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Metastasis-directed therapy: new standard or too early to change paradigm?

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Summary Metastasis-directed therapy (MDT) is an emerging treatment strategy for patients with oligometastatic prostate cancer (PCa), particularly for oligorecurrent disease. This review aims to summarize findings from several prospective trials in the setting of oligorecurrent PCa. We found that MDT is feasible, has high tolerability, and is effective in terms of local control of treated lesions and of deferring disease progression in well-selected patients. Selecting patients for MDT requires thoughtful consideration of factors such as the castration status, the number of detected metastases, and the imaging modality used for metastasis detection. Notably, the studies included in this review varied in terms of these factors, complicating the comparability of their results. Despite the existence of several prospective clinical

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trials in the field, there is an absence of high-level evidence attributable to the lack of phase 3 clinical trials. As a result, current guidelines recommend the administration of MDT exclusively within the context of clinical trials. Despite this, retrospective series indicate that MDT is already frequently utilized outside of clinical trials.

Keywords Prostate cancer · Oligometastatic prostate cancer · Metastasis-directed therapy · Stereotactic radiotherapy · Surgery

Introduction

Metastasis-directed therapy (MDT) is a promising treatment option for oligometastatic prostate cancer (PC), a condition that occupies the clinical spectrum between non-metastatic and widespread systemic disease [1]. Characterized by a limited volume of metastatic cells and locations (predominantly 1–5 metastatic lesions), this specific stage of cancer can occur in both hormone-sensitive (mHSPC) and castration-resistant (mCRPC) forms of metastatic prostate cancer (mPCa), presenting either synchronously or metachronously. Recent advancements in imaging modalities have brought oligometastatic PC into the spotlight, suggesting potential advantages of MDT [2]. Initial evidence from phase 2 trials indicates that MDT, used alone, could improve progression-free survival (PFS) in patients with oligorecurrent PC (OPC; [2, 3]). However, guidelines recommend using MDT only as an investigational approach within clinical trials [4].

In the setting of newly diagnosed metastases (mHSPC), since data on the efficacy of MDT are sparse, current guidelines continue to endorse the combination of androgen deprivation therapy (ADT) with androgen receptor signaling inhibitors (ARSI; [4]), which have been proven to improve overall survival (OS) and PFS [5–8].

Against this backdrop, it is hypothesized that MDT could postpone disease progression and delay systemic treatment in patients with OPC after local therapy with curative intent such as RP or RT. Given the rapid evolution of evidence and several ongoing clinical trials investigating MDT, we aimed to summarize evidence derived from prospective trials deploying MDT in the setting of OPC following RT or RP.

Evidence acquisition

We searched the PubMed database up to 1 October 2023 using pre-defined search criteria as follows: (prospective) AND ((metastatic) OR (oligometastatic)) AND (prostate cancer) AND (prostatectomy) AND ((radiotherapy) OR (radiation therapy) OR (metastasis directed) OR (MDT) OR (radiosurgery) OR (metastasectomy)).

We identified eight publications reporting on prospective clinical trials investigating MDT only in the setting of oligorecurrent prostate cancer since January 2018 (Table 1). Furthermore, we conducted a search on https://clinicaltrials.gov for active phase 3 clinical trials that are utilizing MDT for OPC (Table 2).

Single-arm prospective trials

The POPSTAR trial [9], published in 2018, applied stereotactic radiosurgery (SRS) to 33 OPC patients, consisting of 67% mHSPC and 33% mCRPC, each presenting 1–3 bone or lymph node metastases identified through conventional imaging and sodium fluoride positron emission tomography (PET) scans. Lymph node metastases were exclusive in 36.4% of patients. Aside from confirming feasibility (97% completed full treatment) and tolerability (a single grade 3 Common Terminology Criteria of Adverse Events [CTCAE] adverse event noted), a 24-month median follow-up exposed 1- and 2-year local and disease PFS rates of 97% and 58%, and 93% and 39%, respectively. A 2-year ADT-free survival rate of 48% was observed in mHSPC patients.

Similarly, Kneebone et al. [10] investigated SRS or stereotactic body radiotherapy (SBRT) to treat all lesions observed in 57 OPC patients, who harbored 1–3 lymph node or bone metastases detected via a prostate-specific membrane antigen (PSMA) PET scanning. All participants had mHSPC, with 65% displaying only nodal metastases. The primary endpoint was a biochemical failure, determined by a post-SBRT or SRS PSA level of nadir +0.2 ng/mL. Within a 16-month median follow-up, the median biochemical disease-free survival (bDFS) was 11 months, with a 31.9% bDFS rate observed at 15 months. Notably, the study reported no in-field failures, and no toxicities of grade ≥3 (according to CTCAE) were observed.

