SA-CME (appliedradiology.org/SAM)

# Management of Oligometastatic Prostate Cancer

James R. Broughman, MD; Christopher W. Fleming, MD; Omar Y. Mian, MD, PhD; Kevin L. Stephans, MD; Rahul D. Tendulkar, MD

Metastatic prostate cancer has long been considered incurable and managed with systemic therapies alone. However, there is increasing evidence of an "oligometastatic" state where patients with low-volume metastatic disease may achieve sustained disease-free intervals as well as potentially improved overall survival (OS) with combinations of systemic and local therapy. The concept of oligometastatic disease was first described by Hellman and Weichselbaum who hypothesized that there may be an intermediate state between locally confined disease and fulminant metastatic disease.[1] Accordingly, recent data suggests that aggressive treatment of the primary tumor or metastasis-directed therapy (MDT) may confer a survival advantage in carefully selected patients with metastatic prostate cancer.[2-4]

Among the 190,000 new cases of prostate cancer diagnosed each year in the US, about 20% present with primary metastatic disease.[5,6] Prostate-specific antigen (PSA) screening and imaging advances have led to a relative increase in the detection of cases with early metastatic disease. Even after detection of distant metastases (DM), metastatic prostate cancer is relatively indolent and marked by a long disease course.[7] Due to its long natural history, prostate cancer has been at the forefront of efforts investigating aggressive treatment in oligometastatic disease. In this review we aim to outline treatment approaches for these patients, while highlighting existing literature, ongoing trials, and important areas for future study.

## Defining the Oligometastatic State

Although the definition of oligometastatic disease varies considerably in the literature, most definitions limit the maximum number of metastatic sites to between 3 to 5.[8] Furthermore, a major challenge in synthesizing the available literature is the wide array of clinical scenarios represented. In the landmark paper by Hellman and Weicheslbaum, the authors described two scenarios that both fell under the umbrella of oligometastatic disease, but likely have different clinical courses. The first are "tumors early in the chain of progression with metastases limited in number and location" and "another group of patients with oligometastases who had widespread metastases that were mostly eradicated by systemic agents, the chemotherapy having failed to destroy those remaining because of the number of tumor cells, the presence of drug-resistant cells, or the tumor foci being located in some pharmacologically privileged site." Consequently, more granularity is needed when describing oligometastatic disease. One such effort is the European Society for Radiotherapy and Oncology and European Organization for Research and Treatment of Cancer (ESTRO/EORTC) consensus recommendations for characterization and classification of oligometastatic disease, which identified 9 distinct states of oligometastatic disease.[9] Standardized definitions of oligometastatic disease will lead to a more uniform understanding of study results and allow for cross-study comparisons.

## Role of Prostate-directed Therapy

Many have hypothesized that treatment of the primary tumor in the set-

***Dr. Broughman*** *is a PGY4 chief resident,* ***Dr. Fleming*** *is a PGY5 resident, and* ***Dr. Stephans, Dr. Mian,*** *and* ***Dr. Tendulkar*** *are associate staff, all in the Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, OH.* *Disclosure: Dr. Tendulkar has received honoraria from Varian for educational talks. No other authors have conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

