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CURRENT OPINION

Stereotactic ablative radiation therapy in metastatic prostate cancer

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Purpose of review
The evolving role of stereotactic ablative radiation therapy (SABR) as metastasis-directed therapy (MDT) for oligometastatic prostate cancer (omPCa) will be discussed.

Recent findings
Oligometastatic disease (OMD) is an intermediate state between localized and wide-spread malignant disease. OMD has recently been spotlighted given the increasing demonstration of clinical benefit from local therapies despite presence of metastatic disease and allure of the curative potential of MDT in select cases. Among the different forms of MDT, SABR has rapidly become a widely adopted treatment modality. Significant efforts in this space have focused on omPCa, owing to its relatively indolent biology, presence of a sensitive and specific serum biomarker and recent advances in molecular imaging. While most studies have evaluated the role of SABR MDT in hormone sensitive omPCa, new emerging clinical data also suggests benefits of SABR MDT for even castration-resistant disease.

Summary
Treating omPCa with SABR MDT appears to generate an efficacy signal with minimal morbidity across both hormone-sensitive and castration-resistant disease. However, additional definitive omPCa trial data are needed. Future research efforts should investigate biomarkers for this heterogeneous disease space and the role of SABR MDT in combination with systemic agents to improve upon standard of care treatments.

Keywords
oligometastatic prostate cancer, de novo metastatic disease, metachronous metastatic disease, metastasis-directed therapy, stereotactic ablative radiation therapy, synchronous metastatic disease

INTRODUCTION

Prostate cancer (PCa) is the second leading cause of cancer death in American men, chiefly from an inability to control metastatic disease [1]. The 5-year survival of patients with metastatic disease is only 29% [2]. Nevertheless, a wide spectrum in total metastatic burden exists and interestingly, the number of metastases observed is an important prognostic factor for PCa-specific survival [3–5]. The term oligometastatic disease (OMD) coined in 1995, defines an intermediate state between localized and wide-spread metastatic disease that can be treated with curative intent [6]. However, it was not until recently, with the advent of new molecular imaging, surgical and radiation therapy (RT) techniques, that metastasis-directed therapy (MDT) has been tested formally and shown to provide clinical benefits in clinical trials. Early phase 2 randomized clinical trials have supported the continued exploration and now implementation of stereotactic ablative radiation (SABR) as a form of MDT [7–9]. This narrative review summarizes the current state, ongoing trials, and future directions of SABR MDT in the management of oligometastatic prostate cancer (omPCa).

DEFINING OLIGOMETASTATIC DISEASE

The evolving concept of metastatic disease has dramatically changed the clinical management of these patients. The Halsted progression model developed in the late 19th century resulted in the standard of an invasive comprehensive surgery that dominated

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KEY POINTS

- Oligometastatic prostate cancer is a unique clinical state with an inherently more indolent tumor biology susceptible to metastasis-directed therapy.
- Uncertainties persist regarding the precise definition of oligometastatic disease, and nonstandardized outcome reports make it challenging to compare results across different trials.
- A multimodal approach to patients with oligometastatic prostate cancer is needed to more clearly provide evidence for radiotherapy and systemic therapy, alone or in combination, for improving patient outcomes.
- Further prospective biomarker data are needed to best select patients with oligometastatic prostate cancer most likely to benefit from metastasis-directed therapy ± systemic therapies.

breast cancer therapy until the 1970s [10]. Fisher then proposed an additional hypothesis of cancer as an inherently systemic disease process [11,12]. As a result, subsequent clinical trials evaluated the role of partial mastectomy with adjuvant therapies that is now one standard of care for early-stage breast cancer patients [13]. Almost 30 years ago, Hellman and Weichselbaum postulated "oligometastases" as a transitional state between localized and widespread systemic disease [6]. Sentinel studies supporting this concept have suggested the treatment of all sites of disease with ablative therapies can improve patient outcomes, including progression-free and overall survival in those with OMD [8,9].

Most studies have defined 'oligometastasis' as 1–3 or 1–5 metastatic lesions. In reality, enumeration, which is dependent on imaging sensitivity, is likely a crude surrogate for underlying disease biology that is amenable to MDT [14]. For example, EORTC 40004 trial that examined the impact of MDT using radiofrequency ablation in patients with colorectal cancer metastatic to the liver, allowed up to nine lesions and still revealed a prolonged progression free survival (PFS) [15]. The ongoing SABR-COMET-10 trial (NCT03721341) will report the role of SABR among patients with 4–10 metastatic lesions from different cancer types [16,17]. For patients undergoing SABR, fewer lesions also limits the dose to the surrounding normal tissue eliciting a better adverse effect profile. Technical advances have enabled proposing SABR MDT for patients with even polymetastatic disease (the ongoing ARREST trial (NCT04530513) [18]), in whom widespread dissemination of metastatic cancer has occurred (i.e. nonoligometastatic, >10 sites of metastases) [19].

