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REVIEW

The current role of local treatment in metastatic prostate cancer: systematic review and meta-analysis

Willy Baccaglini[a,b], Antonio F. Rodrigues[c], Saulo B. Teles[c], Nicolle M. Christofe[a], Felipe P. A. Glina[b], Gustavo C. Lemos[a], Rafael Sanchez-Salas[d], Rubén Olivares[e,f] and Arie Carneiro[a]

[a]Department of Urology, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [b]Department of Urology, Centro Universitário FMABC, Santo André, Brazil; [c]Department of Uro-oncology and Robotic Surgery, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [d]Department of Urology, Institute Mutualiste Montsouris, Paris, France; [e]Glickman Urology and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; [f]Department of Urology, Case Western University, Cleveland, OH, USA

ABSTRACT

Background: The aim of this study was to evaluate the current role of local treatment in prostate cancer with a low metastatic burden (or oligometastatic) in relation to survival and safety.

Methods: We performed a meta-analysis of studies published in the MEDLINE, EMBASE, and Cochrane databases until December 2021. Studies comparing local and nonlocal treatment in patients with metastatic prostate cancer were included. The risk of bias within studies was assessed using the Newcastle–Ottawa and Cochrane risk of bias tool. Oligo-metastasis was defined as low-volume metastasis with up to five lesions. The local treatment used was radical prostatectomy or external beam radiation therapy associated with systemic therapy (i.e., androgen deprivation therapy ± abiraterone, docetaxel, enzalutamide, or apalutamide). The endpoints evaluated were overall survival, cancer-specific survival, failure-free survival, and complication rates.

Results: Thirteen studies including 46,541 patients were included. The 5-year overall survival (16.0% vs. 6.5%, respectively; odds ratio (OR) 2.74; 95% confidence interval (CI), 2.18, 3.44; $I^2 = 0\%$; $p < .00001$) and 3-year cancer-specific survival (48.2% vs. 26.3%, respectively; OR 1.87; 95% CI: 1.44, 2.44; $I^2 = 0\%$; $p < .00001$) were higher in the local treatment group than that of the nonlocal treatment group. In addition, failure-free survival at 3 years was higher in the local treatment group than that of the nonlocal treatment group (40.5% vs. 28.4%, respectively; OR 1.72; 95% CI, 1.38, 2.14; $I^2 = 0\%$; $p < .00001$). The low complication rate of Clavien–Dindo grade ≥ 3 indicated that local treatment is feasible and safe in this setting.

Conclusion: Recent data have shown that local treatment combined with systematic therapy, might improve the overall, cancer-specific, and failure-free survivals of patients diagnosed with metastatic prostate cancer. Furthermore, local treatment is both feasible and safe. Further studies evaluating the quality of life of these patients are needed.

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Oligometastatic; radical treatment; radical prostatectomy; radiotherapy

Background

Prostate cancer (PCa) is the most common cancer among men. It has an indolent course in most cases, but 20% of the patients have positive local lymph node involvement and approximately 4% have distant metastasis at diagnosis, which is associated with a higher mortality rate [1,2]. Treatment varies according to the tumor stage. For patients with metastatic PCa (mPCa), the standard treatment is systemic therapy with androgen deprivation therapy (ADT), which is often associated with docetaxel or abiraterone, or more recently enzalutamide or apalutamide [3]. However, the CHAARTED trial stratified the patient group using the definition of low-volume disease (i.e., oligometastatic PCa) and different behaviors between patients with the low-volume disease compared to that of patients with high-volume mPCa [3,4].

The treatment for primary tumors in patients with mPCa using external beam radiotherapy (RT) has been shown to improve survival in newly diagnosed oligometastatic PCa [5]. In addition, our first meta-analysis showed that local treatment (LT) with RT, radical prostatectomy (RP), or brachytherapy (BT) significantly increases the overall survival (OS) in patients with mPCa [6].

Therefore, we decided to conduct an updated systematic review and meta-analysis including the new studies available, with some randomized clinical trials (RCTs), as most of the data included in our previous meta-analysis were from retrospective studies. Thus, we aimed to examine the feasibility and safety of LT in treating mPCa by evaluating the effects of LT on the OS and cancer-specific survival (CSS) in patients with PCa with metastatic disease and choosing the optimal treatment strategy for these patients.

