

# Oligometastatic Prostate Cancer: Reality or Figment of Imagination?

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The term “oligometastatic prostate cancer” refers to a heterogeneous group of disease states currently defined solely on the basis of clinical features. Oligorecurrent disease, de novo oligometastases, and oligoprogressive disease likely have unique biologic underpinnings and natural histories. Evidence suggesting the existence of a subset of patients who harbor prostate cancer with limited metastatic potential currently includes disparate and overwhelmingly retrospective reports. Nevertheless, emerging prospective data have corroborated the “better-than-expected,” retrospectively observed outcomes, particularly in the setting of oligorecurrent prostate cancer. Improved functional imaging with prostate-specific membrane antigen-targeted strategies may enhance the identification of patients with oligometastatic prostate cancer in the short term. In the long term, refinement of the oligometastatic case definition likely will require biologic risk-stratification schemes. To determine optimal treatment strategies and identify patients most likely to benefit from metastasis-directed therapy, future efforts should focus on conducting high-quality, prospective trials with much-needed molecular correlative studies. *Cancer* 2019;125:340-352. © 2018 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

**KEYWORDS:** metastasis, oligometastasis, prostate cancer, radiation, stereotactic radiotherapy.

## INTRODUCTION

Metastasis has been conceptualized on a scale ranging from sequential, echelon-level spread to de facto, widespread dissemination. More recently, a paradigm shift was prompted by Weichselbaum and Hellman, who hypothesized the existence of an oligometastatic state.<sup>1,2</sup> Their assertion that a subset of metastases may be limited in number and location has since been both the subject of criticism<sup>3,4</sup> and the inspiration for pioneering clinical trials investigating local ablative therapy<sup>5-7</sup> for tumors that previously would have been treated with solely systemic approaches. Acceptance of an oligometastatic paradigm with the resultant impact on treatment recommendations is poised to potentially change the landscape of prostate cancer management, given evidence suggesting that as much as 75% of patients with recurrence after primary therapy will have  $\leq 3$  involved sites.<sup>8-11</sup> Moreover, reports documenting an increasing incidence of metastatic prostate cancer in the United States<sup>12</sup> suggest that de novo oligometastatic disease also is likely to become more common.

Whereas mounting evidence supports the existence of an oligometastatic state in prostate cancer, studies primarily have been intervention-focused, with oligometastases defined by the number and/or location of lesions with little investigation into the underlying biology that could deepen our understanding of why select tumors possess a limited metastatic potential compared with others. Furthermore, the literature is heterogeneous, with some reports analyzing outcomes in the oligorecurrent setting and others focusing on outcomes for patients with de novo oligometastatic disease. Therefore, evidence supporting a distinct oligometastatic identity within prostate cancer must be synthesized from somewhat disparate and predominantly retrospective sources. Herein, we review this evidence and summarize an emerging crop of prospective trials to better sort fact from promising fiction in the context of prostate cancer with a paucity of metastases.

## DEFINING OLIGOMETASTASES: CLINICAL AND BIOLOGIC FACTORS

Oligometastatic prostate cancer is a broad term encompassing at least 2 distinct entities that likely have different biologic signatures and behavior.<sup>13</sup> Oligorecurrent prostate cancer generally refers to the development of limited sites of distant dissemination after primary radical prostatectomy (RP) or radiotherapy (RT), whereas de novo oligometastasis references a separate group with prostate cancer that has spread to limited areas before any definitive therapy. Therefore,

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potential treatment strategies for de novo oligometastases must consider the management of an intact primary tumor in addition to distant lesions. A third state known as *oligoprogression* also is emerging and identifies patients who have widespread metastases with only limited sites of progression on systemic therapy.<sup>14-17</sup> Notably, patients with oligoprogressive disease have been poorly represented in retrospective studies, although series that included mixed histologies,<sup>17</sup> and prostate cancer specifically,<sup>15,16</sup> have suggested a worse prognosis compared with those who have traditional oligometastasis.

Most commonly, patients with oligorecurrence or de novo oligometastatic disease have been identified using a specific cutoff for the number of distant sites involved. A list of previously published literature<sup>7,15,16,18-50</sup> with associated oligometastatic definitions is displayed in Table 1,<sup>7,15,16,18-50</sup> with similar definitions used by ongoing, prospective investigations listed in Table 2.<sup>51-71</sup> Of 25 retrospective reviews that included >1 case, 10 (40%) used a definition of  $\leq 5$  metastases, 3 (12%) used a definition of  $\leq 4$  metastases, and 12 (48%) used a definition of  $\leq 3$  metastases to define patients with oligometastases in the recurrent or de novo setting. Furthermore, the single prospective study of oligorecurrent prostate cancer used  $\leq 3$  lesions as a criterion for inclusion.<sup>7</sup> Ongoing prospective studies have taken similarly disparate approaches to defining oligometastasis with 12 of 20 (60%), 3 of 20 (15%), and 5 of 20 (25%) with available information using cutoffs of  $\leq 5$ ,  $\leq 4$ , and  $\leq 3$  metastases for inclusion, respectively. Additional stipulations have focused on sites of involvement, including lesions in only 1 or 2 organs,<sup>15,71</sup> exclusive lymph node involvement,<sup>19-23,28,30,39,40,45,70</sup> or the exclusion of intracranial disease.<sup>7,69,71</sup> Whether prostatic oligometastases are defined optimally by the number and/or location of lesions and which number and locations are most suitable to select for patients with limited metastatic potential have yet to be determined. Prospective evidence from Ost et al in the oligorecurrent setting suggests that improved prognosis may not necessarily be linked to disease burden or site (eg, with vs without lymph node involvement); however, the small sample size used for subgroup analyses is limiting.<sup>7</sup>

