Current evidence on local therapy in oligometastatic prostate cancer

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Purpose of review
Metastatic prostate cancer (PCa) continues to be an invariably fatal condition. While historically, de-novo metastatic PCa was primarily treated with androgen deprivation therapy (ADT) and systemic therapy, there is a growing trend toward incorporating local treatments in the early management of the disease. This is particularly applicable to men with oligometastatic PCa (OMPC), which represents an 'intermediate phase' between localized and disseminated metastatic disease. Local treatment offers an opportunity for disease control before it progresses to a more advanced stage. This review discussed the current evidence for local treatment options for OMPC.

Recent findings
Currently, it has been suggested that men with OMPC may have a more indolent course and, therefore, favorable outcomes may be observed with metastasis-directed therapy (MDT). This review will not address the role of MDT to patients with OMPC but will focus on local treatments of the primary disease. The three main forms of local therapy employed for OMPC are cryotherapy, radiation therapy, and cytoreductive prostatectomy (CRP). Whole gland cryotherapy, either with ADT or with ADT and systemic chemotherapy, has shown some limited promising results. Radiation therapy combined with ADT has also demonstrated improvements in progression-free survival in clinical trials (primarily STAMPEDE Arm G and HORRAD). CRP often combined with ADT has emerged as a potential strategy for managing OMPC, with promising findings primarily from retrospective studies. Currently, several randomized controlled trials are underway to further investigate the role of CRP in the oligometastatic setting.

Summary
OMPC has become a unique category of disease with specific therapeutic implications. Lack of robust clinical data renders treatment selection controversial. Further studies with long follow up are necessary to identify men with oligometastatic disease who will benefit from local treatment.

Keywords
cytoreductive prostatectomy, oligometastatic prostate cancer

INTRODUCTION

Prostate cancer (PCa) remains the second most common cause of mortality in men in the United States and the mortality burden is driven by metastatic disease [1]. The 5-year relative survival is about 32% for men who have developed metastasis compared to more than 99% for those who are nonmetastatic [2]. About one in five men who are diagnosed with PCa present with high-risk or de-novo metastatic disease [3].

In general, the contemporary approach to metastatic PCa (mPCa) is androgen deprivation therapy (ADT), combined with either novel antiandrogens or chemotherapy. However, systemic therapies affect the quality of life and have been associated with increased risk for certain toxicities, particularly when administered long term [4]. Furthermore, despite the increasing number of systemic agents in the therapeutic armamentarium for advanced PCa, none of them is curative and only delay progression [5].

The aim of this review is to highlight definitions, underlying rationale, and summarize current evidence for local treatment in men with oligometastatic PCa (OMPC).

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KEY POINTS

- There is increasing evidence that local treatments may offer oncological benefit in the management of OMPC.
- The three main forms of local therapy employed for OMPC are cryotherapy, radiation therapy, and cytoreductive prostatectomy.
- Radiation therapy combined with ADT has also demonstrated improvements in progression free survival in clinical trials.
- CRP combined with ADT has emerged as a potential strategy for managing oligometastases, with promising findings primarily from retrospective studies.
- Whole gland cryotherapy, either with ADT or with ADT and systemic therapy, has shown limited promising results.

Definition of oligometastatic disease

The term oligometastatic disease was first introduced by Hellman and Weichselbaum in 1995 who proposed the existence of a disease state lying on the spectrum between localized and grossly metastatic cancer [6,7]. Since the proposal of this disease state, multiple studies have been performed in different solids tumors describing the biological characteristics of oligometastasis but also evaluating it as a designated treatment category. The latter is supported by recent literature with studies suggesting that patients with low burden of disease respond better to local treatments compared to those with high burden metastatic disease [8].

In PCa, there is no standardized definition of oligometastasis. Most experts would use the term OMPC for men with three to five lesions. At the 2020 Advanced Prostate Cancer Consensus Conference, there was no complete agreement regarding the number of metastases that define OMPC with two-thirds of the panelist voting for three lesions, 20% for five and almost 15% for two metastases, respectively [9]. However, it is crucial to understand that the diagnosis of oligometastasis is a combination of the actual disease status identified at a certain time point, and also a byproduct of advanced imaging [10]. Finally, neither the size of the metastatic lesion nor the imaging modality that was used to identify it is used in taken into consideration when OMPC is defined [10].