CONTACT Willy Baccaglini baccaglini.urologia@gmail.com Department of Uro-oncology and Robotic Surgery, Hospital Israelita Albert Einstein, Av. Albert Einstein, 627 – Jardim Leonor, São Paulo, SP, Brazil

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Materials and methods

Protocol and information of sources

All authors approved the study protocol, which was registered in the international Prospective Register of Ongoing Systematic Reviews (PROSPERO; registration number CRD42021284096). The protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7,8]. The search was performed using Medline (PubMed), Embase, and Central Cochrane databases for studies published until 30 November 2021. The language of the study was not restricted. A grey search was performed based on the references of the included studies.

Eligibility criteria

Studies that compared LT with ADT to nonlocal treatment (NLT) in patients diagnosed with mPCa were included. LT was defined as RP (regardless of technique, such as open, laparoscopic, or robot-assisted) and RT (regardless of technique, such as conformational radiotherapy (CRT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), volumetric modulated arc therapy (VMAT), and proton beam therapy). Studies associated with other forms of systemic therapy with ADT (i.e., abiraterone, docetaxel, enzalutamide, and apalutamide) were included. The outcomes assessed were OS and CSS at 2, 3, 4, and 5 years and failure-free survival (FFS) at 3 years. RCTs, cohorts, and case-control studies that presented data of patients diagnosed with low-volume mPCa were included.

In cases where two or more studies included the same population, the study with the more complete data or longer follow-up was included. Conference abstracts and noncomparative studies were excluded. Studies that did not analyze the results of treatment for low- and high-volume mPCa separately were also excluded.

Search and study selection

The search strategy was defined based on the PICOS strategy acronym: (P = population; I = intervention; C = comparison group; O = outcomes and endpoints; S = study design) [9]. The following search strategy was used in all databases: (((prostate OR prostatic) AND (cancer OR carcinoma OR tumor OR tumor OR neoplasm) AND (metastatic OR metastasis OR advanced OR 'high risk' OR 'lymph node' OR nodal)) OR (metastatic prostate cancer OR mPCa)) AND ((('local therapy'OR cytoreductive OR cytoreduction OR surgery OR prostatectomy OR 'radiation therapy' OR radiotherapy OR Brachytherapy) AND (Castration OR Orchiectomy OR 'Androgen-deprivation therapy' OR Androgen-deprivation OR 'Gonadotropin-Releasing Hormone Agonists' OR 'GnRHa treatment' OR 'hormone therapy' OR 'hormonal therapy' OR 'Androgen deprivation' OR 'chemohormonal therapy')).

Two authors (AFR and NMC) selected the articles according to the PRISMA statement. If the abstract was not fully understood, the full article was read. In case of discrepancies, a third author (WB) determined whether the article would be included in a blinded manner.

Data items and collection

For each study, two authors (AFR and NMC) extracted the following data: population characteristics (i.e., age), number of patients at the beginning and end of the study, amount of prostate-specific antigen (PSA) (ng/dL), tumor stage according to the TNM classification of malignant tumors, Union for International Cancer Control, 8th ed. 2017, type of intervention (i.e., type of LT including RP, RT, and BT), comparison of intervention (i.e., ADT alone or plus another systemic therapy, including docetaxel, abiraterone, enzalutamide, and apalutamide), definition of low-volume mPCa, and follow-up. Data were extracted using an Excel® spreadsheet developed for this purpose.

Risk of bias assessment

The risk of bias within studies was assessed using the Newcastle–Ottawa scale for cohort and case-control studies and Cochrane risk of bias tool for RCTs. The oncological characteristics of both groups were analyzed to assess their comparability. Additionally, the definition of low-volume mPCa was assessed to evaluate the risk of locally-treated patients with no survival benefits. Complications related to the LT group were assessed and compared to those reported in the literature to avoid discrepancies in morbidity.

Data synthesis and analysis

The meta-analysis was performed using the RevMan 5.4 software from the Cochrane Library. The Mantel–Haenszel and reverse variation tests were used for categorical and continuous variables, respectively. For categorical variables, the odds ratio (OR) was used as a measure of association. All results were reported with 95% confidence intervals (CI). The results were presented using a forest plot. In cases showing acceptable heterogeneity ($I^2 < 50\%$), the fixed model was used, while the random model was used when $I^2 \geq 50\%$. If high heterogeneity was present, a sensitivity analysis was performed to identify one or more studies responsible for $I^2 \geq 50\%$. Finally, if the results of the original and sensitivity analyses were different, both analyses were presented; otherwise, only the original analysis was presented.

Results

Study selection and characteristics

Thirteen studies, with 46,541 patients, were included in the final analysis [5,10–21]. The selection and characteristics of the included studies are presented in Figure 1 and Table 1, respectively.