Perhaps the most promising approach for classification on the metastatic spectrum makes use of the genomic signature of an individual's particular tumor.<sup>72,73</sup> To this end, preclinical evidence has identified distinct microRNAs (miRs) associated with a low malignant phenotype in breast cancer lung colonization.<sup>74</sup> Similarly, an exploratory analysis of tumors from patients who had clinically oligometastatic disease of mixed histologies and received

stereotactic body radiotherapy (SBRT) to all known sites indicated that a candidate classifier using expression of miR-23b, miR-449a, and miR-449b predicted survival for 17 patients who had available expression data.<sup>75</sup> More recently, integrated molecular analysis was used to risk stratify patients with de novo colorectal liver metastasis.<sup>76</sup> Specifically, a low-risk group with a 10-year overall survival (OS) rate of approximately 95% was identified that had favorable clinical features in concert with metastases primarily enriched for innate and adaptive immune activation independent of microsatellite instability status. It is hypothesized that this subtype is most representative of a true oligometastatic state, and its elucidation illustrates that tumor biology and host factors like immune contexture may augment the more traditional indicators of limited metastasis.

Molecular characterization also has been attempted for prostate cancer in the castration-resistant, unselected metastatic setting. For instance, among 16 rapid autopsy tumor samples, intraindividual and interindividual genomic heterogeneity was identified,<sup>77</sup> echoing findings in other histologies and hinting at the potential for distinct molecular subpopulations. Further evidence was provided by Quigley et al, who used deep, whole-genome and whole-transcriptome sequencing of 101 castration-resistant prostatic metastases to observe amplification of an enhancer region upstream from the androgen receptor gene in 81% of men as well as distinct classes of structural variants associated with 1) cyclin-dependent kinase 12 (*CDK12*) mutation with tandem duplications, 2) tumor protein 53 (*TP53*) inactivation with inverted rearrangements and chromothripsis, and 3) *BRCA2* inactivation with deletions.<sup>78</sup> In addition, a novel subtype of castration-resistant disease characterized by biallelic *CDK12* loss, immune activation, and the absence of hypermutation also was detected by performing integrative genomic analysis.<sup>79</sup> It is noteworthy that *CDK12* mutations also were detected in the previously mentioned immune subtype of de novo colorectal cancer metastases in which patients experience favorable survival,<sup>76</sup> suggesting that *CDK12* inactivation may associate with an altered tumor immunophenotype and have implications for curability after metastasis-directed therapy and sensitivity to immune-checkpoint blockade. Taken together, these data form a foundation for the molecular characterization of unselected patients with metastatic prostate cancer and support similar efforts focused exclusively on defining molecular subtypes of oligometastatic prostate cancer. It also is important to note that data from such investigative pursuits have the potential not only to molecularly distinguish

**TABLE 1.** Oligometastatic Prostate Cancer Outcomes

Reference	Study Design	Oligometastatic Definition	Intervention	Outcome(s)
<b>Local therapy to the prostate only</b>				
Jang 2018 <sup>18</sup>	Retrospective	≤5 Oligometastases on bone scan, de novo oligometastases only	Robot-assisted RP (n = 38)	Median PFS, 75 mo; median cancer-specific survival, not reached
Gandaglia 2017 <sup>19</sup>	Retrospective	≤5 Lesions on bone scan with/without pelvic or retroperitoneal lymph node involvement, de novo oligometastases only	RP and extended pelvic lymph node dissection (n = 11), with adjuvant ADT (n = 10)	Clinical PFS at 7 y, 45%; 7-y cancer-specific mortality-free survival, 82%
Heidenreich 2015 <sup>20</sup>	Prospective feasibility study	≤3 Osseous metastases on bone scan	Neoadjuvant ADT with those achieving PSA nadir <1.0 ng/ml undergoing RP (n = 23)	Median time to castration resistance, 40 mo; median clinical PFS, 38.6 mo; median cause-specific survival, 47 mo
<b>Ablative therapy to oligometastases</b>				
Ost 2018 <sup>7</sup>	Prospective randomized, phase 2	≤3 Extracranial metastases on choline PET/CT scan, oligorecurrence only	1) Surveillance with PSA every 3 mo with repeat imaging at PSA progression or clinical suspicion (n = 31; 5 received metastasis-directed therapy); 2) metastasis-directed therapy to all lesions, including surgery or SBRT (n = 31); ADT was started for all at symptomatic progression, progression to >3 metastases, or local progression of known metastases	1) Median ADT-free survival, 13 mo; 2) median ADT-free survival, 21 mo
Franzese 2018 <sup>15</sup>	Retrospective	≤3 Metachronous metastases in 1-2 organs amenable to SBRT, oligorecurrence or oligoprogression	SBRT to oligometastases with/without systemic therapy (n = 64)	Median PFS, 6.6 mo; 1-y LC, 88%
Cysouw 2018 <sup>21</sup>	Retrospective	≤4 Metachronous metastases on [ <sup>18</sup> F]-fluoromethylcholine PET/CT scan	SBRT to oligometastases (n = 40)	Median PFS, 11.5 mo
Tran 2018 <sup>22</sup>	Retrospective	≤5 Lymph node oligorecurrent lesions	Conventional RT to pelvic lymph nodes with ADT (n = 53)	Biochemical DFS at 5 y, 43%; distant PFS at 5-y, 58%
Franzese 2017 <sup>23</sup>	Retrospective	≤4 Lymph node metastases	<sup>11</sup> C-choline-PET guided SBRT to lymph node lesions (n = 26)	Metabolic complete response, 44.7%; metabolic partial response, 38%
Guler 2018 <sup>24</sup>	Retrospective	≤3 Metastases on <sup>68</sup> Ga-PSMA PET/CT scan	RT to oligometastases (n = 23)	LC at 1 y, 100%; 1-y PFS, 51%; 1-y OS, 100%
Zattoni 2016 <sup>25</sup>	Retrospective	Undefined, oligorecurrence in lymph nodes only	Salvage lymph node dissection (n = 117)	Biochemical recurrence-free survival at 5 y, 31%; 5-y radiologic recurrence free survival, 51%; 5-y cancer-specific survival, 97%
Siriwardana 2017 <sup>26</sup>	Retrospective	≤5 Lymph node-only oligometastases on <sup>68</sup> Ga-PSMA PET/CT	Salvage lymph node dissection (n = 35)	At a median follow-up of 12 mo: Biochemical recurrence-free survival, 23%; clinical recurrence-free survival, 66%
Habl 2017 <sup>27</sup>	Retrospective	≤3 Oligometastases, oligorecurrence only	SBRT (n = 15)	Local PFS at 2 y, 100%; median distant PFS, 7.36 mo; median time to ADT, 9.3 mo
Bouman-Wammes 2017 <sup>28</sup>	Retrospective	≤5 Oligometastases on [ <sup>18</sup> F]-fluoromethylcholine PET/CT, hormone-sensitive and oligorecurrence only	SBRT (n = 43)	Median ADT-free survival, 15.6 mo
Triggiani 2017 <sup>16</sup>	Retrospective	1) One to 3 oligometastases in bone or lymph nodes on choline PET or CT + bone scan, oligorecurrence only; 2) oligoprogression with undefined number of metastases after a rising PSA on ADT	1) SBRT, n = 100; 2) SBRT, n = 41	1) Distant 2-y distant PFS at 2 y, 43%; 2-y LC, 92.8%; 2) 2-y distant PFS, 21.6%; 2-y LC, 90.2%
Erie 2017 <sup>29</sup>	Retrospective	≤3 Oligometastases	Image-guided cryoablation or radiofrequency ablation (n = 16)	LC 83% at a median follow-up of 27 mo; 2-y PFS, 43%
Markowski 2017 <sup>30</sup>	Case report	4 Bone oligometastases	SBRT without ADT	Biochemical-failure free survival, 18 mo