Another important consideration is the clinical trajectory of OMD and the temporal state of lesions in correlation to each other and the primary site of disease. Synchronous or *de novo* omPCa patients are diagnosed with primary disease and metastases simultaneously. Metachronous omPCa is the state in which cancer patients have a limited number of recurrent metastases after curative therapy for their primary disease. Oligoprogressive disease is characterized by limited areas of treatment-resistant clones that expand in a background of otherwise stable or responding systemic disease.

RATIONALE FOR STEREOTACTIC ABLATIVE RADIATION THERAPY METASTASIS-DIRECTED THERAPY FOR OMPCA

Seminal work examining SABR MDT in the OMD space has been conducted across different cancer histologies. However, a significant amount of effort has been in PCa and is among the cancer types driving this new area of research and implementation [20]. First, there may be a radiobiological rationale for PCa to have a therapeutic advantage when treated with SABR given the very low α/β radioresponse constant as compared to surrounding normal tissues. Second, PCa recurrence or progression can be detected by the widely accessible and low-cost serum prostate specific antigen (PSA). More recently, with the highly specific prostate-specific membrane antigen (PSMA)-based molecular imaging utilizing positron emission tomography (PET), small metastases can now be localized for MDT. Lastly, these same tests (PSA and PSMA-PET) can also be used to monitor response to MDT.

SABR is at the forefront as a promising treatment modality for OMD [21]. This is attributed to its minimal side effects, brief treatment duration (administered in a limited number of sessions), and cost-effectiveness [22]. In this context, our objective is to examine recent research, emerging concepts, address gaps in knowledge, and outline the future steps in understanding the role of SABR MDT in treating omPCa.

RADIATION THERAPY FOR DE NOVO OMPCA

There is no prospective data demonstrating the benefit of SABR MDT in newly diagnosed or *de novo* omPCa. However, there are three prominent trials that examined the utility of primary prostate RT. The HORRAD trial randomized PCa patients with metastasis to the bone at diagnosis to receive ADT ± prostate RT [23]. HORRAD failed to show an overall survival (OS) benefit but a posthoc subgroup analysis of men with low burden disease suggested

a possible OS benefit that was not statistically significant [hazard ratio (HR) 0.68, $P > 0.05$]. The STAMPEDE Arm H study enrolled chiefly *de novo* metastatic PCa patients and randomized between SOC treatment (lifelong androgen deprivation therapy (ADT) with upfront docetaxel permitted) ± RT to the prostate primary [24▪▪]. RT to the primary prostate did not improve OS of the entire group, but OS was improved (HR 0.64, $P < 0.001$; 5-year absolute benefit of 12%) in patients with a low metastatic burden (defined by CHAARTED [25]). The most recent study, PEACE-1 is an open-label phase 3 trial that randomized 1173 men with *de novo* metastatic PCa to a variety of interventions in addition to ADT: arm A (ADT + docetaxel), arm B (ADT + docetaxel + abiraterone), arm C (ADT + docetaxel + RT to the primary prostate) or arm D (ADT + docetaxel + abiraterone + RT to the primary prostate). In the overall population, patients assigned to receive abiraterone ($n = 583$) had longer radiographic progression free survival (rPFS) (HR 0.54, $P < 0.0001$) and OS (HR 0.82, $P = 0.030$) with a modest increase in toxicity, mostly hypertension [26]. Although not published in print, the influence of RT to the primary prostate in low-volume defined subjects (as per the CHAARTED criteria) was reported to improve rPFS (median 7.5 versus 4.4 years, $P = 0.02$) when given with ADT + abiraterone, but not with ADT alone. OS was not shown to be improved in PEACE-1 with RT to the primary prostate. None of these trials consolidated metastatic sites with MDT and thus how to manage these lesions is still not clear from the current prospective data. Preclinical and translational evidence demonstrates that self-seeding and metastasis-to-metastasis seeding occurs in metastatic lethal PCa and thus complete consolidation of all macroscopic metastatic disease when feasible might change the natural history of metastatic PCa [27]. The results from ongoing SWOG 1802 (NCT03678025) [28], STAMPEDE2 [29▪], University of Maryland TERPS (NCT05223803) [30] and PLATON (NCT03784755) [31] trials will inform the field as to the potential benefits of SABR MDT to all sites of disease in patients with *de novo* omPCa.

