Oligometastatic Prostate Cancer: A Shrinking Subset or an Opportunity for Cure?

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overview

Oligometastatic prostate cancer (OMPC), generally defined by presence of five or fewer metastatic sites on imaging, represents a transitional state between localized and widespread metastatic disease and encompasses a wide spectrum of disease biologies and clinical behaviors. A collaborative effort is ongoing to determine the genomics of OMPC. The prevalence of OMPC varies significantly in the literature and is likely to change further as substantial improvements in imaging improve our ability to reclassify a subset of patients with biochemical recurrence by conventional imaging as OMPC and another subset from OMPC to polymetastatic disease. The mainstay of OMPC treatment remains systemic therapy, either with androgen-deprivation therapy (ADT) alone or in combination with other agents (docetaxel, abiraterone, etc.). Focal therapies, including resection or radiotherapy (RT), to the primary tumor have demonstrated an improvement in outcomes, including failure-free survival in several retrospective studies. RT to the prostate has specifically demonstrated an overall survival (OS) advantage in patients with low-volume disease in a clinical trial. Improvement in outcomes has been observed with focal therapies for retroperitoneal and more distant metastatic sites in retrospective studies. Advancements in our understanding of the biology, imaging modalities, and treatments may allow for aggressive multimodality therapies in an effort to obtain deeper responses and, potentially, cures for selected patients with OMPC with favorable clinicopathologic characteristics. Participation in clinical trials or institutional registries is strongly encouraged for patients with OMPC who opt for an aggressive multimodality approach.

INTRODUCTION

Of the 1.3 million prostate cancer cases diagnosed worldwide in 2018, approximately 20% had metastatic disease.[1] OMPC is one of the clinical states observed along the spectrum of the natural history of prostate cancer (Fig. 1) and has continued to be an area of interest since it was original proposed by Hellman and Weichselbaum[2] in 1995. This interest has been driven by the allure of obtaining deep remission or possibly cure using more intensive or targeted treatment in this patient population while preserving functional and clinical status.

In this article, we review our understanding of the clinical implications of OMPC, exciting advances in imaging that have resulted in improved detection, and advances in therapeutics that have shown promise in improving its outcomes.

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IMPACT OF TUMOR BURDEN AND PATTERNS OF METASTASES ON SURVIVAL IN PROSTATE CANCER

The number and location of metastatic sites have an impact on survival.[3-6] A Surveillance, Epidemiology, and End Results (SEER)–Medicare analysis of 3,857 patients found that median OS was 43 months for lymph node (LN)–only metastases, 24 months for bone-only metastases, 16 months for visceral-only metastases, and 14 months for bone plus visceral metastases.[7]

In a meta-analysis of 8,820 patients enrolled in nine phase III trials of metastatic castration-resistant prostate cancer, 72.8% of patients had bone with or without nodal metastases, 20.8% had visceral metastases, and 6.4% had nodal-only metastasis. Patients with liver metastases experienced the worst median OS (13.5 months; 95% CI, 12.7–14.4 months) followed by those with lung metastases (median OS, 19.4 months; 95% CI, 17.8–20.7 months), bone metastases (median OS, 21.3 months; 95% CI, 20.8–21.9 months), and nodal-only metastases (median OS, 31.6 months; 95% CI, 27.9–35.5 months).[8]

Outcomes are also progressively worse for increasing numbers of nodal[9] and distant metastases, which serve as a surrogate for tumor burden. In a single-center study of 207 patients with LN metastasis treated with radical prostatectomy and bilateral pelvic LN dissection (PLND), median time to biochemical recurrence in patients with one, two, and three or more LNs was 59, 13, and 3 months, respectively.[10] Another study of 703 patients with localized prostate

PRACTICAL APPLICATIONS

- OMPC, generally defined by the presence of five or fewer metastatic sites on imaging, represents a transitional state between localized and widespread metastatic disease and encompasses a wide spectrum of disease biologies and clinical behaviors.
- A growing body of evidence suggests that a subset of patients with OMPC may achieve a deep and prolonged response with multimodality therapy—combination surgery/radiation and systemic therapy—with improvement in disease-specific outcomes, such as time to castration resistance, PFS, and OS.
- Local cytoreductive therapies, such as radical prostatectomy with or without pelvic LN dissection and RT, seem to be well tolerated in patients with OMPC.
- Pelvic RT has been demonstrated to improve outcomes in patients with high-volume metastatic prostate cancer receiving abiraterone plus aDT.
- Participation in clinical trials or institutional registries is strongly encouraged for patients with OMPC who opt for an aggressive multimodality approach.

cancer with clinically positive LNs treated with radical prostatectomy and extended PLND found that patients with two or fewer positive nodes had significantly better cancer-specific survival outcomes at 15 years of follow-up compared with patients with more than two positive nodes (84% vs. 62%; $p < .001$).[11]

It is also well known that patients with high-volume metastatic prostate cancer have poorer outcomes compared with those with low-volume metastatic prostate cancer.[12,13] This will be discussed in further detail in the following sections.

WHAT IS OLIGOMETASTATIC DISEASE?

