Emerging Role for Local Therapy in Oligometastatic Prostate Cancer

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Abstract: Oligometastatic prostate cancer is a subtype of metastatic disease that generally is defined by the presence of 5 or fewer metastatic lesions. Metastatic prostate cancer currently is treated with androgen deprivation therapy and additional systemic therapy, such as novel antiandrogen medications or chemotherapy. The management of metastatic prostate cancer is evolving, however, with the notion that some patients with low-burden metastatic disease may benefit from both local and systemic therapy. Local therapy of the prostate in the setting of oligometastatic prostate cancer is a new concept. Evidence from retrospective studies suggests that cytoreductive therapy, including radical prostatectomy, can improve overall survival in these patients. Ongoing randomized trials are comparing cytoreductive therapy with standard-of-care treatment options. Local therapy in the form of radiation has also been investigated in phase 2 randomized trials. In this review, we discuss the biological and clinical rationales for local therapy, review the current evidence for local therapy, and compare the clinical designs of various ongoing trials.

Keywords
Local therapy, oligometastatic, prostate cancer

Introduction

The treatment of metastatic prostate cancer has evolved vastly in the past 2 decades. Advances have been based on the understanding that metastatic prostate cancer encompasses a wide spectrum of disease states.[1] From biochemical recurrence with lymph node metastasis to widespread metastatic, castration-resistant disease, not all presentations of metastatic prostate cancer are equivalent. In turn, treatment options should be tailored to the particular disease state.

Currently, all forms of metastatic prostate cancer are treated systemically with androgen deprivation therapy (ADT), with the possible addition of chemotherapy or novel antiandrogens.[2] Systemic therapy significantly affects quality of life, particularly when administered over long periods, and generally is noncurative.[1]

The term *oligometastatic disease* was coined in 1995 by Hellman and Weichselbaum to describe cancers with a small number of metastatic lesions.[3] These lesions were proposed to have different rates of progression.

With advances in imaging technology, including more sensitive modalities and novel radioactive tracers, previously undetectable lesions are now being discovered. Therefore, interest in the management of oligometastatic prostate cancer (OMPC) is increasing, particularly as the condition is being diagnosed more often.[4] Mounting evidence also suggests that the responses to nonsystemic forms of therapy are better in patients with low-burden disease than in those with high-burden disease.

Local therapy of the prostate in the setting of metastatic disease is a relatively new concept. In regard to OMPC, local therapy is defined as radical prostatectomy or radiotherapy (RT) directed to the prostate and/or limited metastatic sites. Recent clinical trials have investigated RT to the prostate and/or to specific metastatic lesions. The aim of this review is to summarize the growing evidence on local therapy in OMPC and to identify areas for future clinical research.

Definition of Oligometastatic Prostate Cancer

No standardized definition of OMPC exists. Some consider OMPCs to be cancers with 3 to 5 metastatic lesions. At the 2020 Advanced Prostate Cancer Consensus Conference, 66% of expert panelists voted for the presence of up to 3 metastases as the definition for OMPC, 20% up to 5 metastases, and 14% up to 2 metastases.[5] Several factors must be considered when the results of studies on OMPC are interpreted. Currently, neither the size of the metastatic lesion nor the imaging modality used to identify the lesions is considered when OMPC is defined. Disease in which 5 metastatic lesions are detected on more advanced imaging modalities, such as choline positron emission tomography/computed tomography (PET/CT), is likely not equivalent to disease in which 5 metastatic lesions are detected by conventional bone scan.[1] Whether OMPC represents indolent disease, early metastasis, a byproduct of advanced imaging, or a combination of all three is not well understood and therefore an area of active research.

Biological Rationale for Local Therapy

The biological steps necessary for solid tumors to metastasize are largely the same across cancer types.[6] Circulating tumor cells (CTCs) must break through the basement membrane, cross the stroma, and enter the circulation.[7] Both anatomy and molecular biology influence where CTCs ultimately settle.