In 2022, Glicksman et al. [11] studied 74 hormone-sensitive patients with biochemical recurrence after RP and postoperative RT with or without ADT; all had 1–6 PSMA PET-detected metastases but no evidence of metastases on conventional imaging (i.e., computed tomography [CT] and/or bone scan). Lymph node metastases only were observed in 86.5% of the patients. Most patients received SBRT (87%), while a small fraction (13%) underwent metastasectomy. The primary endpoint was a ≥ 50% PSA decline following MDT. Over a median follow-up of 24 months, half of the patients exhibited a biochemical response (51%), and the median biochemical PFS and ADT-free survival were 21 and 45 months, respectively. One patient experienced grade 3 toxicity (intraoperative ureteric injury).

Finally, the 2022 OLI-P-trial [12, 13] reported results for local ablative RT (aRT) in patients with 1–5 PSMA PET-detected metastases after curative treatment with a life expectancy of ≥5 years. All participants were hormone sensitive and 68.3% of the patients had only

Table 1 Clinical trials employing MDT alone for oligorecurrent prostate cancer

Study	Type	Setting	Intervention	Inclusion	Imaging	*N* (study arm/ control arm)	Median FU	Evaluated clinical outcomes
STOMP (2018) [3]	RCT	100% mHSPC	SBRT or metastasectomy vs. observation	1–3 extracranial metastases, asymptomatic biochemical recurrence following curative treatment (no ADT, no local relapse, serum testosterone levels >50 ng/mL); ECOG ≤ 1	Choline PET	31/31	36	ADT-free survival, PSA progression, local progression
ORIOLE (2020) [2]	RCT	100% mHSPC	SBRT vs. observation	1–3 asymptomatic metastases after primary curative treatment, and no ADT within 6 months of enrolment	Conventional imaging	36/18	19	Progression-free survival, biochemical progression-free survival, distant metastases-free survival
Pan (2022) [14]	nCT	Non-metastatic PC patients based on conventional imaging who experienced early PSA (prostate-specific antigen) progression on ADT	SBRT vs. ADT in control group	1–5 bone or lymph node metastases and early PSA progression on ADT following curative treatment; ECOG ≤ 1, life expectancy > 12 months	PSMA-PET	29/18	21	Metastasis-free survival
POPSTAR (2018) [9]	SA	67% mHSPC, 33% mCRPC	SRS	1–3 bone or lymph node metastases following curative treatment; ECOG ≤ 2	NaF-PET	33	24	Local progression-free survival, distant progression-free survival, ADT-free survival, PSA response
Kneebone (2018) [10]	SA	100% mHSPC	SRS or SBRT	1–3 lymph node or bone metastases following biochemical recurrence after primary curative treatment	PSMA-PET	57	16	Progression-free survival, biochemical progression-free survival, distant metastases-free survival
Glicksman (2022) [11]	SA	100% mHSPC	SBRT or metastasectomy	1–6 metastases following biochemical recurrence after RP and postoperative RT +/– ADT	PSMA-PET	74	24	Biochemical response, PSA progression-free survival, ADT-free survival, salvage treatment-free survival, CRPC-free survival
OLI-P (2022) [12, 13]	SA	100% mHSPC	SBRT or conventional RT	1–5 bone or lymph node metastases following local curative therapy and PSA ≤ 10 ng/mL; Life expectancy ≥ 5 years	PSMA-PET	63	37	PSA progression-free time, time to start systemic therapy, progression-free survival, overall survival. local progression-free time, time to the first tumor-related clinical event

RCT randomized clinical trial, *nCT* multi-armed clinical trial, *SA* single-arm clinical trial, *SBRT* stereotactic body radiotherapy, *SRS* stereotactic radiosurgery, *RT* radiotherapy, *ADT* androgen deprivation therapy, *ECOG* Eastern Cooperative Oncology Group Performance Status Scale, *PSA* prostate-specific antigen, *RP* radical prostatectomy, *PET* positron emission tomography, *PSMA* prostate-specific membrane antigen, *NaF* sodium fluoride, *FU* follow-up, *MDT* metastasis-directed therapy (MDT), *SOC* standard of care, *mHSPC* metastatic hormone-sensitive prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer

nodal disease. With 63 participants who met the inclusion criteria, no treatment-related toxicities were observed 2 years after aRT, meeting its primary endpoint of grade ≥2 toxicity in less than 15% ($p < 0.001$). Only one instance of grade 3 toxicity (bacterial cystitis) was reported within the 37-month median follow-up. The median PSA progression-free survival was 13 months, with 13% of the 47 patients experiencing PSA progression resulting in ADT initiation before reaching the PSA recurrence definition. A subsequent publication [13] reported a 3-year local PFS rate of 93.5%, with distant progression observed in 52% of the patients over a 41-month follow-up within the same study cohort.