No consensus definition exists for oligometastatic disease in prostate cancer. Clinical trials have generally used either three or five metastatic sites on conventional imaging as the cutoff to define oligometastatic disease (Table 1). In clinical practice, it is important to recognize that oligometastatic disease can represent any of the following or their combination: indolent disease biology where the cancer truly is slow growing and/or has limited metastatic potential, diagnosisearly in the metastatic course, or improved detection of the existing metastatic disease as a result of more sensitive imaging modalities.

Support for the assertion that at least a proportion of oligometastatic disease has indolent biology comes from the TROG 03.04 RADAR trial, a randomized phase III trial of 6 versus 18 months of adjuvant ADT with or without zoledronic acid in men with intermediate- and high-risk prostate cancer undergoing RT. Patients with polymetastatic (4 or more) relapse had significantly higher prostate cancer–specific mortality than did those with oligometastatic (3 or fewer bone metastases) relapse (hazard ratio [HR], 2.14; 95% CI, 1.27–3.62; p = .004).[20] It is likely that this is not the case for a substantial proportion of patients with oligometastatic disease, but additional studies are needed to address this question. Advances in imaging modalities that have resulted in an earlier and/or improved detection of oligometastatic disease are detailed in the sections below.

Distinction between de novo—metastatic at the time of initial diagnosis—and recurrent metastatic disease may also be important as these two disease states are likely to have differing biologic and clinical characteristics.[21]

PREVALENCE OF OMPC

Prevalence of OMPC varies significantly in the literature as shown above. It is already possible to reclassify a subset of patients with biochemical recurrence as defined by prostate-specific antigen (PSA) progression without evidence of metastatic disease by conventional imaging as OMPC using more sensitive imaging modalities, such as ^{18}F-fluciclovine PET scan.[22] Improvement in imaging techniques will also result in the reclassification of another subset of patients from OMPC on conventional imaging to polymetastatic disease. It is clear that estimates of prevalence will change further with advances in imaging and treatments for localized disease.

GENOMICS OF OMPC

Genomic landscapes of localized, locally advanced, and metastatic prostate cancers have been studied in great detail,[23-29] but the biology of OMPC remains undefined. In genomic studies of localized and locally advanced prostate cancer, polyclonal tumors were found to be associated with a higher risk of metastatic disease. In addition, the phenomenon of nonlinear clonal evolution in metastatic sites, where clones from metastatic sites can seed other sites, including the primary tumor, has been described in prostate cancer.[26,30,31] A study of 42 samples of primary and metastatic tumors of patients who were treated with stereotactic RT found differences in microRNA expression profiles between samples of patients who developed oligometastatic versus polymetastatic disease. Investigators also evaluated the functional role of microRNAs, finding that miRNA-200c enhancement in the oligometastatic cell line was associated with polymetastatic disease progression.[32] These studies