According to the "seed and soil" hypothesis, cells from a primary tumor (the "seed") colonize hospitable organ sites (the "soil").[8] Yet, communication between the primary tumor and distant organ sites occurs even before the CTCs reach an organ site. The primary tumor prepares distant organs for CTC seeding by creating a favorable pre-metastatic environment.[9] For example, tumor-derived secreted factors, such as vascular endothelial growth factor, promote angiogenesis in the host environment. Several cancers release matrix metalloproteinases that promote extracellular matrix remodeling, making it easier for tumor cells to migrate.[10]

In prostate cancer, primary tumor cells release atypically large extracellular vesicles that interact with the host site. These vesicles, also known as oncosomes, contain genetic material or proteins that are transferred to host organ cells.[11] Prostate cancer classically metastasizes to the bone, where it forms osteoblastic lesions. Oncosomes released from prostate cancer cells have been shown to interact with the bone microenvironment.[12] Receptor activator of nuclear factor–κB (RANK), released from primary prostate tumor cells, engages in a positive-feedback loop with osteoblasts and osteoclasts that ultimately promotes metastasis to the bone.[8] Although the specific mechanisms of prostate cancer metastasis are not completely understood, growing evidence indicates that the primary prostate tumor influences whether and where CTCs metastasize.[8]

One clinical implication of the "seed and soil" hypothesis is that removing the primary tumor may remove what keeps the metastatic niche alive. The "abscopal effect" is the phenomenon in which using RT to shrink a primary tumor concurrently shrinks untreated metastatic tumors.[13] In a variety of solid tumors, the mechanism behind this effect is hypothesized to be immune-related. After radiation of the primary tumor, cell death leads to exposure of the intracellular contents to immune cells. The immunogenic response involves the recruitment of cytotoxic T cells, which identify tumor-derived antigens and destroy remaining tumor cells in distant lesion sites that have not been exposed to radiation.[14,15]

Observations of the abscopal effect have largely been described in case reports and retrospective studies. For example, in a study of 47 patients with metastatic melanoma, use of the immunotherapy agent ipilimumab (Yervoy, Bristol Myers Squibb) in combination with RT reduced the size of index lesions outside the radiation treatment field in 25% of patients.[16] In a study of patients who had prostate cancer treated with brachytherapy, antibodies to tumor antigen developed in 25% of them.[17] A case report of 3 patients with prostate cancer described the regression of distant metastases after cryoablation of the primary prostate tumor.[15] In renal cell carcinoma, immunotherapy in combination with RT is proposed to achieve tumor reduction synergistically in both the primary and metastatic settings.[14]

Another proposed biological mechanism for improved

Table 1. Comparison of the HORRAD and STAMPEDE Trials

	HORRAD ***Post hoc subgroup analysis***	**STAMPEDE**
Number of patients with low-burden disease	160	819
De novo or recurrent disease?	De novo	De novo
Definition of low-burden disease	≤4 osseous lesions	<4 osseous metastases, none outside the vertebral bodies or pelvis; no visceral metastases
Imaging modality used to stage disease	Bone scan	Bone scan and CT
Intervention	RT to the prostate + ADT	RT to the prostate + ADT
Control	ADT	ADT
Median follow-up	47 mo	41.9 mo
HR for all-cause mortality (intervention vs control)	HR, 0.68; 95% CI, 0.42-1.10	HR, 0.68; 95% CI, 0.52-0.90

ADT, androgen deprivation therapy; CT, computed tomography; HR, hazard ratio; mo, months; RT, radiation therapy.

clinical outcomes with local therapy is simply reduction of the total tumor burden. In a preclinical study using human and murine cell lines, a higher tumor burden was associated with a greater expression of cancer stem cell markers.[18] The size of the tumor burden is a significant predictor of long-term outcomes in patients with prostate cancer.[19] Several clinical options are available to reduce the tumor burden, including metastasis-directed therapy (MDT), cytoreductive therapy, and resection of the primary tumor. Retrospective studies support a role for these therapeutic modalities in the setting of limited metastatic disease.[20-22]

Clinical Rationale for Local Therapy

Systemic therapy for prostate cancer can have long-term effects on quality of life. ADT, a cornerstone of the current treatment for metastatic prostate cancer, is associated with loss of bone mineral density, sexual dysfunction, metabolic syndrome, cardiovascular disease, and neurocognitive changes.[23] Long-term hormonal treatment can lead to significant toxicities and diminish quality of life.

Clinical opinions are evolving with the understanding that OMPC may be amenable to local therapy. At the 2017 Advanced Prostate Cancer Consensus Conference, 69% of expert panelists stated that radical local treatment was appropriate in newly diagnosed oligometastatic prostate cancer.[24] The use of local therapy may allow a delay of systemic therapy (albeit a controversial approach) or a shorter course of systemic therapy.[25]

Although the approach of delaying systemic therapy is controversial, newer trials are investigating the effect of local therapy on ADT-free survival. This approach is partly justified by results from Moul and colleagues and by the EORTC 30891 trials, which found no effect on the development of metastatic lesions and no effect on prostate cancer-specific survival, respectively, for early vs delayed ADT.[25,26] However, ADT-free survival is not the best primary outcome in situations in which ADT combined with local therapy improves survival. As discussed in this review, prospective trials have demonstrated a greater survival benefit when local therapy is combined with systemic therapy than when systemic therapy is given alone.