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TABLE 1. (Continued)

Reference	Study Design	Oligometastatic Definition	Intervention	Outcome(s)
Ingrosso 2017 <sup>31</sup>	Retrospective	Isolated lymph node oligorecurrence	SBRT (n = 40)	Biochemical PFS at 2 y, 44%; LC, 98% with a mean follow-up of 30 mo
Pasqualetti 2016 <sup>32</sup>	Case report	5 Metachronous lesions on <sup>18</sup> F-choline PET/CT	SBRT	ADT-free survival, nearly 5 y
Ost 2016 <sup>33</sup>	Retrospective	≤3 Lymph node recurrences	SBRT (n = 72)	Median distant PFS, 21 mo; median ADT-free survival, 44 mo
Muldermans 2016 <sup>34</sup>	Retrospective	Majority with ≤5 oligometastases, most with oligorecurrence	SBRT (n = 66)	LC at 2 y, 82%; 2-y biochemical PFS, 54%; 2-y distant PFS, 45%; 2-y OS, 83%
Wang 2016 <sup>35</sup>	Case report	Solitary spine recurrence	SBRT	ADT-free survival, not reached
Pasqualetti 2016 <sup>36</sup>	Prospective, nonrandomized	≤3 Synchronous, active lesions on <sup>18</sup> F-fluoromethylcholine PET/CT scan, oligorecurrence only	Repeated SBRT until development of >3 active synchronous metastases (n = 29)	Median systemic therapy-free survival, 39.7 mo
Lukovic & Rodrigues 2015 <sup>37</sup>	Case report	Single T10 metastasis, oligorecurrence after RP	SBRT	Biochemical PFS, not reached
Martínez-Fernández 2016 <sup>38</sup>	Case series	Solitary bone oligometastases	SBRT (n = 2)	Biochemical PFS, 13-17 mo
Ost 2016 <sup>39</sup>	Retrospective	≤3 Oligometastases, oligorecurrence only	SBRT (n = 119)	Distant PFS at 3 y, 31%; 3-y OS, 95%
Azzam 2015 <sup>40</sup>	Retrospective	≤4 Oligometastases	SBRT (n = 9)	Median OS, >3 y
Claeys 2015 <sup>41</sup>	Retrospective	<4 Synchronous metastases, oligorecurrence only	Salvage pelvic lymph node dissection (n = 13)	Median biochemical PFS, 4.1 mo; median clinical PFS, 7 mo; 2-y ADT-free survival, 79.5%
Ponti 2015 <sup>42</sup>	Retrospective	Isolated lymph node recurrence	SBRT (n = 16), concomitant ADT (n = 10)	Biochemical PFS at 2 y, 44%; LC at a median follow-up of 29.4 mo, 94%
Peeters 2017 <sup>43</sup>	Case report	Left common iliac lymph node recurrence on ( <sup>11</sup> C)choline PET/CT, recurrence after RP and prostate bed RT	Salvage pelvic lymphadenectomy	Biochemical PFS, 5 y
Decaestecker 2014 <sup>44</sup>	Retrospective	≤3 Synchronous metastases involving bone and/or lymph nodes, oligorecurrence only	Repeated SBRT until ≥3 metastases detected (n = 50)	Median PFS, 19 mo
Schick 2013 <sup>45</sup>	Retrospective	≤5 Regional and/or distant metastases, de novo oligometastases and oligorecurrence	High-dose RT to metastatic sites (n = 50) with neoadjuvant and concomitant ADT (n = 49)	Biochemical PFS at 3 y, 54.5%; 3-y clinical PFS, 58.6%; 3-y OS, 92%
Ahmed 2013 <sup>46</sup>	Retrospective	≤5 Oligometastases	SBRT (n = 17) with adjuvant ADT (n = 15)	LC, 100% at a median follow-up of 6 mo; 12-mo cancer-specific survival, 100%; 12-mo freedom from distant progression, 40%
Berkovic 2013 <sup>47</sup>	Retrospective	≤3 Synchronous metastases in bone and/or lymph node on PET, oligorecurrence only	SBRT repeated until >3 metastases developed (n = 24)	Median ADT-free survival, 38 mo; 2-y LC, 100%; 2-y clinical PFS, 42%
Alongi 2010 <sup>48</sup>	Case report	Isolated pelvic lymph node oligorecurrence on [ <sup>11</sup> C] choline-PET	Helical tomotherapy RT with estramustine	DFS, 24 mo
Pruthi 2007 <sup>49</sup>	Case report	Solitary pulmonary metastasis	Surgical excision	Biochemical PFS, >3 y
<b>Local therapy to prostate and ablative therapy to oligometastases</b>				
Riva 2017 <sup>50</sup>	Retrospective	≤5 Bone metastases, included de novo oligometastases only	ADT and conventional RT to prostate with RT to bone metastases (n = 20; 4 did not receive RT to metastases)	OS at 2 y, 100%