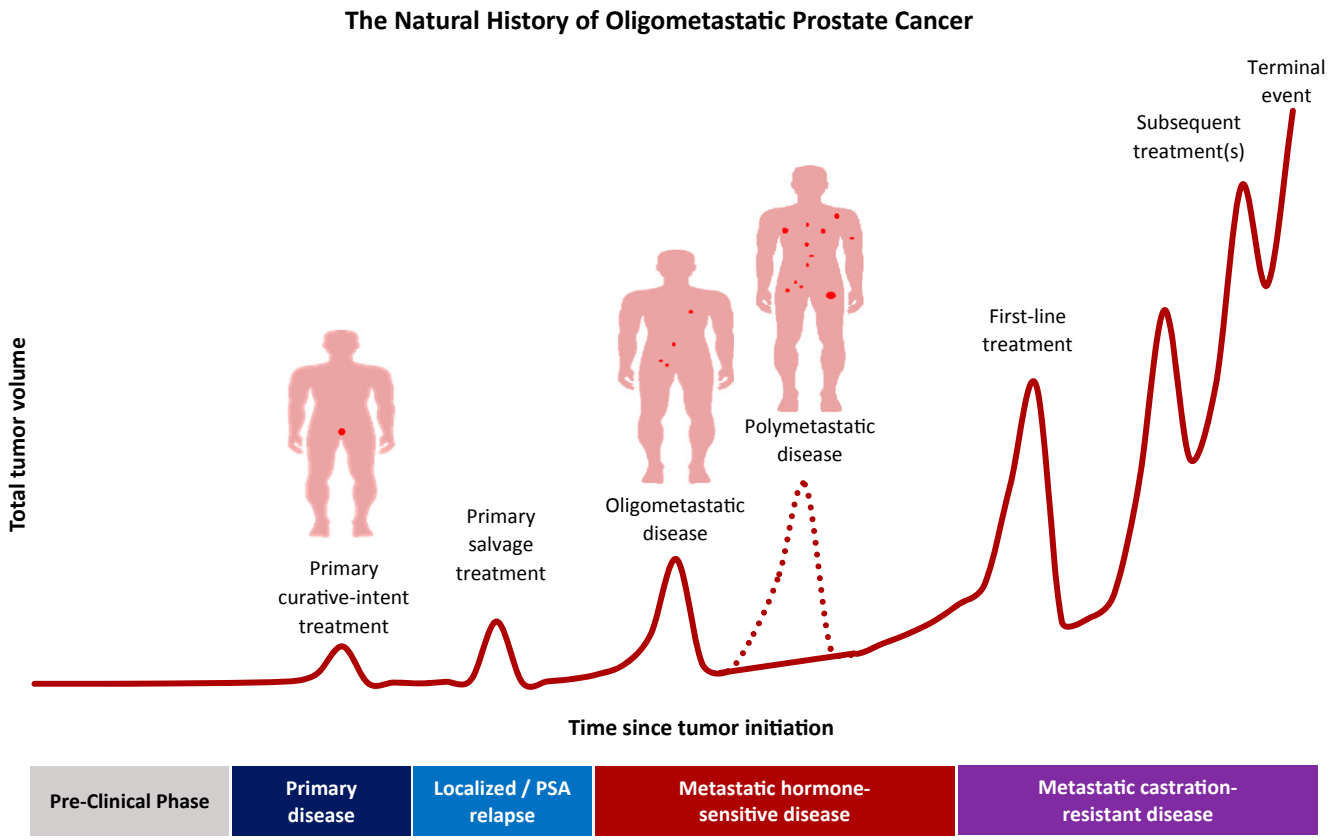

FIGURE 1. Natural History of Oligometastatic Prostate Cancer
Prostate cancer is traditionally divided into various clinical states (colored bar at the bottom), with progressively increasing total tumor burden (y-axis). Relative positions of oligometastatic and polymetastatic disease is demonstrated on this graph with potential implications on total tumor burden and time to castration-resistant disease.

suggest that oligometastatic disease may have a potentially less diverse and differing landscape than polymetastatic disease and the primary tumor. A systematic collaborative effort to elucidate the genomic landscape of OMPC is ongoing.[33]

IMAGING MODALITIES IN THE DETECTION OF OLIGOMETASTATIC DISEASE

Conventional Imaging

CT and ^{99m}Tc bone scans are the two most commonly used imaging modalities for prostate cancer staging and follow-up. Altogether, the sensitivity of CT scan is in the 70%–80% range and bone scan is in the 60%–80% range.[34] Whereas these are widely available, have modest cost, and have been incorporated into clinical practice and guidelines for decades, their limitations have resulted in an evaluation of several novel imaging techniques as detailed below.

Multiparametric Prostate and Whole-Body MRI

MRI offers anatomic and functional assessment using multiple parameters, such as T2-weighted imaging, diffusion-weighted imaging, dynamic contrast-enhanced imaging, and spectroscopic imaging of tumors with a significant improvement in diagnostic performance compared with conventional imaging in the detection of primary tumors and locoregional spread in patients with prostate cancer.[35] Whole-body MRI has shown initial promise as a modality for the assessment of systemic disease. In a study of 96 consecutive patients with newly diagnosed metastatic prostate cancer, whole-body MRI classified 28% of patients with metastatic hormone-sensitive disease and 52% of patients with metastatic castration-resistant prostate cancer as oligometastatic, defined as three or fewer synchronous lesions.[36] Thus, MRI may play a role in appropriate patient selection for aggressive multimodality therapy. It does have limitations, including resource- and time-intensive protocols, variability in scanner performances, susceptibility to motion and other artifacts, and substantially higher cost.

PET Scan

PET is a functional imaging technique that offers the ability to evaluate tumor metabolism. A number of radionuclides

TABLE 1. Definition of Oligometastatic Disease and Imaging Modalities Used in Representative Studies of Oligometastatic Prostate Cancer

Study	Type	Sample Size, No.	Cutoff for Oligometastases, No.	Location of Metastases	Imaging Modality
Singh et al[5]	R; NA	369	≤ 5	Any	^{99m}Tc bone scan
Berkovic et al[14]	P; SA	24	≤ 3	Bone or LN	^{99m}Tc bone scan, ^{18}F-FDG PET/CT, ^{11}C-choline PET/CT
Schick et al[15]	P; SA	50	≤ 4	NR	^{99m}Tc bone scan, ^{18}F-choline PET/CT, ^{11}C-acetate PET/CT
Decaestecker et al[16]	P; SA	50	≤ 3	Bone or LN	^{18}F-FDG PET/CT, ^{18}F-choline PET/CT
Jereczek-Fossa et al[17]	P; SA	69	≤ 1	LN	^{18}F-FDG PET/CT, ^{11}C-choline PET/CT, CT
Ost et al[18]	P; SA	119	≤ 3	Any	^{18}F-FDG PET/CT, ^{18}F-choline PET/CT
Ost et al[19]	P; RA	62	≤ 3	Any	^{18}F-choline PET/CT

Abbreviations: FDG, 18-fluorodeoxyglucose; LN, lymph node; NA, not applicable; NR, not reported; P, prospective; R, retrospective; RA, randomized; SA, single arm.

and tracers have been tested in prostate cancer. Common radionuclides with their associated half-lives are ^{18}F (110 minutes), ^{11}C (20 minutes), and ^{68}Ga (67 minutes). The differences in half-lives have important implications for logistics and feasibility (e.g., shorter half-life isotope generation usually requires an on-site cyclotron), the details of which are beyond the scope of this review. Common tracers include choline, 1-amino-3-fluorocyclobutane-1-carboxylic acid (fluciclovine), prostate-specific membrane antigen (PSMA), 18-fluorodeoxyglucose, and NaF.