Prostate-Directed Radiation Therapy: the HORRAD and STAMPEDE Trials

In 2 large, multicenter, randomized controlled phase 3 trials, it was found that local RT does not improve overall survival (OS) in patients with high-volume metastatic prostate cancer but may improve OS in patients with low-volume metastatic prostate cancer. To date, HORRAD and STAMPEDE are the only published phase 3 trials that have compared prostate-directed RT vs standard of care in patients with metastatic disease (Table 1).

Among the 432 patients enrolled in the HORRAD trial with primarily osseous metastatic prostate cancer, OS did not differ between those who received external beam RT (EBRT) to the prostate plus ADT and those who received ADT alone.[27] Although the HORRAD trial did not set out to investigate OMPC, a post hoc subgroup analysis suggested that patients with fewer than 5 bone metastases (89 given ADT + RT, 71 given ADT alone) might benefit from RT. However, these results did not reach statistical significance (hazard ratio [HR], 0.68; 95% CI, 0.42-1.10; $P>.05$). Notably, the RT dose was relatively low, at 70 gray (Gy) administered in 35 fractions, and pelvic lymph nodes were not irradiated.

The STAMPEDE trial compared EBRT to the prostate vs standard of care, defined as lifelong ADT with or without docetaxel chemotherapy.[28] All 2061 patients across 117 hospitals received ADT and were classified by metastatic burden. The authors defined high-burden metastatic disease as the presence of 4 or more bone metastases, at least 1 of them outside the vertebral bodies or pelvis, or the presence of visceral metastases. Of 819 patients, 40% had a low metastatic burden, defined as any disease pattern that did not fit the criteria for a high metastatic burden. The primary outcome was OS. EBRT improved failure-free survival, with failure defined as biochemical failure, disease progression (local, to the lymph nodes, or distant), or death from prostate cancer (HR 0.76; 95% CI, 0.68-0.84; *P*<.0001). Although EBRT did not improve OS in the total cohort, it did improve 3-year OS in the subset of patients with a low metastatic burden. Of the patients with a low metastatic burden, 81% in the EBRT arm had survived at 3 years, compared with 73% in the control arm (HR, 0.68; 95% CI, 0.52-0.90; *P*=.007).

Interpretation of the outcomes of these 2 trials depends in part on the definition used of low vs high metastatic burden. The STOPCAP meta-analysis of the STAMPEDE and HORRAD trials used the HORRAD definitions of low and high metastatic burden to analyze the results of STAMPEDE. (HORRAD defined low-burden disease as the presence of no more than 4 osseous lesions.)[29] The number of bone metastases influenced the effectiveness of prostate RT. Patients with a low metastatic burden benefited more from RT than did those with a high burden. Specifically, the 3-year survival rate of patients with no more than 4 osseous lesions was 77% (compared with 70% when the STAMPEDE definition of low metastatic burden was used).

The results from HORRAD and STAMPEDE suggest that patients with 4 or fewer newly diagnosed osseous metastatic lesions may benefit from RT to the prostate, in addition to standard of care. Ongoing prospective clinical trials, including the SWOG S1802 and PEACE1 trials, will help to answer remaining questions regarding which patient population will benefit the most from local RT.

Metastasis-Directed Therapy: the STOMP, ORIOLE, and SABR-COMET Trials

Most of the evidence on MDT encompasses stereotactic ablative radiotherapy (SABR) in patients with oligometastatic disease. Surgical metastasectomy is also reported in the literature, although it is less commonly performed than SABR. Two published randomized phase 2 trials (STOMP, ORIOLE) have been conducted in patients with recurrent OMPC after primary definitive therapy. Both trials included patients with up to 3 metastases.

The STOMP trial assessed MDT in 62 patients with oligorecurrent prostate cancer.[30] Oligorecurrent cancer was defined as biochemical recurrence with 3 or fewer extracranial metastatic lesions on [^{11}C]choline PET/CT. In this trial, Ost and colleagues reported longer ADT-free survival with SABR than with surveillance alone (21 vs 13 months; HR, 0.60; 80% CI, 0.40-0.90; log-rank *P*=.11). Biochemical recurrence-free survival was significantly longer in the MDT group (HR, 0.53; 95% CI, 0.30-0.94; *P*=.03). Notably, only 6 patients in this trial underwent metastasectomy, and therefore an accurate assessment of this approach is not feasible.