Abbreviations: ADT, androgen deprivation therapy; CT, computed tomography; DFS, disease-free survival; LC, local control; OS, overall survival; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

oligometastatic disease from oligovisible dissemination but also to influence separate considerations surrounding the appropriateness of metastasis-directed therapy within the context of tumor and patient-related factors.

**IMAGING PROSTATIC OLIGOMETASTASES**  
An accurate assessment of metastatic burden using radiologic and functional imaging techniques is crucial, especially in the absence of reliable molecular predictors

**TABLE 2.** Ongoing Oligometastatic Prostate Cancer Trials

Study Center	ClinicalTrials.gov Identifier	Oligometastatic Definition	Design	Status	Intervention(s)
University of Florida Proton Therapy Institute	NCT01859221 <sup>51</sup>	Undefined, de novo or oligorecurrence	Nonrandomized, phase 2	Active, not recruiting	SBRT to metastases with concurrent conventional RT to prostate if disease present, ADT for all patients
VA Greater Los Angeles Healthcare System	NCT03298087 <sup>52</sup>	≤5 Metastases excluding visceral disease, de novo only	Nonrandomized, phase 2	Recruiting	RP (with postoperative conventional RT to the prostate for pT3a, pN1, or positive surgical margin), SBRT to all metastases, ADT for all patients for a total of 6 mo
Sunnybrook Health Sciences Center	NCT03301701 <sup>53</sup>	≤5 Metastases outside regional pelvic lymph nodes, ≤3 per organ system, de novo only	Randomized feasibility trial	Recruiting	1) RP, SBRT to all metastases, intermittent ADT for all patients with/without chemotherapy; 2) high-dose rate brachytherapy or SBRT to the prostate if medically unfit for brachytherapy, SBRT to all metastases, intermittent ADT for all patients with/without chemotherapy
Castellon Provincial Hospital	NCT02192788 <sup>54</sup>	≤5 Bone or lymph node metastases, oligorecurrence only	Nonrandomized, phase 2	Recruiting	SBRT to metastatic sites
Sunnybrook Odette Cancer Center	NCT02563691 <sup>55</sup>	≤5 Metastases excluding prostate and pelvic lymph nodes; ≤3 per organ system, de novo or oligorecurrence	Nonrandomized, phase 1/2	Recruiting	ADT for a minimum of 1 year followed by intermittent ADT, hypofractionated RT to the prostate and regional nodes if not previously treated, SBRT to all metastases within 3 months of starting ADT, SBRT to new oligometastases during "off" ADT periods
Huntsman Cancer Institute	NCT03304418 <sup>56</sup>	≤5 Bone metastases, de novo or oligorecurrence	Nonrandomized, phase 2A	Recruiting	Radium-223 delivered for 6 cycles, SBRT or hypofractionated RT to all oligometastases with RT to prostate if not previously treated
Shanghai Proton and Heavy Ion Center	NCT02935023 <sup>57</sup>	≤3 Oligometastases, de novo only	Nonrandomized, phase 2	Recruiting	Carbon ion RT to the prostate without local ablative therapy to oligometastases, ADT or chemotherapy
Johns Hopkins University/Sidney Kimmel Cancer Center	NCT02489357 <sup>58</sup>	≤5 Extrapelvic oligometastases with pelvic lymph nodes allowed, de novo only	Nonrandomized pilot study	Active, not recruiting	ADT for 8 mo, pembrolizumab immunotherapy for up to 6 3-wk cycles, whole gland cryoablation of the prostate
Medical University of Vienna	NCT02971358 <sup>59</sup>	≤5 Osseous oligometastases, de novo only	Nonrandomized, phase 1/2	Recruiting	RP with extended lymph node dissection for all
Sidney Kimmel Cancer Center at Thomas Jefferson University	NCT03477864 <sup>60</sup>	≤3 Oligometastases, includes widely metastatic patients, includes de novo or oligorecurrence	Randomized, phase 1	Not yet recruiting	1) Anti-PD-1 monoclonal antibody IV, SBRT to prostate followed by RP; 2) intraprostatic ipilimumab, SBRT to prostate followed by RP; 3) anti-PD-1 monoclonal antibody IV + intraprostatic ipilimumab, SBRT to prostate followed by RP
Montreal University Hospital Center	NCT03525288 <sup>61</sup>	≤5 Regional or distant oligometastases with <3 metastases per nonbone organ, de novo or oligorecurrence	Randomized, phase 2/3	Recruiting	1) PSMA-PET/CT-guided RT to prostate and up to 5 oligometastatic sites with all oligometastases treated 2) standard of care RT
Johns Hopkins University/Sidney Kimmel Cancer Center	NCT02716974 <sup>62</sup>	≤5 Bone and nonregional lymph node oligometastases, de novo only	Nonrandomized, phase 2	Recruiting	Neoadjuvant docetaxel with ADT followed by RP with/without adjuvant RT and consolidative SBRT to oligometastases, total of 1 y of ADT to all
Johns Hopkins University/Sidney Kimmel Cancer Center	NCT03043807 <sup>63</sup>	≤5 Bone and nonregional lymph node oligometastases, de novo only	Nonrandomized, phase 2	Recruiting	Neoadjuvant docetaxel with ADT followed by RT to the prostate or prostate bed and SBRT to oligometastases, up to 2 y ADT for all