Rationale for local therapy in oligometastatic prostate cancer

The concept of cytoreduction is associated with Paget's 'seed and soil' hypothesis from 1889 [11]. This theory suggests that the primary tumor works as the tank of 'seeds' that colonizes locations ('soils') with favorable micro-environment for growth [12]. There is evidence that this communication between primary tumor and metastatic sites continues via secretion of tumor-derived factors, such as vascular endothelial growth factor, extracellular vesicles, cytokines, and others [13]. Therefore, from a biological standpoint, there is a strong rationale for treating the primary since that could eliminate not only the 'seed' but also decrease the tumor-secreted factors that facilitate growth of metastatic sites [14]. This concept is supported by observations of an 'abscopal effect' in which shrinkage of untreated metastatic sites is seen after radiation is delivered to the primary tumor [15]. Furthermore, from a clinical standpoint, higher tumor burden has been associated with worse oncological outcomes in multiple malignancies. Thus, treatment of the primary location of cancer may improve clinical outcomes simply by tumor volume reduction [16]. Additionally, specifically regarding de-novo OMPC, as recently demonstrated by Warner *et al.* [17], genomic assessment of the primary tumor post-radical prostatectomy (RP) can offer valuable insights for the implementation of genomics-guided patient management. In their study, Warner *et al.* [17] observed a significant discordance in genotypes between certain areas of the primary tumor and synchronous metastases. Another concept with the widespread adoption of PET imaging is that when conventional imaging is normal even in high-risk disease, yet PET demonstrates OMPC, robust data do suggest a benefit of RP versus non-local therapy. With recent EAU guidelines, the PSMA PET results should not influence the treatment of the primary in this scenario, discovery of OMPC, if the patient is a RP candidate [18,19▪▪].

Cytoreductive radical prostatectomy

Cytoreductive radical prostatectomy (CRP) with pelvic lymph node dissection has been proposed as a treatment option for local control of oligometastatic disease. Although surgery has demonstrated safety and feasibility [20], there is a lack of high-level evidence for its efficacy with multiple ongoing clinical trials attempting to identify the role of CRP.

Leyh-Bannurah *et al.* [21] using the Surveillance, Epidemiology, and End Results (SEER) database identified 474 men who underwent local treatment (prostatectomy or radiation) for metastatic PCa. The authors demonstrated a reduction in cancer-specific mortality for men undergoing surgery versus those who had systemic therapy alone. The lowest CSM rates were recorded for Gleason $\leq$7, $\leq$cT3, and M1a

substage. While the study could not specifically include men with OMPC as the SEER database lacks comprehensive information about the number of lesions/sites of disease, this study points to the possibility of benefit of CRP in well selected patients [21]. Additional retrospective study similarly suggests a potential benefit as Heidenreich *et al.* [22] compared 23 men with PCa and small number of osseus metastases who had CRP with neoadjuvant ADT to 38 men with ADT alone. They found favorable results for CRP in terms of median time to castration resistance (40 months compared to 29 months, $P = 0.04$), progression-free survival (PFS) (38.6 versus 26.5 months, $P = 0.032$), and cancer-specific survival (CSS) (95.6 versus 84.2%, $P = 0.043$). However, overall survival (OS) was notably similar between the two groups [22]. Jang *et al.* [23] similarly demonstrated this finding in a retrospective study of 38 men who underwent CRP and were compared to 41 men who received ADT alone. The authors demonstrated that men who had surgery had a longer progression-free survival (PFS; hazard ratio 0.388, $P = 0.003$) and CSS (hazard ratio 0.264, $P = 0.004$), yet with a relatively short follow-up duration of 40 months, did not analyze differences in OS [23].

Regarding the risk of postoperative morbidity and mortality complication of CRP, retrospective studies have shown that there is low rate of complications and good functional outcomes that in selected patients do not differ from the results of CRP in treatment-naive men [24]. These data highlight that CRP in this setting is technically feasible and does not necessarily sacrifice quality of life in lieu of cancer control.

Given promising results from such retrospective series, several prospective study efforts have subsequently been undertaken. Buelens *et al.* reported results from the Local treatment of Metastatic Prostate cancer trial (LoMP), a prospective, multicenter trial, that compared standard of care versus standard of care combined with CRP (NCT02138721). A total of 40 patients were recruited in each arm and after median follow up of 25 months, prostate cancer-free survival was 53 versus 21 months ($P = 0.017$) for the addition of surgery versus standard of care alone. Nevertheless, multivariable analysis for cancer-free survival and local event-free survival failed to show a difference between the two groups ($P = 0.5$ and $P = 0.3$, respectively) [25▪▪].

The Testing Radical prostatectomy in men with PCa and oligo-Metastases to the bone (TRoMbone) is a prospective, randomized, nonblinded, feasibility clinical trial performed at the UK for men with synchronous oligometastatic PCa standard of care systemic therapy versus standard of care and CRP. The first publication of this trial focused on the feasibility of randomization to CRP and systemic therapy and reported that of 51 men were randomized within 14 months with 60–83% accrual rate in centers that recruited at least two patients. CRP for men with OMPC was found to be well tolerated and had a similar impact on early functional outcomes as surgery for standard indication [26▪▪]. FUSCC-OMPCa is a Chinese randomized phase 2 clinical trial, with an anticipated enrollment of approximately 200 men (NCT02742675). This study has PFS as primary outcome and aims to compare ADT alone versus ADT combined with surgery or radiation. Similarly, the Southwest Oncology Group randomized phase 3 trial S1802 (SWOG S1802) has commenced recruiting for comparison of ADT alone versus ADT combined with surgery (NCT03678025) with an aim to enroll over 1200 men. Lastly, the German based, g-RAMMP, is comparing systemic therapy and CRP versus best systemic therapy alone (NCT02454543). This trial has not been completed and prematurely closely related to concerns for a best systemic treatment arm alone.