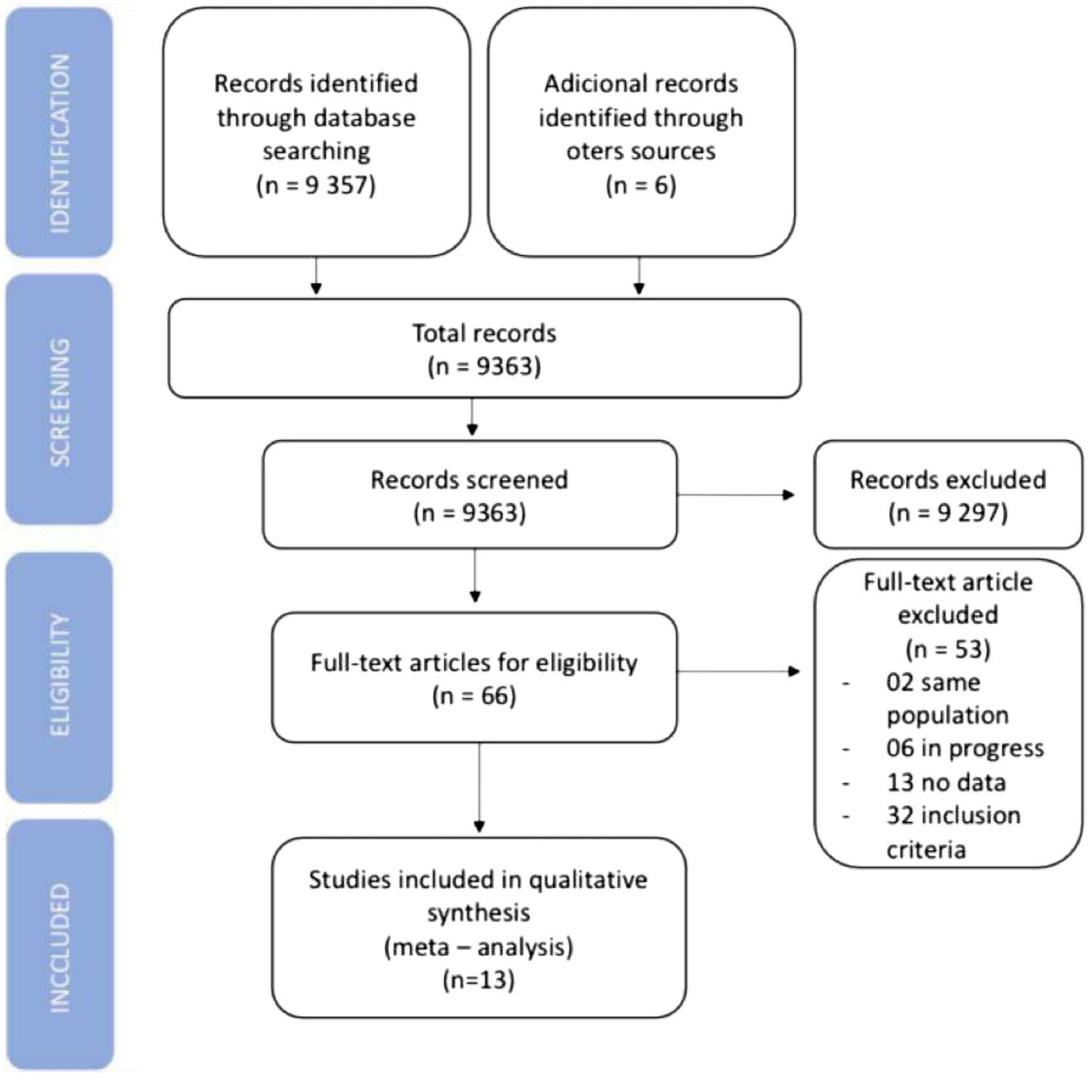


Figure 1. Study selection.

Table 1. Selected studies.