(Continued)

TABLE 2. (Continued)

Study Center	ClinicalTrials.gov Identifier	Oligometastatic Definition	Design	Status	Intervention(s)
University of Wisconsin Carbone Cancer Center	NCT03358563 <sup>64</sup>	≤4 Oligometastases without visceral involvement, de novo only, also includes high-risk without oligometastases	Nonrandomized, phase 1	Recruiting	Neoadjuvant ADT and docetaxel followed by RP
Johns Hopkins University/Sidney Kimmel Cancer Center	NCT02680587 <sup>65</sup>	≤3 Asymptomatic bone or soft tissue oligometastases developing in preceding 6 mo measuring ≤5 cm and ≤250 cm <sup>3</sup> , oligorecurrence only	Randomized, phase 2	Active, not recruiting	1) Observation, 2) SBRT to oligometastases
Fudan University Shanghai Cancer Center	NCT02742675 <sup>66</sup>	≤5 Bone or lymph node oligometastases, de novo only	Randomized, phase 2	Recruiting	1) ADT alone, 2) ADT + plus RP or RT to the prostate
UCSF Helen Diller Family Comprehensive Cancer Center	NCT03007732 <sup>67</sup>	≤4 Bone or lymph node oligometastases, de novo only	Randomized, phase 2	Recruiting	1) ADT in combination with pembrolizumab immunotherapy followed by SBRT to prostate, 2) ADT in combination with intratumoral TLR9 agonist and pembrolizumab immunotherapy followed by SBRT to prostate
Oncology Institute West	NCT02274779 <sup>68</sup>	≤5 Pelvic lymph node metastases, oligorecurrence only	Nonrandomized, phase 2	Active, not recruiting	Intensity-modulated RT to pelvis with a total of 6 mo neoadjuvant/concurrent and adjuvant ADT
The University of Texas MD Anderson Cancer Center	NCT03678025 <sup>69</sup>	≤4 Extracranial metastases, de novo only, also includes nonoligometastatic prostate cancer without prior definitive therapy or intracranial involvement	Randomized, phase 3	Active, recruiting	1) Standard systemic therapy; 2) standard systemic therapy with prostatectomy or RT to primary; all patients with oligometastatic disease may receive metastasis-directed therapy to ≤4 sites before randomization
University Hospital, Ghent	NCT03569241 <sup>70</sup>	≤3 Pelvic lymph node metastases, oligorecurrence only	Randomized, phase 2	Active, recruiting	1) Metastasis-directed therapy (surgery or SBRT) with 6 mo of ADT, 2) metastasis-directed therapy (surgery or SBRT) with 6 mo of ADT and whole-pelvic RT
Royal Marsden Hospital	NCT02759783 <sup>71</sup>	≤3 Extracranial metastatic lesions in a maximum of 2 organ systems, oligorecurrence only, also includes nonsmall cell lung and breast cancer	Randomized, phase 2/3	Active, recruiting	1) Standard of care at discretion of local oncologist, 2) SBRT to oligometastases followed by standard of care

Abbreviations: ADT, androgen deprivation therapy; CT, computed tomography; IV, intravenously; NCT, National Clinical Trial; PD-1, programmed cell death protein 1; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SBRT, stereotactic body radiotherapy; TLR9, toll-like receptor 9; UCSF, University of California, San Francisco; VA, Veterans Affairs.

of metastatic virulence. Standard practice at initial staging generally includes computed tomography (CT) or magnetic resonance imaging after accounting for factors such as life expectancy and the probability of lymph node involvement.<sup>74</sup> Meanwhile, <sup>99m</sup>Tc-methylene-diphosphate (<sup>99m</sup>Tc-MDP) bone scan is the preferred modality for pretreatment identification of osseous metastases in high-risk patients.<sup>80</sup> These modalities also are standard in the appropriate clinical context for individuals who have persistently elevated or rising prostate-specific antigen (PSA) levels after definitive therapy. Nevertheless, conventional diagnostic tools have limitations, potentially leading to a greater proportion of

patients being characterized with oligometastatic disease. For instance, the sensitivity of CT<sup>81</sup> and conventional magnetic resonance imaging<sup>82</sup> for detecting pretreatment lymph node metastases in prostate cancer is approximately 36%. Moreover, bone scan has a reported sensitivity of just 65% for metastatic skeletal lesions.<sup>83</sup> Taken together, these data suggest a great need for improvement regarding the accurate identification of oligometastases.

Functional imaging using various radiotracers has demonstrated promise. Although positron emission tomography (PET) with <sup>18</sup>fluoride (<sup>18</sup>F)-fluorodeoxyglucose has limited applications because of variable uptake in prostate cancer as well as bladder proximity,<sup>84</sup> other