^{11}C-Choline PET Scan

Choline is an essential precursor of cell membrane phospholipids and increased uptake of choline has been associated with cell proliferation. Originally developed as a radiotracer for brain tumor imaging, ^{11}C-choline has been extensively studied during the past 20 years.[37] ^{11}C-Choline was approved as a PET radiotracer by the U.S. Food and Drug Administration in 2012 for use in patients with suspected prostate cancer recurrence and noninformative bone scan, CT, or MRI. In a meta-analysis of 12 studies with a total of 1,270 patients undergoing ^{11}C-choline PET/CT scans, pooled overall sensitivity was 89% (95% CI, 83%–93%) and pooled overall specificity was 89% (95% CI, 73%–96%).[38]

^{11}C-Choline PET scans have known limitations, including a lower sensitivity (7%–44%) for patients with a PSA level of less than 1 ng/mL.[39] As a result of the short half-life of ^{11}C, this imaging modality requires an on-site cyclotron. This logistical difficulty and the development of radiotracers with improved performance characteristics have hampered the widespread adoption of ^{11}C-choline PET scan.

^{18}F-Flucivoclone PET Scan

^{18}F-Fluciclovine is a synthetic amino acid that has differential uptake in cancer cells as a result of their higher rates of metabolism. It was approved as a PET radiotracer in 2016 by the U.S. Food and Drug Administration for the detection of suspected prostate cancer recurrence. In a meta-analysis of six studies with 251 total patients, ^{18}F-fluciclovine PET/CT had 87% (95% CI, 80%–92%) pooled per-patient sensitivity, 66% (95% CI, 56%–75%) pooled per-patient specificity, and 0.93 area under the receiver-operating characteristic for the detection of prostate cancer recurrence.[40] The main limitation with this radiotracer is the limited sensitivity of 21%–41% in various studies of patients with a PSA level of less than 1 ng/mL.[39]

^{18}F-Fluciclovine and ^{11}C-choline PET/CT have been prospectively compared in a head-to-head fashion in 89 patients with biochemically recurrent prostate cancer.[41] ^{18}F-Fluciclovine had higher sensitivity (37% vs. 32%) and specificity (67% vs. 40%) compared with ^{11}C-choline. ^{18}F-Fluciclovine also had a higher true-positive rate (6 of 28 patients; 21%) than ^{11}C-choline (4 of 28 patients; 14%) with ^{11}C-choline at PSA levels of less than 1 ng/mL.

PSMA PET Scan

PSMA is a class II membrane glycoprotein with carboxypeptidase activity encoded by the folate hydrolase 1 (*FOLH1*) gene. It was discovered in the LNCaP prostate cancer cell line and is expressed on the apical surface of endothelial cells.[42] It is weakly expressed in normal prostate tissue but strongly upregulated in more than 80% of metastatic prostate cancers. It has been established that PSMA is not fully prostate specific but also expressed in the neovasculature of a wide variety of solid organ malignancies. In addition to prostate tissue, PSMA is only expressed in salivary and seromucous glands of head and neck, duodenal epithelium, and proximal renal tubules, which makes it a biomarker with high specificity for patients with known prostate cancer.[43,44]

As a result of its relative specificity, PSMA conjugated to radionuclides has been extensively evaluated for imaging in prostate cancer. Of these conjugates, ^{68}Ga-PSMA PET/CT has shown the most promise. In a recent meta-analysis of localized or locally advanced prostate cancer, 15 ^{68}Ga-PSMA PET/CT studies with 1,256 patients were evaluated. For patients with PSA levels of less than 1.0 ng/mL, pooled sensitivities for the detection of primary cancer lesion and pelvic LN metastasis were 70% and 61%, respectively, and pooled specificities were 84% and 97%, respectively.[34,45] In another meta-analysis of 16 studies involving 1,309 patients, the overall percentage of positive ^{68}Ga-PSMA PET among patients was 40% (95% CI, 19%–64%) for primary staging and 76% (95% CI, 66%–85%) for biochemical recurrence. A higher pre-PET PSA increased the likelihood of a positive PET scan for patients with biochemical recurrence. For the PSA categories 0–0.2, 0.2–1, 1–2, and greater than 2 ng/mL, 42%, 58%, 76%, and 95% of scans, respectively, were positive. Shorter PSA doubling time increased ^{68}Ga-PSMA PET positivity. Cumulative sensitivity and specificity of ^{68}Ga-PSMA PET were both 86% on a per-patient basis.[46]

18-Fluorodeoxyglucose PET Scan

Standard 18-fluorodeoxyglucose PET scan is widely used in multiple tumor types, but its role in prostate cancer imaging is controversial because of suboptimal performance characteristics that are sometimes attributed to the biology of prostate cancer with low rates of glycolysis.[47]

SURGERY AND RT IN THE SETTING OF OLIGOMETASTATIC DISEASE

It has long been hypothesized that the treatment of primary disease may improve outcomes in metastatic prostate cancer.[48] In fact, 69% of expert panelists in the Advanced Prostate Cancer Consensus Conference 2017—endorsed by the European Association of Urology and the European Organization for Research and Treatment of Cancer—agreed that radical local treatment should be regarded as the appropriate type of treatment for patients with newly diagnosed OMPC.[49]

Biologic Rationale

The likely mechanism for improvement in outcomes with treatment of primary and metastatic sites is thought to be the reduction in total tumor burden. In addition to cytoreduction, RT's synergistic activity with ADT is mediated by several different mechanisms, such as double-strand DNA breaks with resultant apoptosis.[50,51] Emerging evidence also suggests an immunomodulatory effect of the ADT and RT combination.[52]

Clinical Rationale

Systemic therapies for metastatic prostate cancer are noncurative and associated with significant toxicities over the long durations of exposure. Use of focal therapies may allow a subset of patients to delay or interrupt systemic therapy and decrease the burden of adverse effects.