The ORIOLE trial was a multicenter randomized phase 2 trial[31] that compared SABR with surveillance in 54 patients who had previously undergone definitive treatment. Metastases were identified on CT, magnetic resonance imaging (MRI), or radionuclide bone scan. The rate of disease progression at 6 months was lower with SABR than with surveillance (19% vs 61%; *P*=.005). SABR was also associated with better survival at 6 months (HR, 0.3; *P*=.002). The SABR arm also underwent prostate-specific membrane antigen (PSMA) PET/CT at baseline. Owing to blinding logistics, in 16 of 36 patients with PSMA-avid lesions on PET/CT at baseline, some lesions were not included in the treatment fields. Therefore, the authors were able to compare total SABR for all baseline PSMA-avid lesions vs incomplete SABR for some baseline PSMA-avid lesions. Total SABR directed to all PSMA-avid lesions reduced the risk for new lesions at 6 months in comparison with incomplete SABR directed to some PSMA-avid lesions. This finding suggests a role for more advanced imaging in the selection of patients who may benefit most from MDT.

Direct comparisons of the STOMP and ORIOLE trials are limited by differences in the imaging modalities used, study designs, and outcomes assessed. Nevertheless, the fact that both STOMP and ORIOLE found clinical benefits with SABR vs surveillance regardless of the imaging modality is significant. STOMP did not report on OS but did find longer ADT-free survival and longer biochemical recurrence–free survival in patients treated with MDT. ORIOLE assessed OS, although with a relatively short follow-up time of 6 months.

One of the strengths of the ORIOLE trial was its study of the effect of SABR on the systemic adaptive immune response. Phillips and colleagues sequenced T-cell receptors from mononuclear blood cells and found that SABR induced an expanded T-cell receptor response.[31] It is hoped that further studies will enable us to understand whether the longer progression-free survival observed with SABR could be due to a radiobiological mechanism inducing the immune system.

Both ORIOLE and STOMP supported the findings of the SABR-COMET randomized phase 2 trial.[32] In SABR-COMET, 16 patients with prostate cancer received either SABR or systemic therapy. Although the study was not adequately powered to provide significant conclusions regarding SABR in prostate cancer (2 patients in the control arm, 14 in the SABR arm), it found a median OS benefit of 22 months in all patients. Most notably, as new lesions developed, they were treated with salvage SABR. This additional treatment was associated with increased survival.

Combined, these trials suggest that patients with oligorecurrent disease may benefit more from SABR than from surveillance. Longer progression-free survival and OS favor SABR over surveillance. However, larger prospective validations with longer follow-up times are needed before definitive clinical recommendations on the use of SABR for oligorecurrent disease can be made.

Oligorecurrence tends to occur frequently in bone and pelvic nodes.[33] The ongoing RAVENS trial (NCT03361735) is investigating progression-free survival in patients with up to 3 metastases who receive SABR alone vs SABR and radium Ra 223 dichloride (Xofigo, Bayer), a pharmaceutical agent hypothesized to treat micrometastatic bone lesions.[34,35] The STORM trial (NCT03569241) is investigating management approaches for pelvic nodal recurrences.[36]

Several ongoing clinical trials are investigating SABR in metastatic prostate cancer, although not all trials are designed to study oligometastatic disease. The CORE trial (NCT02759783) has completed recruitment and to date has the largest cohort expected to undergo SABR for metastatic prostate cancer (n=245).[37] It will include patients with breast, prostate, or non–small cell lung cancer and randomize them to standard of care or SABR with standard of care.

Safety of Local Radiation Therapy

The safety and feasibility of metastasis-directed RT have been investigated in several studies, including the aforementioned trials. Although a detailed comparison of radiation regimens is beyond the scope of this review, in general most studies have reported few high-grade toxicities as a result of SABR.[38] The side effects depend in part on the location of treatment (nodal vs bone). Reported side effects of SABR include urinary urgency and frequency, diarrhea, nausea, colitis, and bone fracture.[38,39]

The POPSTAR trial was designed to investigate the safety and feasibility of SABR in OMPC. In this study, Siva and colleagues enrolled 21 patients with up to 3 bone metastases on sodium fluoride F 18 PET/CT. Standardized uptake values (SUVs) before SABR and 6 months after SABR were compared. The maximum SUV was reduced in 29 of 33 lesions, reflecting a decreased uptake of sodium fluoride F 18 and therefore decreased osteoblastic activity. Fractures occurred in 3 patients.