ting of metastatic disease could lead to improved clinical outcomes due to cytoreduction, reduced seeding of new metastases, and stimulation of an anti-tumor immune response. Indeed, some prospective studies across various disease sites have reported improved outcomes with treatment of the primary tumor,[10-12] although this remains controversial.[13,14] Within the realm of prostate cancer, there is increasing prospective data to support prostate-directed radiation therapy (RT) in carefully selected patients with metastatic disease. The HORRAD and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials have established a survival benefit to prostate-directed RT in patients with low-volume metastatic disease. HORRAD was a phase III randomized trial investigating the addition of prostate-directed RT to lifelong androgen deprivation therapy (ADT) in men with newly diagnosed prostate cancer with bone metastases.[15] Patients received 70 Gray (Gy) in 35 daily fractions or 57.76 Gy in 19 fractions 3 times per week to the prostate. There was no difference in OS for the entire cohort; however, an unplanned subgroup analysis suggested a potential benefit in patients with 4 or fewer bone lesions, although this did not reach significance (HR 0.68, 95% CI 0.42-1.10). STAMPEDE is a multi-arm, phase III randomized trial that investigated the role of delivering RT to the prostate in men with newly diagnosed metastatic prostate cancer receiving lifelong ADT.[3] Patients could receive either 36 Gy in 6 weekly fractions, or 55 Gy in 20 daily fractions. Radiation fields did not include pelvic nodes or any metastatic sites. Prostate-directed RT was well tolerated with only 5% experiencing acute grade 3-4 radiation toxicity (4% GU and 1% GU). While no OS benefit was seen in the entire population, a pre-specified subgroup analysis of patients with low-volume disease showed a statistically significant improvement in 3-year OS from 73% to 81%. High-volume disease was defined as 4 or more bone metastases with 1 or more outside the vertebral bodies or pelvis, or visceral metastases; all other patients were considered to have low-volume disease. The Systemic Treatment Options for Prostate Cancer (STOPCAP) meta-analysis of the 2 preceding trials reclassified STAMPEDE patients into low- or high-volume using the HORRAD definition of 4 or fewer bone lesions, and found a statistically significant survival benefit in low-volume patients, with RT improving the 3-year survival rate from 70% to 77%.[16]

Taken together, these studies support prostate-directed RT for patients with limited metastatic disease. Additional ongoing trials such as Patients With Metastatic Hormone-naïve Prostate Cancer (PEACE-1), Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (G-RAMMP), Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone (TRoMbone), STAMPEDE arm M, and SWOG 1802 will further clarify the role of prostate-directed therapy, including surgery, in the era of modern systemic therapy for metastatic prostate cancer.[17-21]

## Role of Metastasis-directed Therapy

An important limitation of defining oligometastatic disease by the number of lesions is reliance on imaging techniques that are neither perfectly sensitive nor specific. Emerging imaging techniques have allowed for more accurate characterization of disease burden. The most promising of these is prostate-specific membrane antigen (PSMA) positron emission tomography – computed tomography (PET-CT), which has demonstrated superior performance compared to conventional imaging and other contemporary radiotracers.[22,23] Unfortunately, PSMA PET-CT is not approved by the Food and Drug Administration and, therefore, is unavailable in the US. A readily available alternative is $^{18}$F-fluciclovine (Axumin) PET-CT, which is commercially available in the US and demonstrates superior sensitivity and specificity compared to conventional imaging modalities.[24] These imaging improvements have led to detection of metastases in some patients who would have previously been classified as having localized disease, and polymetastases in some who would have been classified as having oligometastatic disease. Additionally, advanced imaging allows for accurate characterization and subsequent treatment of the full extent of oligometastatic disease.

The importance of pretreatment imaging on the efficacy of MDT was shown by the randomized phase II Observation in Oligometastatic Prostate Cancer (ORIOLE) study.[25] Fifty-four men with recurrent, hormone-sensitive prostate cancer with 3 or fewer lesions were randomized to stereotactic body radiation therapy (SBRT) to all metastatic lesions or observation. Salvage RT to the prostate bed or pelvis was permitted, and patients were allowed to receive ADT or other systemic therapy during initial management or salvage treatment, but not within 6 months of enrollment. SBRT patients received 19.5 to 48.0 Gy in 3 to 5 fractions. Those randomized to MDT underwent a PSMA scan prior to MDT; however, the treating radiation oncologists were blinded to the results of PSMA and selected targets were based only on CT, MRI, or bone scan. PSMA scans were then compared to treatment plans, and patients were categorized as having had total (n = 19) or subtotal (n = 16) consolidation of PSMA-avid lesions. The proportion

of men with disease progression at 6 months was 10% in the SBRT arm vs 61% in the observation arm ($P$=0.005). Within the SBRT group, patients who had undergone total consolidation had significantly reduced rates of new metastases at 6 months compared with those who had undergone subtotal consolidation (16% vs 63%, $P$ = 0.006). There were no grade 3 or higher adverse events, and no significant differences in quality of life (QOL) between the two groups. Median distant metastasis-free survival was 29 months in men with no untreated lesions and 6 months in men with any untreated lesions. These results highlight the importance of optimal pretreatment imaging in maximizing the efficacy of MDT.