SURGERY IN OMPC

Resection of Primary Prostatic Tumor

Retrospective studies have demonstrated a delay in the time to castration resistance in patients with bony metastatic disease,[53] progression-free survival (PFS), and cancer-specific and OS[7,53-56] after resection of primary prostatic tumor. In one such retrospective SEER-based review of 13,692 patients with metastatic prostate cancer, 474 patients with local treatment were identified: 313 received radical prostatectomy (RP) and 151 RT. In multivariable analysis, local therapy resulted in a lower cancer-specific mortality, with an HR of 0.40 (95% CI, 0.32–0.50; $p < .001$) versus no local therapy. Compared with no local therapy, this benefit was maintained in the treatment subgroups (RP group: HR, 0.35; 95% CI, 0.35–0.46; $p < .001$; RT group: HR, 0.48; 95% CI, 0.35–0.66; $p < .001$).[54]

There are no published prospective studies to help answer this question, but several trials are currently in progress. The first of these is the TRoMbone trial, a randomized phase II trial assessing the feasibility of RP in men with bone-only oligometastatic prostate cancer treated in the United Kingdom. It has completed the planned enrollment of 50 patients and results are expected soon.[57] The SWOG S1802 randomized phase III trial is ongoing in the United States with a planned enrollment of 1,273 patients, making it the largest such trial in this space.[58] A similar randomized phase III trial, G-RAMMP, is ongoing in Germany with a planned enrollment of 452 patients.[59]

PLND

In addition to the retrospective studies above, support for regional LN dissection (i.e., pelvic lymphadenectomy) comes from a pilot study of multimodal therapy. In this study, patients received a minimum 6 months of ADT—started before surgery—with surgical resection of primary and retroperitoneal LNs and RT to the prostate bed with or without pelvic or para-aortic LNs and up to 10 bone metastases or nonregional LN.[60] Of the 20 patients treated, 17 (85%) had Gleason scores of 8 or greater, 14 (70%) had pathologic T3 or higher disease, 11 (55%) had pelvic nodal (N1) disease, seven (35%) had extrapelvic nodal (M1a) disease, and 15 had (75%) bony metastatic (M1b) disease.

Fourteen patients (70%) received RP and PLND, and the remainder (6 patients; 30%) received RP plus PLND and retroperitoneal LN dissection. Two patients (13%) received postoperative RT to the prostate bed and pelvic LN basins on the basis of surgical findings of grossly positive margins or nodal disease with extranodal extension. Twelve patients

(80%) received hypofractionated stereotactic body RT (SBRT) to osseous metastases, which encompassed all visible disease on bone scan in 10 patients. Most patients were treated at one to three sites of bone metastasis, and three patients were treated at four or five sites. Of these, 10 were treated postoperatively after a median of 4 months (range, 2–15 months) of ADT, and two patients with symptoms were treated preoperatively.

Altogether, 95% of patients achieved an undetectable PSA with multimodal treatment, including 25% after ADT alone and an additional 50% and 20% after surgery and RT, respectively. The proportion of patients who achieved undetectable PSA increased with each component of multimodal therapy. Within the follow-up period, 20% of patients—all with M1b disease—achieved the primary endpoint of undetectable PSA after testosterone recovery, which persisted for 5, 6, 27 or more, and 46 or more months.

Resection of Distant Oligometastatic Sites

Multiple retrospective studies have demonstrated an improvement in outcomes with metastasis-directed therapies (MDT), including retroperitoneal LN dissection for patients with nodal-only recurrences of prostate cancer.[61] In one such study of patients with biochemical recurrence, 1,816 patients in the standard-of-care cohort received ADT only, whereas patients in the MDT cohort underwent either salvage LN dissection (166 patients) or SBRT to PET-avid nodes (97 patients). MDT was associated with an improved cancer-specific survival (HR, 0.33; 95% CI, 0.17–0.64), suggesting that this may be an option in selected patients.[62]

The utility of MDT was validated in the STOMP trial, which was a multicenter, randomized, phase II study of patients with asymptomatic biochemically recurrent, hormone-sensitive oligometastatic disease (3 or fewer lesions on ^{11}C-choline PET/CT scan). Patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions (surgery or SBRT). MDT was associated with a higher ADT-free survival (median, 21 months; 80% CI, 14–29 months) compared with surveillance alone (median, 13 months; 80% CI, 12–17 months), translating into a 40% less likelihood of needing systemic therapy for oligometastatic disease (HR, 0.60; 80% CI, 0.40–0.90; p = .11). Six patients developed grade 1 toxicity in the MDT arm, but no grade 2–5 toxicities were observed. Quality of life (QOL) was similar between arms at baseline and at 3 months and 1 year of follow-up.[19]

A key limitation of the STOMP trial pertaining to surgical resection for oligometastatic disease is that only six patients underwent surgical resection in the trial, five of whom received PLND and only one lung metastatectomy. Thus, there are insufficient data to inform decision-making for surgical resection of oligometastatic disease that has spread beyond the retroperitoneal LNs. When possible, enrollment in a clinical trial should be considered for such patients.