Article	Type of study	Age – I/C (years)	PSA – I/C (ng/ml)	Intervention	Comparison	Follow-up	N° I/C	Outcome
Culp 2014	RC	64/72	Interval	RP or BT	NLT	60 months	8185/8185	OS, CSS
Antwi 2014	RC	Cutoff*	Interval	RP or BT	NLT	36 months	7858/7858	–
Satkunasivam 2015	RC	74/78	Interval	RP, EBRT	NLT	60 months	4069/4069	OS; CSS
Heidenreich 2015	CC	61/64	135.2/105.9	RP	NLT	36 months	61/61	OS, CSS
Cho 2016	RC	69	126/221	EBRT	NLT	36 months	140/140	OS
Loppenberg 2016	RC	65/69	16/46.7	RP or BT	NLT	36 months	38929/15501	OS
Rusthoven 2016	RC	66/69	Interval	EBRT	NLT	60 months	6382/6382	OS
Yano 2017	RC	no data	no data	EBRT	NLT	40 months	57/186	OS, CSS, FFS
Parker 2018	RCT	68/68	97/98	EBRT	NLT	37 months	1032/1029	OS, FFS
Boeve 2018	RCT	67/67	125/149	EBRT	NLT	47 months	216/216	OS, FFS
Lan 2019	RC	67.8/ 71.17	Interval	RP	NLT	35 months	35/76	CSS; FFS
Simforoosh 2019	RC	61.5/64.6	84/108	RP	NLT	21 months	26/23	OS, FFS
Lumen 2021	PC	64-70/74	19-40/47	RP or EBRT	NLT	36 months	74/35	OS, FFS, CSS

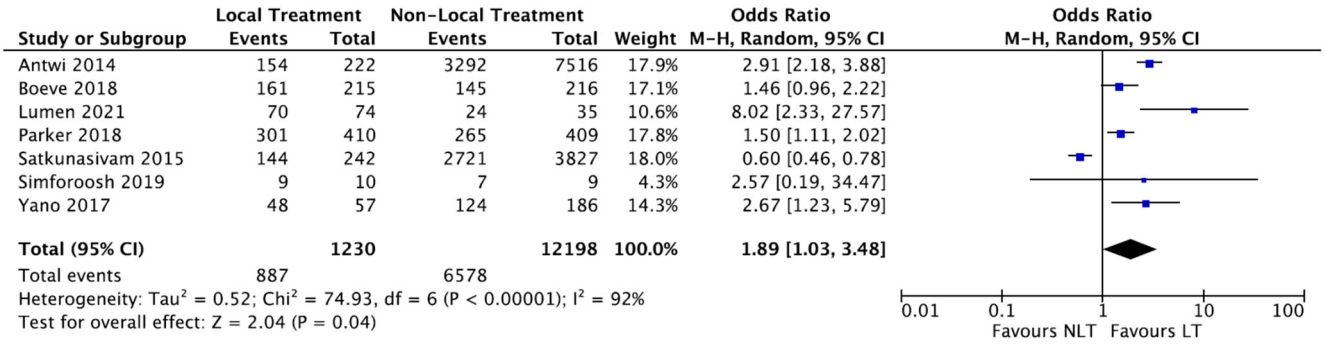
RC: retrospective cohort; PC: prospective cohort; CC: case control ; RCT: randomized clinical trial; RP: radical prostatectomy; BT: brachytherapy; EBRT: external-beam radiation therapy; NLT: no local treatment; OS: overall survival; CSS: cancer-specific survival; FFS: failure free survival.
*Over or less than 65 year.

Synthesis of results

Overall survival

The LT group was associated with a higher OS rate in all analyses compared to that of the NLT group. Seven studies enrolling 13,428 patients showed a higher OS in 2 years in the LT group than that in the NLT group (72.1% vs. 53.9%, respectively; OR 1.89; 95% CI, 1.03, 3.48; $I^2 = 92\%$; $p < .00001$) [5,11,12,17,18,20,21] Figure 2(A)). Finally, three studies enrolling 12,420 patients showed a higher OS in 5 years in the LT group than that in the NLT group (16.0% vs. 6.5%, respectively; OR 2.74; 95% CI, 2.18, 3.44; $I^2 = 0\%$; $p < .00001$) [10–12] Figure 2(B)).

a)



b)

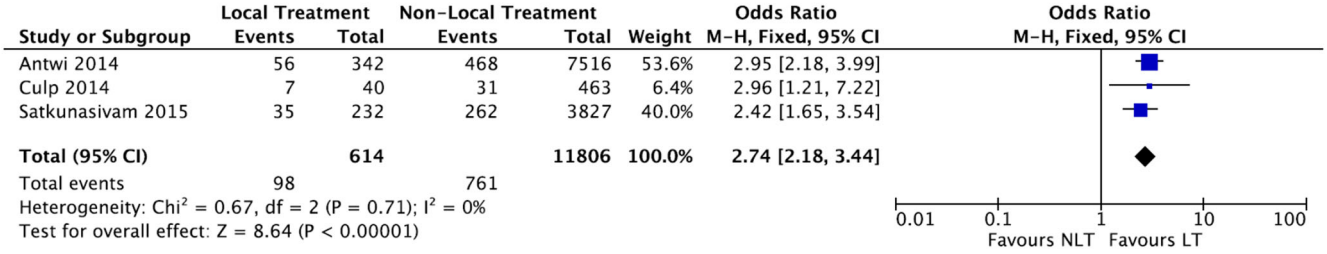


Figure 2. Comparison between LT and NLT in relation to OS in 2 years (A) and 5 years (B).