Traditionally, management of metastatic prostate cancer has consisted of lifelong ADT alone. However, long-term ADT and its hypogonadal sequelae negatively impact QOL with side effects including hot flashes, fatigue, weight gain, mood changes, and sexual dysfunction. Advances in radiation planning have made it possible to deliver ablative doses of radiation to sites of metastatic disease with minimal toxicity while delaying initiation of ADT. The role of MDT in delaying systemic therapy was demonstrated in the phase II STOMP trial, which randomized patients with biochemically recurrent prostate cancer with 1 to 3 lesions (nodal or metastatic) on choline PET-CT to observation vs MDT (surgery or SBRT) to all detected lesions, with the primary endpoint of ADT-free survival.[26] Patients undergoing SBRT received 30 Gy in 3 fractions. ADT was given for progression of symptoms, progression to more than 3 metastases, or progression of known lesions. Asymptomatic progression in 3 or fewer new lesions could be treated with further MDT. Tolerance of MDT was excellent with no grade 2 or higher toxicity reported. The time to both PSA progression and initiation of ADT was longer in the MDT arm, with an increase in median ADT-free survival from 13 to 21 months. PSA doubling times ≤ 3 months were predictive of a larger magnitude of benefit from MDT. Five-year ADT-free survival increased 8% to 34% with MDT, showing that some patients may delay systemic therapy for a prolonged period. Additionally, 76% of the MDT group remained castration sensitive at 5 years, as opposed to 53% in the surveillance group.[27] Longer follow-up is required to determine the effect of MDT and delayed onset of metastatic castrate-resistant prostate cancer on survival.

Despite attempts to delay systemic therapy using MDT, ADT remains the standard-of-care treatment for patients with metastatic prostate cancer, and delivery of consolidative MDT with concurrent ADT may represent a viable form of treatment intensification. Results of the phase II Stereotactic Ablative Radiotherapy Versus Standard of Care Palliative Treatment in Patients With Oligometastatic Cancers (SABR-COMET) trial support the use of concurrent MDT and systemic therapy. Patients with 1-5 metastatic lesions and a controlled primary tumor were randomized to receive standard-of-care treatment with or without SBRT to all oligometastatic sites. Sixteen patients with prostate cancer were included (16% of the study population). Importantly, standard-of-care systemic therapy was recommended as indicated, and choice of systemic agent was left to the discretion of the treating medical oncologist. Nearly 60% of patients in both arms received systemic therapy after MDT. Patients in the MDT arm had improved median progression-free survival from 5.4 to 11.6 months ($P$ = 0.001), as well as improved OS from 28 to 50 months ($P$ = 0.006) with no significant change in QOL.[28] The results of SABR-COMET illustrate the potential survival benefits of integrating MDT into standard-of-care systemic therapy.

## Role of Systemic Therapy

Although ADT remains the backbone of treatment for metastatic prostate cancer, the optimal duration of systemic therapy in the oligometastatic setting is unknown. Patients with widespread metastatic disease generally receive lifelong ADT. Conversely, patients with high-risk localized disease treated with RT are recommended to receive up to 3 years of long-term ADT.[29,30] Presumably, just as oligometastatic tumor burden lies between these two states, so too does optimal ADT duration.