In the ORIOLE trial, none of the patients who received MDT experienced grade 2 or higher toxicity, as defined by the Common Terminology Criteria for Adverse Events (CTCAE). Of 36 patients treated with MDT, 6 were reported to have grade 1 toxicity.[31] In the STOMP trial, no CTCAE grade 3 toxicities occurred. In the STAMPEDE trial, severe acute bladder toxicity developed in 4% of the patients undergoing radiotherapy, and 1% had severe acute bowel toxicity (bowel obstruction). The toxicity results of HORRAD await publication. A meta-analysis of 21 studies in which a total of 943 patients received SABR for OMPC found favorable safety profiles, with an acute grade 3 to 5 toxicity rate (defined according to the CTCAE or the toxicity criteria of the Radiation Oncology Therapy Group) of 1.2% and a late grade 3 to 5 toxicity rate of 1.7%.[40]

Observational studies have also found low rates of significant toxicities with RT to the prostate, although these were not conducted solely in an OMPC population. A pooled analysis of 2142 patients with low- or intermediate-risk prostate cancer, according to National Comprehensive Cancer Network (NCCN) risk guidelines, found that stereotactic body RT was not associated with a long-term increase in genitourinary toxic events.[38] In this study, 12.4% of patients with unfavorable intermediate-risk disease had a 7-year OS rate of 86.5%. A retrospective study among 66 men with OMPC (most with ≥2 metastases) who received SABR (1-5 fractions of 5-18 Gy) found no grade 3 toxicities.[41]

The current evidence supports the conclusion that local RT for OMPC is safe and feasible. Furthermore, local RT has been shown across prospective and retrospective studies to control disease progression.

Radical Prostatectomy in OMPC

No prospective studies on resection of the primary tumor have been published to date, although several clinical trials are ongoing (Table 2). One of the largest retrospective studies of local therapy for metastatic prostate cancer was a Surveillance, Epidemiology, and End Results (SEER) Program–based review of 474 patients who received local therapy (313 radical prostatectomy, 151 RT to the prostate).[42] Among these 474 patients, 54 (11%) were classified as having TNM stage M1a disease, 325 (68%) M1b disease, and 95 (20%) M1c disease. Although the study could not specifically include patients with OMPC (SEER does not provide complete information on the number of lesions/sites of disease) and data on the use of systemic therapies were not available, mortality was decreased with

Table 2. Ongoing Trials of Radical Prostatectomy in Oligometastatic Prostate Cancer

Trial (Identifier)	Design	Inclusion	Arms	Primary Outcome(s)	Endpoints
SWOG S1802 (NCT03678025)	Randomized phase 3 open-label study	Histologically or cytologically confirmed PCa, intact prostate, with metastases on technetium bone scan and CT or MRI	SST vs SST + prostatectomy or radiation	OS	Time from randomization to date of death from any cause ≤8 y
TroMbone (ISRCTN15704862)	Randomized phase 2 feasibility study	Newly diagnosed, locally resectable oligometastatic PCa (1-3 skeletal lesions, no visceral lesions) in patients fit for radical prostatectomy	Standard of care vs standard of care + RP	Quality of life, time to castration resistance (PSA)	Change in EQ-5D-5L from baseline at 3 and 6 mo Change in PSA measurements at 3 mo
g-RAMMP (NCT02454543)	Randomized phase 3 open-label study	Histologically confirmed, locally resectable PCa (1-5 bone metastases confirmed on bone scintigraphy, CT, MRI, or PET; no visceral lesions) PSA ≤200 ng/mL at diagnosis	RP + BST vs BST alone	Cancer-specific survival	Time from randomization to death from PCa ≤5 y
FUSCC-OMPCa (NCT02742675)	Randomized phase 2 open-label study	Histologically and cytologically confirmed PCa (≤5 bone metastases on bone scan, CT, or MRI)	ADT vs ADT + definitive treatment (surgery or radiation)	Radiographic progression-free survival	Time from randomization to radiographic progression of disease ≤2 y
SIMCAP (NCT03456843)	Randomized phase 2 open-label study	Histologically confirmed PCa, newly diagnosed metastatic PCa, no previous local therapy	ADT with or without docetaxel vs ADT for ≥1 month before CP with or without docetaxel	Failure-free survival; failure defined as PSA progression, clinical progression, radiographic progression, or death from PCa	Failure-free survival 2 y after randomization