In addition, OS was higher in all analyses when the RP group was compared to the NLT group. Four studies with 11,774 patients demonstrated a higher OS in 2 years for the RP group than that in the NLT group (66.4% vs. 42.3%, respectively; OR 2.32; 95% CI, 1.19, 4.54; $I^2 = 78\%$; $p = .01$) [11,12,20,21] Supplementary Data **1 A).** Further, three studies enrolling 12,259 patients showed higher OS in 5 years in the RP group than that of the NLT group (15.3% vs. 6.4%, respectively; OR 2.64, 95% CI, 1.96, 3.56; $I^2 = 21\%$; $p < .00001$) [10–12] Supplementary Data **1 B).**

Finally, all analyses comparing RT and NLT showed better OS for LT. Six studies with a total of 11,851 patients showed a higher OS in 2 years in the RT group than that in the NLT group (71.5% vs. 49.1%, respectively; OR 2.02; 95% CI, 1.49, 2.74; $I^2 = 69\%$; $p < .00001$) [5,12,16–18,21] Supplementary Data **2A).** Three studies, including 4,874 patients, showed a higher OS in 3 years in the RT group than that in the NLT group (49.2% vs. 26.2%, respectively; OR 2.10; 95% CI, 1.41, 3.14; $I^2 = 65\%$; $p = .0003$) [5,12,14] Supplementary Data **2B).** Additionally, five studies enrolling 11,760 patients showed a higher OS in 4 years in the RT group than that in the NLT group (30.3% vs. 20.0%, respectively; OR 1.90; 95% CI, 1.17, 3.10; $I^2 = 87\%$; $p = 0.01$) [5,12,16–18] Supplementary Data **2C).**

Cancer-specific survival

Three studies with 4,421 patients showed a higher CSS in 2 years in the LT group than that in the NLT group (70.2% vs. 42.6%, respectively; OR 2.24; 95% CI, 1.75, 2.86; $I^2 = 2\%$; $p < 0.00001$) [12,17,21] Figure 3(A)**).** In addition, three studies enrolling 4,241 patients showed a higher CSS in 3 years in the LT group than that in the NLT group (48.2% vs. 26.3%, respectively; OR 1.87; 95% CI; 1.44, 2.44; $I^2 = 0\%$; $p < 0.00001$) [12,13,19] Figure 3(B)**).**

Failure-free survival

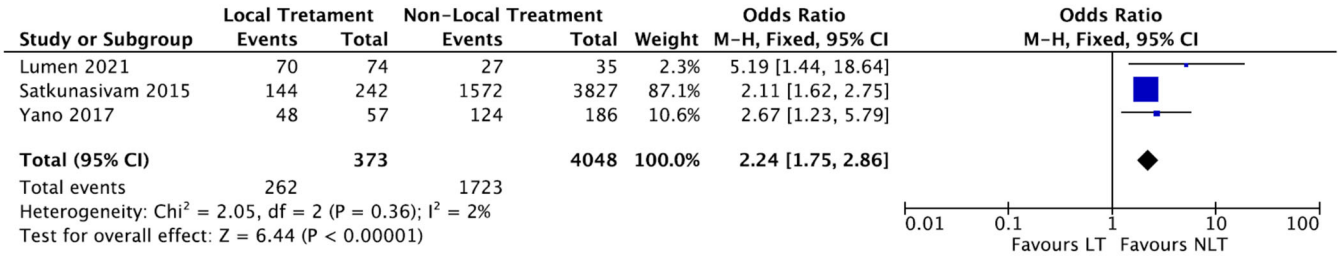
Three studies assessed the FFS between the LT and NLT groups. The HORRAD trial and Yano *et al.* defined FFS as PSA progression-free survival [17,18], while the STAMPEDE trial defined FFS as evidence of at least one of the following: biochemical failure; progression either locally, in lymph nodes, or distant metastases; or death from PCa. Three studies with a total of 1,486 patients demonstrated a higher FFS in 3 years in the LT group than that in the NLT group (40.5% vs. 28.4%, respectively; OR 1.72; 95% CI, 1.38, 2.14; $I^2 = 0\%$; $p < 0.00001$) [5,17,18] Figure 4**).**

Complication rates and functional outcomes following local treatment

Two studies compared RP to NLT and reported the complication rates and functional outcomes. Heidenreich *et al.* reported a major complication rate (Clavien–Dindo $\geq$3) for RP of 13%. In addition, two of the 23 patients (8.7%) presented with deep vein thrombosis related to RP and one (4.3%) experienced a pulmonary embolus. Furthermore, the authors reported similar urinary continence rates between the LT and NLT groups (20.8% vs. 16.7%, respectively; $p > .05$) [13].