The optimal choice of systemic therapy is also unknown, but likely includes the addition of a second agent to ADT. The Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) and TITAN trials found a survival benefit with the use of enzalutamide and apalutamide, respectively, for metastatic patients with either high- or low-volume metastatic disease.[31,32] The STAMPEDE arm randomizing patients to ADT with or without abiraterone enrolled half nonmetastatic patients; an OS benefit was seen with the addition of abiraterone for all patients, including those with nonmetastatic and low-volume metastatic disease.[33] Data for docetaxel in limited volume disease has been mixed, with the STAMPEDE investigators finding benefit for both high- and low-volume patients,[34] whereas the Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED) trial found a benefit for only those with high-volume disease.[35]

Accordingly, for optimal disease control, data suggests that systemic therapy and MDT, as well as treatment of the prostate, should be incorporated into the treatment of oligometastatic patients. However, the optimal ADT duration and sequencing of systemic and local therapy remains unknown.

## Treatment of Isolated Nodal Recurrences

Isolated pelvic nodal disease represents a unique scenario within the array of oligometastatic disease states, in that regionally metastatic disease signifies an early intermediate point on the spectrum between locally confined and diffusely metastatic disease. A Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis of nearly 4,000 patients with metastatic prostate cancer demonstrated a median OS of 43 months, 24 months, 16 months, and 14 months for those with nodal metastases, bone metastases, visceral metastases, and bone plus visceral metastases, respectively.[36] As such, the potential for durable disease control with curative-intent salvage therapies is higher in this cohort than in other types of oligometastatic patients, and aggressive definitive therapy such as ADT and whole-pelvis RT with an additional boost to gross disease should be considered. SBRT can be considered; however, at least one pattern of failure analysis found that 68% of relapses after nodal SBRT occurred in other regional nodal regions.[37] Therapeutic lymphadenectomy is a reasonable alternative to RT. A recent systematic review of 27 series reporting outcomes after lymph-node dissection for recurrent prostate cancer found complete biochemical response in a mean of 44% of cases, showing the potential for nodal-confined disease.[38] The ideal extent of lymph-node dissection is unknown, but more extensive dissection has been associated with improved PSA response.[39] The ongoing Salvage Treatment of Oligorecurrent Nodal Prostate Cancer Metastases (STORM) trial seeks to provide insight into optimal management for these patients; men with oligorecurrent prostate cancer isolated to the pelvic lymph nodes will receive 6 months of ADT along with MDT, and are subsequently randomized to pelvic RT or not.[3]

## Conclusion

There is increasing evidence of an oligometastatic state, an intermediate between localized and polymetastatic disease, in which patients may experience prolonged survival with multimodality combinations of local and systemic therapy. Prostate cancer has become a flagship for the oligometastatic paradigm due to a relatively indolent disease course and early detection of metastatic disease using PSA screening and advanced imaging. Because oligometastatic prostate cancer encompasses a vast array of disease biology and clinical trajectories, the optimal management of oligometastatic disease remains unclear. Systemic therapy remains the cornerstone of treatment for patients with metastatic disease, but several studies demonstrate benefits to the integration of local therapy to the prostate and metastatic sites. Further study is needed to identify genomic and clinicopathologic classifiers to better select patients most likely to benefit from MDT.