RADIATION THERAPY IN OMPC

Treatment of Primary Prostatic Tumor and Pelvic LNs

Two randomized trials evaluating the value of adding prostate RT to standard-of-care therapy in patients with newly diagnosed metastatic prostate cancer have been published.

HORRAD trial The HORRAD trial was a multicenter, randomized controlled trial of 432 patients with PSA levels of more than 20 ng/mL and bone-predominant metastatic prostate cancer. Patients were randomly assigned (1:1) to external beam RT (70 Gy in 35 fractions or 57.76 Gy in 19 fractions) to the prostate with ADT (RT group) or ADT alone (control group). Pelvic LNs were not included in the radiation field.

No benefit was observed with the addition of RT. Median OS was 45 months (95% CI, 40.4 to 49.6 months) in the RT group and 43 months (95% CI, 32.6–53.4 months) in the control group (adjusted HR, 1.11; 95% CI, 0.87–1.43; p = .4). Survival outcomes were comparable between the two groups for patients with fewer than five lesions (HR, 0.68; 95% CI, 0.42–1.10), five to 15 lesions (HR, 1.18; 95% CI, 0.74–1.89), and more than 15 lesions (HR, 0.93; 95% CI, 0.66–1.32).

There are several important limitations of the HORRAD trial. First was the lack of assessment of visceral and bone metastatic disease, as patient selection was based on bone scan alone. Another hint that this trial actually had patients with much higher metastatic burden was the high median PSA of 142 ng/mL. The treatment regimen also used a lower dose of RT (70 Gy to prostate only; regional LNs were not included) than the current practice of 72–82 Gy, including the LNs. Despite the lack of statistical power, there was a suggestion that survival curves began to separate at the 2-year mark for patients with lower-risk disease (PSA $<$ 142, fewer than 5 bone metastases, and Gleason $\leq$ 8).

STAMPEDE trial The STAMPEDE trial is an ongoing multicenter, multiarm, randomized controlled trial at 117 centers in the United Kingdom and Switzerland.[63] An analysis of 2,061 enrolled patients with newly diagnosed metastatic prostate cancer with no prior therapies randomly assigned (1:1) to standard of care (treatment consisted of ADT with or without docetaxel) versus standard of care plus RT (RT group; RT dose was 55 Gy in 20 fractions or 36 Gy in 6 fractions) was recently reported.[63] High metastatic burden was defined as per the CHAARTED trial definition of four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. All other patients were considered to have low metastatic

burden. Approximately 42% of patients in either group had low-burden metastatic disease.

In the cumulative intent-to-treat population, RT improved failure-free survival compared with standard of care alone (HR 0.76; 95% CI, 0.68–0.84; $p < .0001$), but OS was not improved (HR 0.92; 95% CI, 0.80–1.06; $p = .266$). However, in a prespecified subgroup analysis in patients with a low metastatic burden (819 patients), RT improved failure-free survival (HR 0.59; 95% CI, 0.49–0.72; $p < .0001$) and 3-year OS (81% vs. 73%; HR 0.68; 95% CI, 0.52–0.90; $p = .007$). Patients with a high metastatic burden did not benefit from RT in terms of failure-free survival or OS.

The mixed results from these two trials require oncologists to recognize their limitations before integrating RT into their treatment algorithm. For example, in the STAMPEDE trial analysis detailed above, standard-of-care therapy comprised ADT alone for over 80% of patients. Whether the benefit seen with RT persists with combination systemic therapies is unclear. While both doses of RT (36 Gy in 6 weekly fractions, or 55 Gy in 20 daily fractions) were well tolerated in the short term, the ideal dose of RT to maximize outcomes and minimize long-term toxicities is unknown.

Despite these limitations, it is reasonable to offer patients with low-volume, newly diagnosed metastatic prostate cancer the option of RT to improve outcomes. Continued assessment of genomic and clinicopathologic characteristics of these patients is needed to further refine the subset most likely to benefit from this approach. A large, randomized phase III trial (SWOG S1802) is currently enrolling patients with newly diagnosed metastatic prostate cancer to either standard systemic therapy (ADT or ADT plus abiraterone acetate) or standard systemic therapy in combination with the definitive treatment of the primary tumor with RP or RT. [58] This large trial has planned enrollment of 1,273 patients and will hopefully enable us to answer this question in a more decisive fashion.

Metastasis-Directed RT

RT to retroperitoneal LN metastases has been evaluated in several retrospective and a couple of prospective trials as detailed in the Resection of Distant Oligometastatic Sites section above.

A retrospective cohort study of 40 patients with newly diagnosed prostate cancer with oligometastatic diseases treated with a combination of prostate high-dose rate brachytherapy, external beam RT, and ADT has been recently published.[64] Of these patients, only three (7%) had retroperitoneal nodal metastases and only 15 (38%) had distant bone-only metastases. Eighteen patients received metastasis-directed RT. Castration-resistant prostate cancer–free interval favored the metastasis-directed RT arm for these patients but did not reach statistical significance.