Regarding adverse events, Simforoosh *et al.* reported that four patients in the RP group (15.4%) presented with Clavien–Dindo grade $\geq$3 (i.e., two patients had rectovesical

a)



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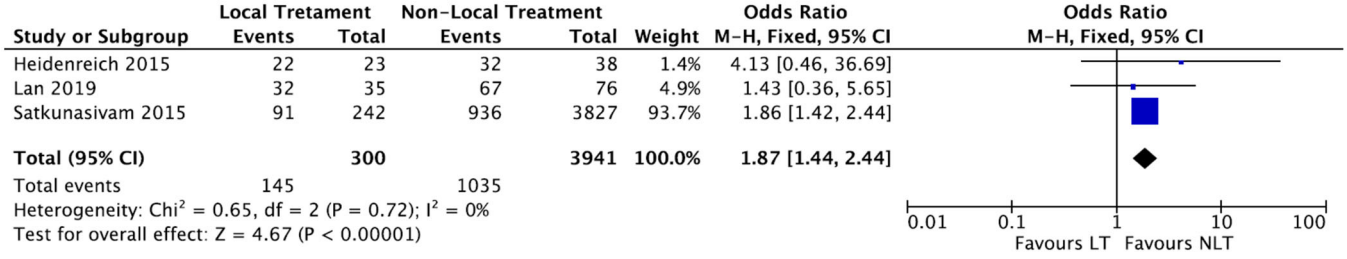

Figure 3. Comparison between LT and NLT in relation to CSS in 2 years (A) and 3 years (B).

a)

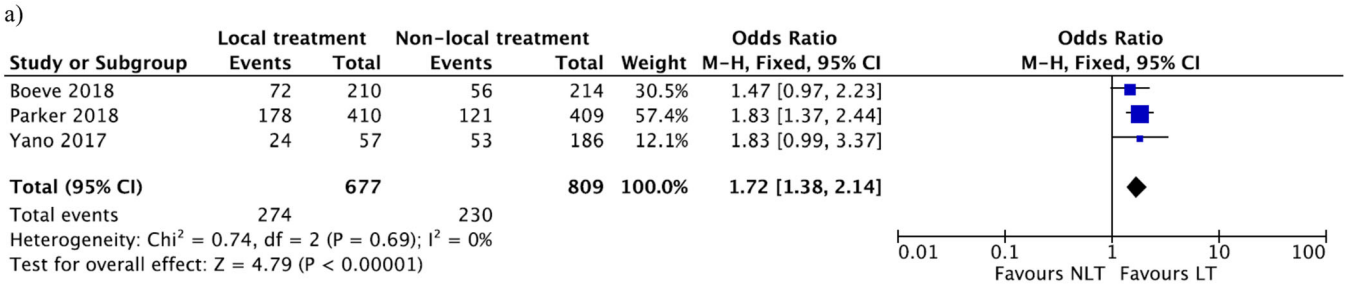

Figure 4. Comparison between LT and NLT in relation to FFS in 3 years.

fistulas, one had palliative cystectomy because of a very small, thick, contracted bladder, and one pelvic hematoma drainage). However, the authors did not analyze the complications of patients with low- and high-volume mPCa separately. In the NLT group, four patients (17.3%) required transurethral resection of the prostate (TURP) to resolve symptoms, one (4.3%) required bilateral percutaneous nephrostomy, and four (17.3%) required the placement of a permanent Foley catheter because their physical conditions were too poor to undergo intervention. Additionally, the authors compared the impact of each treatment on bone pain; four patients with low-volume mPCa (44.4%) complained of pain in the NLT group, while no patients in the LT group had any complaints of pain [20].

Based on the toxicity rate of ERBT according to Radiation Therapy Oncology Group and EORTC criteria, Cho *et al.* reported that none of the patients in the LT group experienced severe ($G \geq 3$) genitourinary or gastrointestinal toxicity. However, this study did not assess the adverse events in the NLT group [14,22]. The STAMPEDE trial assessed local events during and after the treatment period, such as TURP, acute kidney injury, urinary tract infection and obstruction, and the need for ureteric stents, surgery for bowel obstruction, Foley catheter, nephrostomy, and colostomy. The authors found no differences in local events between the groups [5]. Lumen *et al.* reported local event rates of 14.6%, 31.8%, and 37.1% in patients treated with RP, RT, and NLT, respectively. No differences were observed between the groups with regard to the type of local event, except for urinary retention with one (2.1%), five (19.2%), and ten (28.6%) patients in the RP, RT, and NLT groups, respectively [21].