## References

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13(1):8-10.
2. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet.* 2019;393(10185):2051-2058.
3. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet.* 2018;392(10162):2353-2366.
4. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase ii, randomized study. 2019;37(18):1558-1565.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
6. Wu JN, Fish KM, Evans CP, Devere White RW, Dall'Era MA. No improvement noted in overall or cause-specific survival for men presenting with metastatic prostate cancer over a 20-year period. *Cancer.* 2014;120(6):818-823.
7. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999;281(17):1591-1597.
8. Foster CC, Weichselbaum RR, Pitroda SP. Oligometastatic prostate cancer: reality or figment of imagination? *Cancer.* 2019;125(3):340-352.
9. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol.* 2020;21(1):e18-e28.
10. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med.* 2001;345(23):1655-1659.
11. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet.* 2001;358(9286):966-970.
12. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol.* 1999;17(7):2092-2099.
13. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *The Lancet Oncology.* 2015;16(13):1380-1388.
14. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Eng J Med.* 2018;379(5):417-427.
15. Boevé LMS, Hulshof M, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *Eur Urol.* 2019;75(3):410-418.
16. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a stopcap systematic review and meta-analysis. *Eur Urol.* 2019;76(1):115-124.
17. Kiss B, Volkmer AK, Feng D, et al. Magrolimab and gemcitabine-cisplatin combination enhance phagocytic elimination of bladder cancer. *J Clin Oncol.* 2020;38:e17035-e17035.
18. Cuellar MA, Medina A, Girones R, et al. Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy as bladder-sparing therapy in patients with localized muscle invasive bladder cancer: A SOGUG study. *J Clin Oncol.* 2020;38:TPS5097-TPS5097.
19. Batista da Costa J, Gibb EA, Bivalacqua TJ, et al. Molecular characterization of neuroendocrine-like bladder cancer. *Clinical Cancer Research.* 2019:clincanres.3558.2018.
20. Balar AV, James ND, Shariat SF, et al. Phase III study of pembrolizumab (pembro) plus chemoradiotherapy (CRT) versus CRT alone for patients (pts) with muscle-invasive bladder cancer (MIBC): KEYNOTE-992. *J Clin Oncol.* 2020;38:TPS5093-TPS5093.

SA-CME (appliedradiology.org/SAM)

21. Chemoradiotherapy with or without atezolizumab in treating patients with localized muscle invasive bladder cancer (S1806). ClinicalTrials.gov identifier: NCT03775265. Aceessed July 20, 2020.
22. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet.* 2020;395(10231):1208-1216.
23. Calais J, Ceci F, Eiber M, et al. (18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol.* 2019;20(9):1286-1294.
24. Chen B, Wei P, Macapinlac HA, Lu Y. Comparison of 18F-fluciclovine PET/CT and 99mTc-MDP bone scan in detection of bone metastasis in prostate cancer. *Nuc Med Com.* 2019;40(9):940-946.
25. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol.* 2020;6(5):650-659.
26. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase ii trial. *J Clin Oncol.* 2018;36(5):446-453.
27. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence (STOMP): Five-year results of a randomized phase II trial. *J Clin Oncol.* 2020;38(6_suppl):10-10.
28. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: long-term results of the SABR-COMET phase ii randomized trial. *J Clin Oncol.* 2020:JCO2000818.
29. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol.* 2003;21(21):3972-3978.
30. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med.* 2009;360(24):2516-2527.
31. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med.* 2019;381(2):121-131.
32. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med.* 2019;381(1):13-24.
33. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med.* 2017;377(4):338-351.
34. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol.* 2019;30(12):1992-2003.
35. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED Trial. *J Clin Oncol.* 2018;36(11):1080-1087.
36. Gandaglia G, Karakiewicz PI, Briganti A, et al. Impact of the site of metastases on survival in patients with metastatic prostate cancer. *Eur Urol.* 2015;68(2):325-334.
37. Ost P, Jereczek-Fossa BA, Van As N, et al. Pattern of progression after stereotactic body radiotherapy for oligometastatic prostate cancer nodal recurrences. *Clin Oncol.* 2016;28(9):e115-120.
38. Ploussard G, Gandaglia G, Borgmann H, et al. Salvage Lymph node dissection for nodal recurrent prostate cancer: a systematic review. *Eur Urol.* 2019;76(4):493-504.
39. Siriwardana A, Thompson J, van Leeuwen PJ, et al. Initial multicentre experience of (68) gallium-PSMA PET/CT guided robot-assisted salvage lymphadenectomy: acceptable safety profile but oncological benefit appears limited. *BJU Int.* 2017;120(5):673-681.