STEREOTACTIC ABLATIVE RADIATION THERAPY METASTASIS-DIRECTED THERAPY FOR METACHRONOUS OMPCA

Metachronous or oligorecurrent PCa have been shown to have a better prognosis than *de novo* omPCa [32,33] and more recently shown to have a more indolent biology [33,34▪]. Furthermore, with the expanding use of PSMA PET scans, recurrence of disease can be detected earlier than conventional imaging [35▪]. SABR-COMET was an open-label phase 2 trial that enrolled a mixed population, including PCa, of oligometastatic cancer patients [9]. In this multicentric study, patients were randomly assigned (1 : 2) to palliative standard of care ± SABR to all metastatic lesions with the primary endpoint being OS. Of note, 14 out of 16 enrolled PCa patients were assigned to the SABR MDT arm as histology was not stratified. After a median follow-up of 51 months, the 5-year OS rate was 17.7% in control versus 42.3% in the SABR arm ($P = 0.006$). The STOMP trial was a multicenter, randomized phase 2 trial that enrolled 62 PCa patients who had received prior treatment with curative intent and had evidence of biochemical recurrence with testosterone >50 ng/ml and evidence of omPCa on choline PET-CT (≤3 extracranial sites) [36]. Patients were randomized 1 : 1 to surveillance or MDT (with either SBRT or metastatectomy). With a median follow-up of 5.3 years, the 5-year ADT-free survival was 8% in the surveillance arm compared to 34% for the MDT group (HR: 0.57, $P = 0.06$) [37]. The Baltimore ORIOLE trial was a randomized phase 2 trial of 54 men with metachronous omPCa (≤3 sites) by conventional imaging [38]. Patients were randomized in a 2 : 1 fashion to receive SABR MDT or observation. Treatment with SABR improved median PFS (not reached versus 5.8 months; $P = 0.002$). Recently pooled data from the two trials demonstrated that MDT improved PFS from 5.9 months to 11.9 months (HR 0.44, $P < 0.001$) [39▪]. The feasibility of applying SABR MDT safely and effectively was evaluated by the National Health Service (NHS) England. This prospective, registry-based, single-arm, observational evaluation study was completed in 17 commissioned NHS radiotherapy centers in England and enrolled 406 oligorecurrent omPCa with ≤3 extracranial lesions. After a median follow-up of 13 months, OS was 92·3% at 1 year and 79.2% at 2 years with the most reported grade 3 adverse event (AE) being fatigue [40]. Results from the prostate cohorts of the phase 2/3 CORE (NCT02759783) [41,42] and SABR-COMET-3 (NCT03862911) [43,44] trials will shed more definitive light on the role of SABR MDT in addition to SOC.

STEREOTACTIC ABLATIVE RADIATION THERAPY METASTASIS-DIRECTED THERAPY FOR OMCRPC

The majority of metastatic PCa patients progress to CRPC years after starting ADT, which carries a poor prognosis [45]. Despite the descriptor, CRPC is still androgen receptor dependent and resistant clones emerge in a subset of the total disease volume. Ablation of these resistant clones may offer clinical benefit in omCRPC. There are a number of

retrospective studies to support SABR MDT benefit in omCRPC [46 and references within]. As an example, our own experience suggested that compared with change in systemic therapy alone SABR MDT was associated with improved median time to PSA failure (9.7 versus 4.2 months, $P = 0.066$) and distant failure (12.7 versus 8.9 months, $P = 0.045$) [46]. There are also two single-arm phase 2 experiences that mirror our retrospective experience. Zhang and colleagues treated 89 oligoprogressive CRPC patients resistant to multisystemic therapy that had ≤3 choline-PET-CT detected lesions all treated with SABR MDT [47]. Median OS was 29.3 months, and 1- and 2-year OS were 96% and 80%, respectively, with no grade ≥3 AEs. ICE-PAC was a phase 2 single arm trial that enrolled 31 patients with refractory omCRPC to investigate the combination of SABR MDT with avelumab. The disease control rate was 48% [15/31; 95% confidence interval (CI) 30–67%] and objective response rate (ORR) was 31% (5/16; 95% CI 11–59%). In comparison, the response of nonprogressive lesions that were not irradiated within patients was 33% (4/12; 95% CI 10–65%), perhaps suggesting a systemic antitumor response evoked from the SABR MDT and avelumab [48▪].