Prospective randomized clinical trials and multi-arm clinical trials

Published in 2018, STOMP [3] was the first RCT to assess MDT alone in OPC. The study randomized 62 patients with 1–3 extracranial metastases (diagnosed after RP or RT via choline PET) into two groups: MDT via SBRT/metastasectomy or observation. All patients were hormone-sensitive, and 54.8% had only nodal

Table 2 Ongoing clinical phase 3 trials employing MDT

Study	Setting	Intervention	Planned cohort size	Primary endpoint
NCT05352178 (SPARKLE)	Oligorecurrent disease	MDT alone vs. MDT + 1 month of ADT vs. MDT + 6 months of ADT	873	Poly-metastatic-free survival (PMFS)
NCT04302454 (ADOPT)	Oligometastatic disease	MDT alone vs. MDT + ADT	280	Metastases progression-free survival (MPFS)
NCT04787744 (VA STARPORT)	Oligorecurrent disease	SOC systemic therapy + MDT vs. SOC systemic therapy	464	Radiographic progression-free survival (rPFS)
NCT04423211	Oligorecurrent disease	MDT + SOC treatment vs. SOC treatment alone	804	Progression-free survival (PFS)
NCT04983095 (METRO)	Oligometastatic disease	MDT + SOC treatment vs. SOC treatment alone	114	Failure-free survival
NCT04115007 (PRESTO)	Oligometastatic disease	MDT + SOC treatment vs. SOC treatment alone	350	Castration-resistant prostate cancer-free survival

ADT antiandrogen therapy, *MDT* metastasis-directed therapy, *SOC* standard of care

metastases. The primary endpoint was ADT-free survival. Over a 36-month median follow-up, the MDT group had a median ADT-free survival of 21 months versus 13 months in the observation group (hazard ratio [HR]: 0.6, 80% confidence interval (CI): 0.40–0.90, log-rank $p = 0.1$). The MDT group had no symptomatic or local progression compared to three and six cases, respectively, in the control group.

The 2020 ORIOLE trial [2] randomly assigned OPC patients with 1–3 asymptomatic metastases and no ADT within the last 6 months to either SBRT or observation (2:1 ratio). All 54 patients were hormone sensitive and diagnosed via conventional imaging, with 58% having only nodal disease. The primary endpoint, progression at 6 months (progression of PSA, progression on conventional imaging, PCa-related symptoms, ADT initiation, or death), occurred in 19% (SBRT) versus 61% (observation) of patients ($p = 0.005$). Within a 19-month median follow-up, median PFS was not reached in the SBRT group versus 6 months in observation (HR: 0.3, 95% CI: 0.11–0.81, $p = 0.002$). With SBRT a 98.6% local control rate was achieved at 6 months. Although PSMA PET was conducted in treatment planning, the team was blinded to findings, leading to 16% of 36 SBRT-treated patients harboring supposedly untreated lesions. More patients with untreated lesions experienced progression (38% vs. 5%, $p = 0.03$), and their median PFS was 11.8 months versus not reached in patients without untreated lesions (HR: 0.26, 95% CI: 0.09–0.76, $p = 0.006$). No grade 3 or higher adverse events were reported in either group including the SBRT group.

In 2022, Pan et al. [14] evaluated metastasis-free survival (MFS) efficacy and toxicity in non-metastatic PC patients based on conventional imaging who experienced early PSA progression on ADT after RP or RT. All patients underwent PSMA and fluorodeoxyglucose (FDG) PET imaging. The three-armed trial recommended SBRT for patients with ≤5 nonvisceral metastases (SBRT group), while those without detectable metastases or refusing SBRT continued ADT (N^-/M^- and ADT groups). Out of 74 screened, 67 met the inclusion criteria: 47 with N^+/M^+ disease (29 in SBRT group, 18 in ADT group), and 20 with N^-/M^- disease. Lymph node metastases only were found in 34% of the SBRT group and 50% of the ADT group. Over a 21-month median follow-up, the ADT group's MFS was shorter than that for the SBRT group (11 months vs. not reached; HR: 4.69, 95% CI: 4.04–40.3, $p < 0.001$). Similarly, the N^-/M^- group's median MFS was not reached, indicating no significant difference between the SBRT group and the N^-/M^- group ($p = 0.3$). Multivariable analysis revealed SBRT as the sole MFS prognostic factor for MFS in N^+/M^+ patients (HR: 0.10, 95% CI: 0.03–0.32, $p < 0.001$). No grade ≥3 toxicities occurred in the SBRT group.