radiotracers attempt to overcome these challenges. One of the more extensively studied tracers is sodium- $^{18}\text{F}$  ( $\text{Na}^{18}\text{F}$ )-PET/CT, which has demonstrated superior detection of osteoblastic prostate metastasis compared with  $^{99\text{m}}\text{Tc}$ -MDP bone scan.<sup>83,85</sup> Specifically, malignant lesions observed on  $\text{Na}^{18}\text{F}$ -PET/CT were identified on  $^{99\text{m}}\text{Tc}$ -MDP bone scan only 65% of the time<sup>85</sup>; however, a limitation of this modality is its reliance on registered cross-sectional imaging for the detection of soft tissue lesions. One class of radiotracers that is not limited in this context is choline PET/CT, which has a per-patient, pooled sensitivity of 84% and 85% in the pretreatment and recurrent settings, respectively,<sup>86</sup> for the detection of bony and soft tissue metastatic lesions, with uptake correlated to tumor choline kinase  $\alpha$  expression.<sup>87</sup>  $^{18}\text{F}$ -fluciclovine PET/CT has even greater metastasis detection rates in the recurrent setting compared with  $^{11}\text{C}$ -choline<sup>88</sup>; however, its use remains primarily investigational. Radiotracers targeted to prostate-specific membrane antigen (PSMA) also have produced encouraging results and make rational sense, because this transmembrane protein is widely expressed by prostate cancer cells.<sup>73</sup> It is noteworthy that, in a retrospective review of 21 patients who had de novo metastatic disease with  $\leq 3$  metastases on conventional imaging,  $^{68}\text{Ga}$ -PSMA PET downstaged 12 to localized disease and upstaged 1 to polymetastatic disease.<sup>89</sup> Given such data, consideration should be made to the inclusion of newer functional imaging strategies as a component of screening or investigational endpoints on prospective protocols for oligometastatic prostate cancer, as was done in 8 of the 21 protocols (39%) listed in Table 2.<sup>52,54,61,64,65,67,68,70</sup>

### OLIGOMETASTATIC PROSTATE CANCER OUTCOMES

Although defining, identifying, and biologically characterizing oligometastatic prostate cancer all pose unique challenges, deciding how best to manage patients who have prostatic oligometastases is a distinct, clinically pressing issue. Outcomes associated with various treatment approaches in the oligorecurrent and de novo oligometastatic settings are summarized in Table 1. Since the first case report in PubMed by Pruthi et al in 2007,<sup>49</sup> at least 34 additional reports have suggested generally favorable oncologic outcomes. Of these, all but 2 reports<sup>7,20</sup> are retrospective with 3 of 36 (8%) including RP without local metastasis-directed therapy, 32 of 36 (89%) including local metastasis-directed therapy alone, and 1 of 36 (3%) including local therapy to primary and distant sites. Of the retrospective

reports, the largest includes 119 treatment-naive patients who had  $\leq 3$  sites of oligorecurrence and received SBRT to all involved sites, with 92 of 119 (77%) undergoing pretreatment choline PET.<sup>39</sup> The 3-year distant PFS rate of 31% and the 3-year OS rate of 95% are favorable and suggest a subset of patients likely benefitted from aggressive local therapy; however, conclusions from these data are limited in the absence of a comparative control arm.

In the de novo oligometastatic setting, one more commonly investigated treatment approach is local ablative therapy to the prostate with or without pelvic lymph nodes and without metastasis-directed therapy.<sup>90</sup> Until recently, support for this strategy has been extrapolated from retrospective series that included patients with unselected metastatic burden.<sup>91</sup> For example, Sooriakumaran et al reported outcomes for 106 men with de novo metastatic prostate cancer who underwent RP and observed that 79.2% were complication-free postprocedure, with 88.7% alive after a median follow-up of 22.8 months.<sup>91</sup> A few investigators similarly have reported favorable outcomes in retrospective cohorts that exclusively included patients with oligometastatic disease.<sup>18-20</sup> For example, Heidenreich et al conducted a feasibility study of RP for select men ( $n = 23$ ) with de novo oligometastatic disease who achieved a PSA nadir  $< 1.0$  ng/mL on neoadjuvant androgen-deprivation therapy (ADT).<sup>20</sup> In that trial, the median time to castration resistance was 40 months, and the median clinical PFS was 38.6 months, both of which compared favorably with 29 months ( $P = .04$ ) and 26.5 months ( $P = .032$ ), respectively, for patients in a control group ( $n = 38$ ) who received ADT alone. Notably, the STAMPEDE trial now provides phase 3 evidence in support of prostate-directed RT for patients who have de novo metastatic prostate cancer and low disease burden, defined as the absence of  $\geq 4$  bone metastases with 1 or more outside the vertebral bodies or pelvis, visceral metastases, or both. Within this subgroup, there was an observed 8% improvement in 3-year OS (81% vs 73%) and an impressive 17% improvement in 3-year failure-free survival (50% vs 33%) for prostate-directed RT in addition to the standard of care compared with the standard of care alone.<sup>92</sup> Furthermore, heterogeneity of treatment effect on OS was detected as a function of metastatic burden ( $P_{\text{interaction}} = .0098$ ), with no evidence of an effect for patients with high metastatic burden.<sup>92</sup>

Few reports have investigated a more aggressive approach using combined local therapy to the primary tumor and metastasis-directed therapy in the de novo

oligometastatic setting. In 1 cohort, Riva et al reported their experience with 20 patients who received ADT plus hypofractionated RT to the prostate with or without seminal vesicles/pelvic lymph nodes, with 16 of 20 also receiving palliative RT or SBRT to at least 1 metastatic site.<sup>50</sup> Of 12 patients who subsequently experienced biochemical progression, the median time to progression was 23 months from the start of ADT, and the 2-year OS for the cohort was 100%. These outcomes compare favorably with the 2-year OS of 72% and a median failure-free survival of 11 months for patients with de novo metastatic prostate cancer who received ADT alone on the STAMPEDE trial.<sup>93</sup> Although many smaller, retrospective reviews and case reports also have suggested “better-than-expected” PFS or OS in the recurrent or de novo oligometastatic settings, these must be interpreted with caution given historic lessons arguing against the early adoption of novel treatment approaches without convincing phase 2 and 3 support.<sup>4,94</sup>