Risk of bias assessment

The risk of bias in the included studies is presented in Supplementary Data **3**. Ten studies were retrospective [10–14,16,17,19,20] and three were prospective [5,18,21], of which two were RCTs [5,18]. The three prospective studies were registered at www.clinicaltrials.gov. The risk of bias within studies, which was assessed using the Newcastle–Ottawa scale and Cochrane risk of bias yool, was low.

In addition, the risk of bias across studies was assessed with regard to the following characteristics: definition of low-volume metastatic PCa, definition of standard of care and NLT, and type of LT. Regarding the volume of mPCa, most studies did not analyze the patients with low and high metastatic burden separately [10–12,14–16,20], and some studies even included patients with visceral disease (M1c according to TNM staging) [10–12,14,15,17]. Other studies classified

metastatic burden according to the number of bone lesions [5,13,18–20]. Finally, Parker *et al.* applied the definition used in the CHAARTED trial; high metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, visceral metastases, or both, while all other assessable patients were considered to have low metastatic burden [3,5].

The definition of the standard of care varied across studies, and consequently, the definition of NLT. Studies in which the inclusion period occurred before the publication of the CHAARTED trial considered NLT to be ADT alone [6,10–14,17,19,20]. Other studies included patients who received ADT alone or ADT plus another systemic treatment in both arms (i.e., LT and NLT), such as docetaxel, cabazitaxel, enzalutamide, abiraterone, and apalutamide [5,16,18,21]. Löppenberg *et al.* [15] defined NLT as patients undergoing ADT alone, watchful waiting, and ADT plus RT not targeted to the prostate.

Lastly, the type of LT also varied across studies. Since RP was considered as LT, some studies did not report the RP technique used (such as open [20], laparoscopic, and robot-assisted) [10,11]. In addition, there was heterogeneity among studies in relation to LT, mainly regarding the RT administered. Yano *et al.* [17] use a dose of 70 Gy in all patients, while the other studies show variations. Cho *et al.* [14] use two different doses (conventional or hypo-fractionated, 55 Gy/20fx and 70 Gy/28fx, respectively), Rusthoven *et al.* [16] also use two therapeutic regimens of low and high dose (65 Gy or $\geq$65 Gy, respectively). Parker *et al.* [5] also present two schedules: daily doses 55 Gy in 20 fractions for 4 weeks or 36 Gy in 6 fractions for 6 weeks). Boeve *et al.* [18] changed during the study: from 70 Gy in 35 fractions for 7 weeks to 57 Gy in 19 fractions 3 times a week for 6 weeks. Five studies [10–12,15,21] did not describe radiotherapy regimens.

Discussion

Currently, this study is the most updated meta-analysis available in the literature that assessed the impact of LT in patients with oligometastatic PCa. The 2-, 3-, 4-, and 5-year OS, CSS at 2 and 3 years, and FFS at 3 years were higher in the LT group than that of the NLT group. Finally, the present study showed that LT is feasible and safe to treat oligometastatic PCa as well as non-metastatic PCa.

Our previous study found a higher OS in the LT group compared to that of the NLT group at 3 and 5 years [6]. Moreover, the first group was associated with a higher 5-year CSS rate. Seven studies were included in the previous review. Furthermore, the previous study only included retrospective studies in the analysis, while the present study incorporated two RCTs published to date [5,18]. Therefore, the present study reinforced the results from our previous study and provided new evidence to support LT for oligometastatic PCa.

Previous RCTs have shown different outcomes among patients with low-and high-volume mPCa [3,5,23]. Accordingly, metastases-directed therapy (MDT) has been proposed for patients relapsing after radical treatment for localized PCa, with the aim of delaying systemic treatment. The ORIOLE trial evaluated the role of MDT in patients with oligo-recurrent mPCa by comparing stereotactic ablative radiotherapy (SABR) with surveillance. Oligo-recurrence was defined as the presence of $\leq$3 lesions on conventional imaging. Progression after 6 months was lower with SBRT than that with surveillance [24,25]. Another phase II trial compared surgery ± SABR with surveillance, which defined oligo-recurrence based on choline-positron emission tomography/computed tomography only [26]. ADT-free survival was longer with MDT than that with surveillance [26]. Currently, there are no data assessing the OS in this setting.