ADT, androgen deprivation therapy; BST, best standard therapy; CP, cytoreductive prostatectomy; CT, computed tomography; EQ-5D-5L, European Quality of Life 5 Dimensions 5-Level Version; MRI, magnetic resonance imaging; OS, overall survival; PCa, prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; RP, radical prostatectomy; SST, standard systemic therapy; y, years.

local therapy vs systemic therapy. Other studies on the effectiveness of cytoreductive prostatectomy (CRP) for OMPC have shown mixed results. In a retrospective study of 111 patients with up to 5 metastases on bone scan (35 treated with CRP + ADT, 76 with ADT alone), no correlation of CRP with clinical progression-free survival or cancer-specific survival was found.[43] A case-control study among a highly selected group of men that compared ADT plus CRP vs ADT alone found that at 37 months, more patients in the ADT group than in the ADT-plus-CRP group required palliative interventions.[20]

CRP with MDT may also prevent disease progression. In a retrospective study of 58 patients with up to 5 metastatic lesions, the subjects received systemic therapy followed by CRP with or without SABR. Castration-resistant prostate cancer–free survival (defined as survival without confirmed biochemical or radiologic progression in the presence of castration levels of plasma testosterone <1.7 nmol/L) was longer in those who received SABR to metastatic sites than in those who did not receive the added therapy.[44]

Regarding the safety of radical prostatectomy, some studies have shown lower complication rates in men who undergo cytoreductive therapy than in those who receive nonsurgical therapy.[45,46] The following ongoing clinical trials will help answer questions regarding the safety of radical prostatectomy in the setting of OMPC.

TroMbone

TroMbone is a randomized phase 2 trial based in the United Kingdom that is investigating radical prostatectomy in 50 patients with only osseous OMPC (ISRCTN15704862). Patients with 1 to 3 metastases found on conventional imaging were randomly assigned to receive standard-of-care systemic therapy or systemic therapy with radical prostatectomy and extended pelvic lymph node dissection. The trial has ended and publication is pending.

SWOG S1802

The Southwest Oncology Group randomized phase 3 trial, based in the United States, is the largest trial to date investigating radical prostatectomy in OMPC, with a goal of enrolling 1273 patients (NCT03678025). Patients will be randomized to standard-of-care systemic therapy or systemic therapy with radical prostatectomy.

g-RAMMP

g-RAMPP is a phase 3 trial that is comparing best systemic therapy and radical prostatectomy vs best systematic therapy alone (NCT02454543). A total of 452 patients with 5 or fewer bone metastases, including stage N1 disease, have been enrolled.

FUSCC-OMPCa

FUSCC-OMPCa is a randomized phase 2 study based in China in which an estimated 200 participants are enrolled (NCT02742675). The trial is comparing ADT alone vs ADT plus definitive treatment with radiation or surgery. The primary outcome is progression-free survival.

Conclusion

Support is growing for local therapy in patients with OMPC. The trials on local RT to the prostate and MDT represent shifting views of a controversial topic. Clinical trials have shown survival benefit when local RT is added to standard of care. Local therapy may also be more suitable for patients with oligorecurrent cancer in comparison with surveillance alone. Because the side effects of systemic therapy can be significant, local therapy may offer an intermediate solution with fewer adverse effects on quality of life. Trials of radical prostatectomy in OMPC are ongoing. Clinical recommendations will be strengthened by a standardized definition for OMPC, larger prospective randomized trials, and meta-analyses to redefine the patient cohorts best suited for local therapy.

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Declarations of Interest

NIH and Philips Healthcare have a Cooperative Research and Development Agreement. NIH has intellectual property in the field, including patents and patent applications ("System, methods, and instrumentation for image guided prostate treatment," US Patent No. 8948845, inventor/author Dr Pinto). NIH and Philips (InVivo Corporation) have a licensing agreement. NIH and Dr Pinto receive royalties for a licensing agreement with Philips/InVivo Corporation. NIH does not endorse or recommend any commercial products, processes, or services. The views and personal opinions of the authors expressed herein do not necessarily reflect those of the US Government, nor do they reflect any official recommendation or opinion of the NIH or the National Cancer Institute. Drs Khondakar, Owens-Walton, Daneshvar, Williams, O'Connor, and Yerram have no disclosures.

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