Ost et al provided the first prospective evidence in a phase 2 study in which patients who had oligorecurrent prostate cancer and  $\leq 3$  extracranial metastases on choline PET/CT were randomized to receive either surveillance with PSA every 3 months ( $n = 31$ ) or metastasis-directed therapy (surgery or SBRT) to all lesions ( $n = 31$ ).<sup>7</sup> The primary endpoint was ADT-free survival, and ADT was started for symptomatic or local progression or upon the development of  $>3$  metastases. After a median follow-up of 3 years, the median ADT-free survival was 21 months in the intervention arm compared with 13 months for patients who were randomized to surveillance ( $P = .11$ ), and the patients who had PSA doubling times  $\leq 3$  months experienced a larger magnitude of benefit with metastasis-directed therapy compared with those with who had longer PSA doubling times (hazard ratio [HR], 0.14 vs 0.44;  $P_{\text{interaction}} = .01$ ). All patients who received ADT because of local/symptomatic progression were randomized to undergo surveillance, whereas similar numbers of men in both arms started ADT because of polymetastatic progression, suggesting the possibility of enrolled subpopulations that included those with true oligorecurrence versus those with oligovisible metastases.<sup>95</sup> Although these results highlight the potential of metastasis-directed therapy to delay the commencement of systemic therapy and its side effects,<sup>96</sup> there was no statistically significant improvement in 1-year quality of life, possibly because of the lack of power to detect such a difference. In addition, the trial’s design has been criticized for a

nonstandard control arm, given the known OS benefit from immediate versus delayed ADT for men with biochemically recurrent prostate cancer.<sup>97</sup> Nevertheless, this trial provides the most convincing evidence to date supporting the ongoing investigation of local ablative therapy for oligorecurrent prostate cancer.

## PROSPECTIVE TRIALS INVESTIGATING OLIGOMETASTATIC PROSTATE CANCER

Growing numbers of prospective protocols registered on the US National Library of Medicine/National Institutes of Health clinicaltrials.gov registry will provide more robust evidence to support or refute the efficacy of alternative therapeutic management strategies for patients who have oligometastatic prostate cancer in the coming years. Those protocols are summarized in Table 2 and include heterogeneous definitions of oligometastatic disease, treatment settings, and treatment strategies. Most of the protocols (11 of 21; 52%) include only patients with de novo oligometastatic disease, whereas 5 of 21 (24%) include patients with de novo or recurrent oligometastases, and 5 of 21 (24%) include only men with oligorecurrence. Given the relative dearth of retrospective evidence focusing on metastasis-directed therapies in the de novo oligometastatic setting, these protocols will address a significant gap in the literature and provide much needed clinical guidance. The majority of protocols are nonrandomized phase 1 and 2 studies (12 of 21 protocols; 57%), with 6 of 21 (29%) randomized phase 1 and 2 protocols and 3 of 21 (14%) randomized phase 2 and 3 or phase 3 protocols, suggesting that the wait may be many years for definitive phase 3, randomized evidence powered to detect a difference in OS in this setting. The recent activation of a randomized phase 3 protocol sponsored by the Southwest Oncology Group<sup>69</sup> represents progress toward this goal and includes patients with de novo oligometastatic and nonoligometastatic prostate cancer who are assigned to receive either standard systemic therapy or standard systemic therapy plus RP or RT to the prostate. All patients with oligometastatic disease are allowed to receive metastasis-directed therapy to  $\leq 4$  sites before randomization. It is worth noting that the STOMP trial published by Ost et al<sup>7</sup> was designed primarily to identify a suitable intervention arm for a subsequent phase 3 protocol, with the authors concluding that the results warranted such investigative progression.

Perhaps the most anticipated of these randomized, phase 2 protocols is the ORIOLE trial, which was opened for enrollment in April 2016 and sponsored by the Sidney Kimmel Comprehensive Cancer



Center at Johns Hopkins.<sup>65,98</sup> By using a fairly specific approach to define hormone-sensitive oligorecurrence after primary RP or RT, the inclusion criteria require  $\leq 3$  asymptomatic metastases measuring  $\leq 5.0$  cm in greatest dimension or  $< 250$  cm<sup>3</sup> in volume that developed within 6 months before enrollment with a PSA doubling time  $< 15$  months and an Eastern Cooperative Oncology Group performance status  $\leq 2$ . Eligible individuals are randomized in a 2:1 fashion to receive SBRT in 1 to 5 fractions to all metastases versus observation. A minimization approach in which treatment allocation depends on the characteristics of individuals already enrolled will ensure even distribution of patients with respect to: 1) initial treatment, including RP or RT; 2) prior ADT; and 3) a PSA doubling time  $< 6$  months versus 6 to 14.9 months. The primary endpoint is 6-month progression, with a hypothesis that SBRT will reduce 6-month progression from an expected value of  $> 80\%$  in the observation arm<sup>99,100</sup> to 50% in the intervention arm. Based on a 1-sided type I error of 0.05, the sample size of 54 patients (36 in the SBRT arm, 18 in the observation arm) is associated with 85% power to detect a difference between arms.

Patients who are randomized to SBRT also will undergo an investigational PSMA-based 2-(3-[1-carboxy-5-([6-<sup>18</sup>F-fluoro-pyridine-3-carbonyl]-amino)-pentyl]-ureido)-pentanedioic acid (<sup>18</sup>F-DCFPyL) PET/CT,<sup>101</sup> and the results will be compared with conventional bone scan and CT imaging in an attempt to characterize the potential benefits of using this functional imaging technique for the initial detection of oligorecurrent prostate cancer and subsequent progression after metastasis-directed therapy. Of note, additional lesions detected on <sup>18</sup>F-DCFPyL PET/CT will not be treated with SBRT. Moreover, a rich set of planned correlative studies include analyses of circulating tumor cells, deep sequencing of circulating tumor DNA, and T-cell repertoire profiling, with the goal of further characterizing biologic and immunologic alterations induced by SBRT in this patient population. Screening for hereditary pathogenic mutations in 30 genes that commonly occur in metastatic castration-resistant prostate cancer also will be performed and should advance efforts to tailor treatment approaches biologically for individuals who have oligorecurrent prostate cancer. Given an estimated study completion date of October 2018,<sup>65</sup> these data undoubtedly will build on the foundation already established by Ost et al<sup>7</sup> in the near future.