One of the biggest concerns is the safety of LT. Sooriakumaran *et al.* [27] published a series of 106 patients who underwent RP (open or robotic) for mPCa. The authors found similar general and peri-surgical complications in patients who underwent LT for mPCa compared to those with localized or locally advanced PCa. Additionally, Heidenreich *et al.* showed no difference in urinary incontinence and overall complication rates between patients with oligometastatic PCa and high-risk localized PCa treated with RP.

The HORRAD trial was the first trial to evaluate RT as LT in patients with metastatic castration-sensitive PCa. Four hundred and thirty-two patients were randomized to receive ADT alone or ADT plus IMRT with IGRT. There was no difference between groups in relation to OS, but the median time to PSA progression was significantly improved in the LT group [18]. The STAMPEDE trial, a primary phase III study, showed an improvement in OS with the addition of RT to systemic treatment for oligometastatic PCa. However, only 18% of patients had additional docetaxel and no patients had additional abiraterone; thus, no clear recommendation can be made regarding triple combinations. Recently, updated data from the STAMPEDE trial revealed a correlation between the number of metastases and OS or FFS in patients who underwent LT. Moreover, patients with only node metastasis presented better results, which reinforces the importance of selecting a patient candidate for LT [5].

To date, no phase III study has assessed the benefit of RP as LT in this setting. Lan *et al.* [19] evaluated the impact of RP and found no benefit, which may be due to the short follow-up period of 35 months. In addition, the authors defined low-volume mPCa as $\leq$5 bone lesions, regardless of localization, and did not follow the definition stated by the CHAARTED trial [3,19]. Thus, this definition might diminish the benefits of RP as LT. Despite our study including retrospective studies, an improvement in all outcomes (i.e., OS, CSS, and FFS) was observed in patients who underwent RP as LT. Additionally, a North American population-based study including 4,280 patients from the Surveillance, Epidemiology, and End Results database (2004–2016) examined whether RP might result in better survival than that of RT for mPCa. After propensity score matching, the 5-year CSS rates were 53% and 47% in RP and RT, respectively; therefore, it appeared that surgery might be an option to treat these patients [28].

The risk of bias within studies was low, as assessed using the Newcastle–Ottawa scale and Cochrane risk of bias tool. However, there were several points to highlight when the included studies were compared in relation to the selected outcomes. First, systemic therapy has changed since the CHARTED study was first published in 2015. Some studies did not include either chemotherapy or new antiandrogen drugs, such as abiraterone, enzalutamide, and apalutamide, as NLT. Therefore, the oncological outcomes of systemic treatment have evolved in recent years, which may reduce the potential benefit of LT. In contrast, some studies included patients with high-volume metastatic disease and visceral metastasis. Patients with more aggressive disease are likely to diminish the benefits of LT when evaluated together with those with low-volume disease. Lastly, the LT administered in the included studies varied significantly, whether in the case of those treated with RP or RT, which can also generate doubts when defining which and how to locally treat patients with metastatic PCa. Finally, the differences in survival between RP and RT was not evaluated due to the lack of studies comparing these two treatments.

This study had some limitations. First, most of the data included were from retrospective studies, except for three RCTs. In addition, no RCT focused on the impact of RP as LT in this population. Second, the definition of oligometastatic mPCa varied across studies, and the lack of standardization in terminology, for example, incorporating a higher number of lesions in this group, might reduce the real impact of LT. In parallel, only the most recently published studies included patients treated with ADT plus docetaxel, abiraterone, enzalutamide, and apalutamide. In addition, there was heterogeneity among studies in relation to LT, mainly regarding the RT administered. Finally, further studies evaluating the quality of life based on patient-reported outcome measures between LT and NLT are needed and will aid in the selection for the optimal treatment strategy for these patients.

Conclusion

Recent data have shown that LT along with systemic therapy improves the OS, CSS, and FSS of patients diagnosed with oligometastatic PCa. Furthermore, LT was shown to be safe, even with RT or RP. Further studies are needed to evaluate the quality of life of patients treated with LT.

Author contribution

BW: Protocol/project development, data management, data analysis, and manuscript writing/editing. RAF and MNC: Data collection, manuscript writing/editing. TSB: Data analysis, manuscript writing/editing. GFPA: Data management, manuscript writing/editing. LGC and CA: Protocol/project development, manuscript review. S-SR and OR: Manuscript writing/editing, manuscript review.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Saulo B. Teles http://orcid.org/0000-0002-1993-8627

Data availability statement

The data that support the findings of this study are available from the corresponding author, WB, upon reasonable request.

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