Recently, Rajwa *et al.* [27] were the first to report outcomes of CRP for OMPC diagnosed on PSMA-PET. In their study, which included 116 patients, 36 individuals (31%) experienced complications. Notably, only six patients (5%) suffered complications of grade 3 or higher. While the study provided insightful data, it was constrained by the short-term follow-up of the patients. Despite this limitation, the study reported promising results in terms of castration resistance-free survival and OS, with rates of 85.8 and 98.9%, respectively [27].

There are multiple ongoing clinical trials as summarized in Table 1 [28–34].

Focal therapy

Another approach that has been attractive for local control of oligometastatic PCa is focal therapy, particularly in the form of cryotherapy. There is limited evidence that cryotherapy not only leads to reduction of the tumor size in the prostate but also may trigger an immunological effect. The latter may be induced by the release of cancer antigens during the freezing-thawing cycles that leads to an inflammatory microenvironment and a further activation of an immune response by the host (abscopal phenomenon) [10,35].

In 2017, Sheng *et al.* [36] were the first to describe the use of cryotherapy for men with oligometastatic PCa. The authors performed a retrospective study of 49 men with de-novo oligometastatic PCa; 23 men received cryosurgery as local treatment combined with ADT whit the control group received

Table 1. Ongoing clinical trials in cytoreductive radical prostatectomy for oligo-metastatic prostate cancer

Study identifier	Type of study	Study criteria	Additional agents	Outcomes	Estimated enrollment
SIMCAP (NCT03456843) [28]	Randomized phase 2 open-label study	Histologically confirmed PCa without previous local therapy	ADT +/- docetaxel versus ADT for ≥1 month before RP with or without docetaxel	FFS[a] at 2 years after randomization (primary) CSS, overall complication rate time to BCR, OS (secondary)	190
g-RAMMP (NCT02454543) [29]	Randomized phase 3 open-label study	Histologically confirmed PCa with 1–5 bone metastases confirmed on imaging and no visceral metastases, PSA ≤200 ng/ml	BST alone versus BST with RP	CSS (primary) Development of castration resistance, PFS, OS (secondary)	452
SWOG 1802 (NCT03678025) [30]	Randomized phase 3 study	Histologically confirmed PCa with <28 weeks of standard systemic therapy	BST alone versus BST with definitive local treatment (radiation of CRP)	OS (primary), PFS	1273
Oligomet_DK (NCT04086290) [31]	Phase 1–2	Histologically confirmed PCa with ≤ 3 bone metastases localized to the spine, pelvis or humeral/femoral bones as evaluated by 68Ga-PSMA PET/CT and MRI	CRP+SBRT+ADT	Proportion of men with Grade ≥ 3 adverse events the first year (primary) Proportion of men achieving PSA < 0.1 ng/ml (secondary)	20
Safety and Early Efficacy of RP for Newly Diagnosed Very High Risk Locally Advanced and OMPC (NCT02971358) [32]	Phase 1–2	Histologically confirmed very high-risk PCa and/or MPC with ≤5 bone metastasis	CRP +/- BST	Rate of perioperative complications within 90 days after surgery (primary) Time to start ADT (secondary)	200
FUSCC-OMPCa (NCT02742675) [33]	Phase 2	Histologically confirmed PCa with ≤5 nodal or bone metastases	BST versus BST + CRP or radiation therapy	PFS (primary) OS, time to PSA progression, Quality of life outcomes (secondary)	200
Testing Radical Prostatectomy in Chinese Men With PCa and oligo Metastases to the Bone (NCT03988686) [34]	Open labelled trial	Histologically confirmed PCa with one to three skeletal lesions and no visceral metastases	BST versus BST + CRP	Time to castration resistance (primary) Quality of life outcomes (secondary)	120

ADT, androgen deprivation therapy; BST, best standard therapy; CRP, cytoreductive prostatectomy; CSS, cancer-specific survival; FFS, failure-free survival; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy.
[a]Failure defined as PSA, clinical or radiographic progression or death from prostate cancer.