Discussion

The efficacy of MDT in enhancing local control is supported across the results of all referenced clinical trials. These trials also highlight the favorable tolerability and feasibility of MDT. However, a crucial consideration is that MDT primarily serves to postpone disease progression, rather than halt it entirely, thereby helping to delay the need for systemic treatment. Furthermore, the positive response rates to MDT observed might also support the hypothesis of tumor cell seeding by the metastases themselves rather than from the primary tumor, suggesting a potential mechanism behind the efficacy of localized treatments in oligometastatic settings [15]. While these outcomes are indeed promising, the limitations inherent to the studies without evidence on long-term oncologic outcome improvements (OS, CSS, or any other improved surrogate endpoint). Given that patients with oligorecurrent PC typically exhibit long median OS rates under systemic treatment [16], the emphasis on quality of life and potential treatment side effects becomes increasingly significant. Consequently, even if MDT does not markedly enhance OS, it could still play a role in the PC treatment landscape. This is due to its ability to delay systemic treatment, potentially mitigating the side effects associated with it and resulting in extended periods of high-quality life. On the other hand, MDT could also be used

for therapy intensification. At present, the body of evidence primarily comprises phase 2 trials with relatively small sample sizes. Discrepancies in endpoints and definitions across studies further confound the interpretation of outcomes. Furthermore, the use of varied imaging modalities for diagnosis could potentially skew these outcomes, given that patients diagnosed via conventional imaging may be "under"-staged compared to those diagnosed using PSMA-PET [17].

In this brief review, we did not include studies examining MDT in conjunction with systemic treatment, or those conducted in alternative contexts such as primary synchronous OPC. However, recent findings from a phase 2 RCT suggest MDT + ADT may surpass ADT alone in oligometastatic prostate cancer patients with five or fewer metastases, particularly in terms of median PFS (not reached vs. 16 months, HR: 0.25, $p < 0.001$; [18]). This underscores that the applicability of MDT may not be confined solely to oligorecurrent PC, and combination therapies could offer enhanced efficacy. Although MDT has shown the capability of delaying systemic treatment, antiandrogenic combination therapy remains the standard of care in the oligometastatic setting [4]. Considering the side effects and the lifelong administration of this therapy, it could be argued that combining MDT with ADT, which might increase efficacy, would potentially allow for a pause in antiandrogenic therapy in cases of good and stable PSA response. However, further prospective studies are needed to clarify this question, and the definitive role of MDT in systemic PCa treatment requires robust evidence from large-scale phase 3 RCTs (the currently registered phase 3 trials are presented in Table 2). As per current guidelines [4], the application of MDT should be limited to the context of clinical trials until such evidence becomes available. Nevertheless, in clinical practice, MDT is widely used in different forms [19–23]. This is largely due to the rising use of PSMA PET, which uncovers a previously unidentified stage of disease—PSMA PET-avid lesions undetectable with conventional imaging—a scenario that current guidelines do not specifically address. In this context, clinicians frequently resort to MDT as a means to impact disease progression and delay the onset of ADT-related toxicities, with a minimal risk of severe AEs. The ESTRO-ACROP consensus statement [24], despite its low level of evidence, provides valuable guidance for clinical decision-making in determining the appropriate setting and site for MDT application.

Conclusion

Metastasis-directed therapy (MDT) presents a promising therapeutic avenue for treating oligorecurrent prostate cancer following local therapy with curative intent. However, until substantial evidence from large phase 3 RCTs emerges, the application of MDT should remain within the realm of clinical trials. Furthermore, when considering MDT, it is crucial to determine the metastatic load as reliably as possible in advance via prostate-specific membrane antigen–positron emission tomography–computed tomography (PSMA-PET-CT), to ensure the treatment encompasses all metastases.

Take-home message

Metastasis-directed therapy (MDT) provides adequate local disease control and is safe and well tolerated by patients. Additionally, it can postpone disease progression, thereby delaying the need for systemic treatment. However, the current lack of level 1 evidence has led to guidelines not recommending its use outside of clinical trials. Nevertheless, it is being adopted in clinical practice, particularly for patients with prostate-specific membrane antigen–positron emission tomography (PSMA PET)-avid lesions and normal conventional imaging—a disease stage for which there are currently no clear guideline recommendations. Therefore, it is crucial that patients deciding on MDT for oligometastatic disease are thoroughly informed about the current lack of level 1 evidence and the current guideline recommendations.

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Conflict of interest J. Klemm, P. Rajwa, M. Miszczyk, S. Brönimann, E. Laukhtina, I. Tsuboi, A. Matsukawa, M.K. Parizi, P.I. Karakiewicz and S.F. Shariat declare that they have no competing interests.

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