Several clinical trials are ongoing to evaluate the role of RT to nonretroperitoneal distant metastatic sites in prostate cancer (NCT02206334, NCT01859221, NCT03160794, NCT00544830, NCT03449719, and NCT03784755), and many of these trials specifically assess the oligometastatic disease population.[65-70]

Analysis of POPSTAR trial, a single-arm, prospective clinical trial that assessed the safety and feasibility of SBRT (20 Gy, single fraction per site) to all metastatic sites in patients with oligometastatic prostate cancer (3 or fewer sites of nodal or bony metastases as detected by NaF PET scan) was recently published.[71] Thirty-three patients received SBRT to 50 oligometastatic sites, 32 of which successfully completed treatment (feasibility rate, 97%; 95% CI, 84%–100%). Only one grade 3 adverse event (fracture) and no grade 4 or 5 events were observed. In 22 patients who had hormone-sensitive disease, freedom from ADT treatment at 24 months was 48% (95% CI, 31%–75%). These data suggest that SBRT to distant nodal and bony metastatic sites is feasible, well tolerated, and potentially effective in delaying time to systemic therapy.

SYSTEMIC THERAPY FOR OMPC

Systemic therapy with ADT alone or in combination with another agent remains the standard of care for patients with OMPC. In patients with newly diagnosed hormone-sensitive OMPC, abiraterone plus ADT, docetaxel plus ADT, or ADT alone are potential U.S. Food and Drug Administration–approved options. We recommend individualizing therapy on the basis of patient characteristics (age and comorbidities), disease characteristics (time from primary therapy to relapse, absolute PSA, and PSA doubling time), pattern of metastatic disease (visceral with or without bone metastases and axial skeletal metastases), and willingness to tolerate additive risks of combination therapies.

Docetaxel Plus ADT

Three trials—STAMPEDE,[72] CHAARTED,[73] and GETUG-AFU15[74]—have evaluated the use of docetaxel in metastatic hormone-sensitive prostate cancer. Definitions of burden of metastatic disease (high vs. low) used in these trials were consistent and are detailed in Table 2. In the updated analysis of the CHAARTED trial, median OS was 57.6 months for chemohormonal therapy versus 47.2 months for ADT alone (HR 0.72; 95% CI, 0.59–0.89; $p = .0018$). Survival benefit was limited to patients with high-volume disease, with a median OS of 51.2 months in the chemohormonal therapy arm versus 34.4 months in the ADT-alone arm (HR 0.63; 95% CI, 0.50–0.79; $p < .001$). No OS benefit was observed in patients with low-volume disease (HR 1.04; 95% CI, 0.70–1.55; $p = .86$).

A network meta-analysis of these trials confirmed the magnitude of OS benefit in patients with high-volume

TABLE 2. Definition of High- Versus Low-Volume Disease Used in Contemporary Studies in Prostate Cancer

Trial	High Volume	Low Volume
Glass et al[12]	(Extensive disease)	(Minimal disease)
	Appendicular skeletal metastases and/or visceral metastases	Nodal metastases and/or axial skeletal metastases
CHAARTED trial[73]	≥ 4 bone metastases with one or more outside the vertebral bodies and pelvis and/or visceral metastases (extranodal)	All others
STAMPEDE trial[72]	Same as the CHAARTED trial	Same as the CHAARTED trial
GETUG-AFU15 trial[74]	Same as the CHAARTED trial	Same as the CHAARTED trial
LATITUDE trial[75]	Two or more of the following: visceral metastases, > 3 bone metastases, Gleason score ≥ 8	Only one of the following: visceral metastases, > 3 bone metastases, Gleason score ≥ 8

disease receiving chemohormonal or abiraterone plus ADT therapy. Pooled HR for OS in docetaxel plus ADT compared with ADT alone was 0.75 (95% CI, 0.63–0.91; I2 = 51%; 3 trials; 2,951 patients). However, only abiraterone plus ADT appeared to improve OS compared with ADT alone in patients with low-volume metastatic hormone-sensitive prostate cancer (pooled HR 0.65; 95% CI, 0.45–0.96).[76]

QOL is an important consideration in this patient population as they tend to have preserved functional status and minimal symptom burden at baseline. In the CHAARTED trial, chemohormonal therapy had a statistically worse 3-month QOL compared with ADT alone, there was a reversal in QOL at 12 months (chemohormonal therapy performing better than ADT alone), and QOL remained minimally changed over time in both arms, which suggests that chemohormonal therapy does not have a negative impact on intermediate- or long-term QOL.[77]

Sequencing of Docetaxel Plus ADT in Multimodality Therapy

As a result of the limited duration of chemotherapy, surgical intervention, such as resection of residual disease or primary tumor as above, should be undertaken after the completion of six cycles of chemotherapy to prevent treatment interruption and minimize surgical complications, such as infection and bleeding. There is limited experience regarding the sequencing of chemohormonal therapy and radiation. RTOG 0521 was an open-label, randomized, multicenter trial of 612 patients with high-risk localized prostate cancer. Patients were randomly assigned to RT plus docetaxel and ADT arm with six cycles of docetaxel 75 mg/m^2 every 21 days starting 28 days after the completion of 72.0–75.6 Gy in 40–42 fractions of RT. The control arm (RT + ADT) received similar doses of RT. Two years of concurrent ADT was also administered to patients in both arms, starting 8 weeks before RT. The combination approach had an acceptable adverse effect profile.

