Appendix A. Supplementary data

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