ADT alone. The cryotherapy group had longer time to castration resistance (36 versus 25 months, $P = 0.001$) and increased PFS (35 versus 25 months, $P = 0.002$) without any reported major complications from cryotherapy. Furthermore, they showed that men who underwent cryotherapy were less likely to require palliative urological treatments compared to those receiving ADT. Nevertheless, the lack of cancer-specific and OS data as well as the use of strict inclusion criteria (prostate volume ≤50 ml; no T3b–T4 or bulky disease, decrease in serum PSA level to <1.0 ng/ml after 6 months of neoadjuvant ADT) make generalizability of these findings very limited [37].

More recently, a pilot study was performed by Ross *et al.* [38] to investigate the role of whole gland cryotherapy in men with oligometastatic PCa. In this trial, 12 men received pembrolizumab for 3 weeks in combination with ADT for 8 months with cryotherapy performed within 3 days of initiation of pembrolizumab. The study showed that 42% of patients achieved PSA of less than 0.6 ng/ml

after 1 year, with a median PFS of 14 months and a median systemic therapy-free survival of 17.5 months. In terms of safety, the combination of cryotherapy, short-term ADT, and pembrolizumab treatment was well tolerated, with no recorded adverse events of grade greater than 3. While it is hard to generalize these results since there is no long-term follow-up, no comparison group and the number of patients is small, the authors demonstrated that cryotherapy, when used in conjunction with immunotherapy, may have potential in management for OMPC [38].

Several trials are currently ongoing to further identify the role of focal therapy in combination with systemic treatments and immunotherapy for oligometastatic PCa (NCT02861573, NCT03879122).

Radiation therapy

The role of radiation therapy has been better defined in the management of OMPC compared to the other modalities and most of the supporting data comes from two large, multicenter, randomized, controlled, phase 3 studies: the STAMPEDE and HORRAD trials. These two trials are the only ones that up to date have compared radiation therapy (RT) of the primary versus standard of care in men with metastatic PCa.

The STAMPEDE Arm G trial randomized 2051 men with newly diagnosed metastatic PCa to undergo external beam radiation therapy (EBRT) of the prostate and ADT with or without docetaxel or ADT with or without docetaxel alone [39]. High-burden metastatic disease per STAMPEDE was defined as the presence of four or more bone metastases, at least one of them outside the vertebral bodies or pelvis, or the presence of visceral metastases. At a median follow-up time of 37 months, there was no difference in median OS among the two groups in the entire cohort. However, in a subgroup analysis of men with low metastatic burden, it was shown that EBRT improved failure-free survival, where failure was defined as biochemical failure, disease progression (local, lymph nodes, or distant), or death from PCa [hazard ratio 0.76; 95% confidence interval (95% CI) 0.68–0.84; $P < 0.001$]. Importantly, an effect on OS was noted with 81% of the men who underwent EBRT were alive at 3 years compared to 73% of those in the control group (hazard ratio, 0.68; 95% CI, 0.52–0.90; $P = 0.007$).

In the HORRAD trial, 432 men with newly diagnosed metastatic PCa were randomly assigned to receive either EBRT combined with ADT ($N = 216$) or ADT alone ($N = 216$). The trial revealed no statistically significant difference in the median OS between the two groups [40]. Nevertheless, a post-hoc subgroup analysis suggested that men with fewer than five bone metastases might derive survival benefit from radiation therapy, although this difference did not achieve statistical significance (hazard ratio 0.68, 95% CI 0.42–1.10, $P > 0.05$). Yet, when contextualized with STAMPEDE Arm 3, this study notably administered a relatively low radiation dose of 70 Gy over 35 fractions and did not include irradiation of the pelvic lymph nodes.

Interestingly, following publication of the HORRAD and STAMPEDE trials, Burdett *et al.* [41] performed a systematic review and meta-analysis where the HORRAD definition of low and high metastatic burden of disease was used to analyze data from both studies (with low burden defined as no more than four osseous metastases). Radiotherapy of the primary did not clearly improve survival or PFS in unselected men with metastatic hormone sensitive PCa. However, an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases was demonstrated [41].

In summary, these two trials suggest that there is a potential benefit of adding prostate radiation therapy to the standard of care for men with four or less osseous metastatic sites. Currently, there are multiple ongoing prospective clinical trials (SWOG 1802, PEACE1) trying to better characterize the patient population that would benefit the most.

CONCLUSION

Overall, there is increasing evidence that local treatments may offer oncological benefit in the management of OMPC. Nevertheless, the data are still not robust and while definitive answers are under investigation, the current evidence suggests that patient selection is likely to play an essential role. Patient-related factors including age, burden of disease, tolerance of side effects and cost should be explored to identify the best candidates. Clinicians offering adjunct local treatment for OMPC should discuss the side effects and the lack of long-term data on these treatments. Finally, the multiple randomized controlled trials that are currently ongoing for all local treatment modalities will hopefully define the role of local therapy in the oligometastatic disease state.

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Conflicts of interest

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