Very recently, ARTO a phase 2 multicentric trial, randomized patients with omCRPC (≤3 nonvisceral lesions on imaging per discretion of physician) on abiraterone plus GnRH agonist or antagonist to receive SABR MDT to all sites of disease. Primary endpoint was the rate of biochemical response (BR), defined as a PSA decrease ≥50% from baseline measured at 6 months from treatment start. BR was detected in 92% versus 68.3% in the SABR versus control arms, respectively [odds ratio (OR) = 5.3, $P < 0.001$]. Complete BR, defined as PSA <0.2 ng/ml at 6 months from treatment was detected in 56% versus 23.2% in the SABR versus control arms, respectively (OR = 4.22, $P < 0.001$) [49▪▪]. The ongoing PILLAR (NCT03503344; apalutamide ± SABR MDT) [50], FORCE (NCT03556904; abiraterone, docetaxel, or enzalutamide ± SABR MDT) [51,52] and PCS-IX (NCT02685397; GnRH agonist and enzalutamide ± SABR MDT) [53] trials will help validate ARTO and inform the field further about the potential benefit of SABR MDT in combination with other systemic therapies in this subgroup of patients.

STEREOTACTIC ABLATIVE RADIATION THERAPY METASTASIS-DIRECTED THERAPY AND SYSTEMIC THERAPY COMBINATIONS IN OMPCA

One paradigm that justifies only local therapy is to consider isolated macroscopic lesions as the only sites of disease capable of seeding new metastatic lesions. Another viewpoint is simultaneous influence of micrometastatic disease, where concurrent systemic therapy with MDT is the optimal treatment. EXTEND is a phase 2 clinical trial that enrolled 87 patients with omCSPC (≤5 metastases) to test the synergy between ADT and SABR MDT. Patients were randomized to receive intermittent ADT ± SABR MDT to all sites of oligometastases. With a median follow-up of 22.0 months, median PFS was significantly better in the combined therapy arm (HR = 0.25, $P < 0.001$) and the rate of new metastases at 2 years fell from 42% to 33% in the SABR MDT group ($P = 0.04$) [54▪▪].

Combination of ADT with second-generation androgen receptor targeting agents has shown to be beneficial for metastatic PCa across the CSPC-CRPC spectrum [55]. In addition, improvements in OS by radiopharmaceuticals such as radium-223 [56] and PSMA-targeted drugs [57,58] for metastatic CRPC are intriguing agents to combine with SABR MDT in omPCa. Although there were a substantial number of patients in several trials with presumably low-volume metastatic disease, the combination of these agents with SABR MDT has not been formally evaluated.

Ongoing trials will evaluate the combination of SABR MDT with other novel systemic therapies. DART (NCT04641078) is looking at the efficacy of combination of SABR ± short-term darolutamide in extending metastasis-free survival in omCSPC [59]. Similarly, the Baltimore RAVENS trial (NCT04037358) is a phase 2, nonblinded, randomized successor to the ORIOLE trial that is comparing SABR ± radium-223 dichloride in patients with omCSPC (≤3 metastases with at least one bone metastasis) with the primary endpoint of extending PFS with radium-223 dichloride [60,61].

CONCLUSION

Data from randomized phase 2 trials of SABR for omPCa have demonstrated a benefit signal for both omCSPC and omCRPC, but we are still lacking phase 3 definitive evidence confirming these findings. Additional studies are necessary to address several critical questions, such as identifying patients who may not benefit from this treatment strategy, determining those who could derive the most significant benefits, that is, potentially achieving a cure, and better defining the best integration of SABR MDT with systemic therapy in these groups. Ongoing studies in this area are expected to provide additional insights, contributing to a clearer understanding of the clinical benefits of using SABR MDT in the context of omPCa.

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Conflicts of interest

P.T.T. has consulted and has received personal fees for NATSAR Pharmaceuticals, Johnson and Johnson, Regeneron, Bayer Healthcare, Lantheus, Pfzier and RefleXion Medical Inc. P.T.T. also has a patent for 9114158 issued to Natsar Pharmaceuticals with royalties paid from Natsar Pharmaceuticals. The remaining authors declare no conflict of interest.

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