Abiraterone Plus ADT

The strongest evidence to support the use of abiraterone plus ADT in patients undergoing multimodality therapy comes from the STAMPEDE trial as discussed above.

In a meta-analysis of the LATITUDE[75] and STAMPEDE trials, a 38% reduction in the risk of death was observed with abiraterone plus ADT compared with ADT alone (HR 0.62; 95% CI, 0.53–0.71; $p = 0.55 \times 10^{-10}$). This translated into a 14% absolute improvement in 3-year OS. Abiraterone plus ADT also demonstrated a 28% improvement in 3-year clinical/radiographic PFS compared with ADT alone (HR 0.45; 95% CI, 0.40–0.51; $p = 0.66 \times 10^{-36}$). There were more grade 3 and 4 acute cardiovascular and hepatic toxicities with abiraterone plus ADT.[78]

QOL outcomes with abiraterone plus ADT therapy in the LATITUDE trial have been reported.[79] Median time to deterioration of functional status—assessed by the Functional Assessment of Cancer Therapy-Prostate scale—was 12.9 months (95% CI, 9.0–16.6 months) in the abiraterone plus ADT arm compared with 8.3 months (95% CI, 7.4–11.1 months) in the ADT plus placebo arm (HR 0.85; 95% CI, 0.74–0.99; p = .032). Abiraterone plus ADT showed an improvement in pain progression, prostate cancer symptom severity, functional decline, and overall QOL compared with the ADT plus placebo group.

The duration of such therapy remains undefined, but experience from the LATITUDE trial suggests that as many as 25% of patients are expected to discontinue abiraterone therapy at the 2-year mark primarily because of adverse effects.[75]

Sequencing of Abiraterone Plus ADT in Multimodality Therapy

Abiraterone has no known propensity to increase perioperative complication risk. In a randomized phase II trial of 12 versus 24 weeks of neoadjuvant abiraterone, prednisone, and ADT in patients undergoing RP, no significant increase in perioperative complications was found.[80] Data regarding the concurrent use of abiraterone and RT from the STAMPEDE trial is detailed above and this combination seems to be feasible and well tolerated.

Enzalutamide Plus ADT

Data from the randomized phase III trial of ADT with either enzalutamide or placebo (1:1 allocation) in patients with

newly diagnosed metastatic hormone-sensitive prostate cancer was presented recently.[81] Of the 1,150 patients enrolled, 354 (48%) had low-volume disease by CHAARTED trial definition. Enzalutamide plus ADT significantly improved radiographic PFS in the intention-to-treat population (not reached in enzalutamide arm vs. 19.4 months in placebo arm; HR 0.39; 95% CI, 0.30–0.50; $p < .0001$). OS data is not yet mature. Subgroup analysis showed that compared with placebo plus ADT, enzalutamide plus ADT improved radiographic PFS in patients with low-volume disease (HR 0.24; 95% CI, 0.13–0.45) and those with high-volume disease (HR 0.44; 95% CI, 0.33–0.57). The results of this large phase III trial support the use of enzalutamide plus ADT for patients with low-volume metastatic hormone-sensitive prostate cancer. While the median number of metastatic sites were not reported, it is likely that a significant proportion of patients with low-volume disease will meet the criteria for oligometastatic disease, allowing enzalutamide plus ADT to be used as an option for these patients.

Ongoing Clinical Trials

Several trials that are currently ongoing in the metastatic hormone-sensitive prostate cancer space are expected to include patients with oligometastatic disease. For example, ARASENS is a randomized phase III trial of darolutamide in combination with docetaxel for men with metastatic hormone-sensitive prostate cancer (NCT02799602). The STAMPEDE trial is also testing a combination of abiraterone, enzalutamide, and ADT in patients with metastatic hormone-sensitive prostate cancer (NCT00268476). And finally, PEACE1 is a four-arm randomized phase 3 trial that is testing a combination of docetaxel and abiraterone in patients with metastatic hormone-sensitive prostate cancer (NCT01957436). A meta-analysis of data for patients with oligometastatic disease enrolled on these trials would potentially allow for a better treatment customization for this subgroup.

Concern Regarding Overtreatment of Oligometastatic Disease

There have been several exciting developments in therapeutic options for patients with oligometastatic disease as detailed above. This raises the concern as to whether we are or will be overtreating at least a subset of patients with oligometastatic cancer disease. An example would be an 80-year-old man with two sites of metastatic recurrence (pelvis and L2 vertebral body) 5 years after a RP. An argument could be made to treat this patient with ADT alone, ADT plus abiraterone indefinitely, or even ADT plus focal RT. The number of treatment options is only expected to increase in the coming years, and it is important to periodically revisit the question of the optimal treatment approach for oligometastatic disease as well as continue efforts to better genomically characterize these patients to increase our confidence in the treatment decision.

CONCLUSION

OMPC is a challenging disease state to treat as it likely represents diverse disease biologies with varying clinical trajectories. Treatment options are rapidly evolving and there seems to be sufficient evidence to justify multimodality therapy in selected patients to achieve deeper responses. Whenever possible, such an approach should be undertaken within the setting of a clinical trial or an institutional registry to inform decision-making in the future.

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