## FUTURE DIRECTIONS

The implication of all the previously reviewed evidence is that there is indeed a subset of patients with metastatic prostate cancer whose tumors have limited potential for dissemination, and the most convincing data comes from the oligorecurrent setting. Specifically, the STOMP trial<sup>7</sup> demonstrated that 19% of patients (6 of 31) with oligorecurrence in the surveillance arm did not develop a trigger to start ADT after a median follow-up of 3 years, whereas an even greater proportion could avoid ADT in the metastasis-directed therapy arm (12 of 31 patients; 39%). These proportions for both arms are higher than the 9.2% (12 of 131 patients) of unselected men with confirmed metastatic prostate cancer who did not develop an indication for ADT on the deferred treatment arm of the Medical Research Council trial of immediate versus deferred ADT for advanced prostate cancer.<sup>102</sup> Furthermore, 50% of patients with M1 disease enrolled on the deferred arm of the Medical Research Council trial who developed an indication to commence ADT did so within 9 months,<sup>102</sup> suggesting that select patients with oligorecurrent disease like those enrolled by Ost et al have a more indolent disease course than would be expected for the average patient with metastatic prostate cancer. It is noteworthy that 35% of men who were treated per protocol on the surveillance arm of the STOMP trial even experienced a spontaneous reduction in PSA without any oncologic therapy, which further supports the argument that these patients have a unique and favorable natural history.<sup>7</sup>

Despite these reassuring observations, data from Ost et al also reveal substantial heterogeneity in the behavior of presumed oligorecurrence defined exclusively using clinical characteristics. Sixteen of 31 patients (55%) in the surveillance arm and 19 of 31 (61%) in the metastasis-directed therapy arm ultimately developed polymetastatic progression, as discussed above. This proclivity for dissemination was observed despite all patients having undergone functional imaging with choline PET/CT—a finding that strongly advocates for a biologic rather than clinical or radiographic definition of oligometastasis. MicroRNA expression patterns<sup>75,103</sup> or integrated molecular subtyping<sup>76</sup> likely will be enlightening in this regard. Therefore, tumor specimen banking and the inclusion of molecular correlative studies in prospective protocols investigating oligometastatic prostate cancer should be highly encouraged. Collaborative efforts to pool tissue for correlative studies also should be prioritized to gain a further understanding of the biologic underpinnings

of this emerging, distinct disease entity. Although these endeavors likely will better answer whether or not a truly oligometastatic state exists in prostate cancer, they also likely will shed light on separate but equally intriguing questions regarding optimal clinical management strategies. For instance, elderly men with significant comorbidities and “molecularly favorable” oligometastatic disease may be unlikely to benefit from even well-tolerated therapies.

For individuals with oligometastatic prostate cancer, longer life expectancies, and minimal comorbidities, for whom treatment remains a prudent consideration, additional research is needed to identify appropriate therapeutic paradigms. For example, it remains unknown whether ablative therapy to the primary site alone, to primary and regional disease sites, or to the primary site and all involved distant sites is required in the de novo oligometastatic setting. Maximal debulking makes intuitive sense for several reasons, including: 1) reduced potential for metastatic seeding from the primary and/or baseline metastatic sites,<sup>104,105</sup> and 2) enhanced sensitivity to systemic therapy after tumor debulking in accordance with the Norton-Simon hypothesis.<sup>106</sup> Conversely, reports have suggested “better-than-expected” outcomes with ablative therapy that excludes distant sites,<sup>18-20</sup> and the as yet incompletely understood promise of the abscopal effect<sup>107</sup> ultimately may make less than complete ablation a preferred treatment option for at least a subset of men. This may even be more plausible given emerging evidence of immune-checkpoint inhibitor activity in metastatic castration-resistant prostate cancer<sup>108,109</sup> and the predominantly theoretical oncologic advantages of combined RT and immunotherapy.<sup>110</sup> Disagreement even exists surrounding the necessity of any upfront metastasis-directed therapy in the oligometastatic setting, because combined ADT with docetaxel or abiraterone, as prescribed in the STAMPEDE trial,<sup>93</sup> may eliminate resistant clonal subpopulations in treatment-naïve patients and prevent treatment-induced lineage crisis.<sup>111,112</sup> With so much uncertainty, sorting out how best to manage patients with the smallest number of prostatic metastases is likely to be one of the biggest challenges facing genitourinary oncologists in the coming decades.

## CONCLUSION

The term “oligometastatic prostate cancer” currently refers to a heterogeneous group of clinically defined disease states, including oligorecurrence and de novo oligometastases. Commonly used features to distinguish such

individuals with limited metastatic disease include the absolute number of lesions (e.g.,  $\leq 5$  metastases) and, less frequently, caveats like lesion location. This reliance on clinical features for case definition necessarily makes investigation into superior imaging modalities for the detection of prostate cancer oligometastases of considerable import. To this end, PSMA-targeted functional imaging currently has the greatest promise, and its inclusion as part of the prospective ORIOLE randomized, phase 2 trial in the oligorecurrent setting should provide further insights into its utility. While awaiting the results from this and other protocols currently registered on clinicaltrials.gov for patients with oligometastatic prostate cancer, evidence from a disparate group of previously published outcomes suggests that an oligometastatic state likely exists for at least a subset of patients with prostate cancer. The most convincing testament to this possibility comes from the groundbreaking phase 2 trial in the oligorecurrent setting published by Ost et al, in which individuals in both the surveillance and metastasis-directed therapy arms had higher than expected rates of ADT avoidance. Nevertheless, the appropriateness of metastasis-directed therapy within the context of tumor-related molecular factors and clinical variables like comorbidities is a separate issue that remains relatively less well answered. To better risk stratify patients who have oligometastatic disease and to determine optimal treatment strategies, future efforts should focus on conducting high-quality, prospective trials and determining a biologic categorization of patients who have disease with limited metastatic potential.

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