Metastasis-directed therapy in oligometastatic prostate cancer

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Purpose of review
To summarize the recent findings on the subject of metastasis-directed therapy (MDT) in the treatment of oligometastatic prostate cancer (omPCa).

Recent findings
Evidence from two randomized clinical trials (RCTs) and a meta-analysis show favorable toxicity profiles, and the potential to delay androgen-deprivation therapy (ADT) for up to two years in nearly half of patients with metachronous hormone-sensitive omPCa. Another RCT showed promising results of MDT as treatment-escalation method combined with androgen receptor signaling inhibitors (ARSI) in first-line treatment for castration-resistant omPCa.
Surveys by radiation oncologists and consensus guidelines advocate for MDT across various omPCa scenarios. Multiple single-arm trials present encouraging results; however, the evidence for the benefit of MDT is still weak requiring further investigation to assess its impact on pivotal endpoints, such as survival and quality of life.

Summary
MDT is a promising approach in omPCa, and can be used to defer ADT in newly diagnosed metachronous omPCa patients, or to add to ARSI treatment at first diagnosis of castration-resistance. Ongoing prospective trials are needed to guide its optimal utilization in other settings, and patients should be informed about the evolving landscape of systemic therapies with proven survival benefits alongside MDT options.

Keywords
metastasis-directed therapy, prostate cancer, radiotherapy

INTRODUCTION

Metastasis-directed therapy (MDT) has primarily been investigated within the context of metachronous oligometastatic prostate cancer (omPCa) to defer or avoid androgen-deprivation therapy (ADT) [1,2]. A recent meta-analysis has confirmed that MDT presents a favorable toxicity profile and offers a chance to delay ADT initiation for at least two years in approximately half of the cases [3▪]. Many patients concerned about ADT-related adverse effects are currently considering this option. However, the data supporting MDT consists in majority of single-arm trials. This contrasts with the enthusiastic uptake of MDT into daily clinical practice.

The complexity of the diverse MDT strategies across the different metastatic disease states render an overall judgment on its value sheer impossible. Initially utilized to mitigate toxicity in metachronous omPCa patients, MDT is gaining popularity in the context of treatment escalation, but yet lacks strong evidence in this setting as well. This article

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KEY POINTS

- Recent evidence, albeit of limited quality, continues to support metastasis-directed therapy (MDT) as a method to defer androgen-deprivation therapy (ADT)-related toxicity.
- MDT intensification of SOC with androgen receptor signaling inhibitors and ADT can be beneficial as first-line therapy for oligometastatic prostate cancer.
- MDT provides robust local metastatic site control, and is associated with low toxicity.
- Single arm trials investigating new applications of MDT are continuously emerging, creating new hypotheses for MDT use.
- Overall survival and health-related quality of life benefits of MDT treatment remain to be confirmed in well designed randomized controlled trials.

aims to provide readers with a summary of recent findings regarding MDT in the treatment of omPCa.

METHODS

A nonsystematic literature search was conducted on 8 November 2023 to retrieve records published since 2022 concerning MDT in omPCa treatment. Articles were retrieved using MEDLINE via PubMed and the top 100 hits from the Google Scholar search engine (Supplementary File 1, Supplemental Digital Content, http://links.lww.com/COU/A46). Additional citations were identified through backward citation search and co-authors' suggestions. The results were presented as a narrative review.

GENERAL OVERVIEW OF METASTASIS-DIRECTED THERAPY IN CONTEXT OF PROSTATE CANCER

Regardless of existing knowledge gaps, MDT has gained widespread acceptance as a treatment option across various settings of omPCa, including common use beyond clinical trials to bolster treatment in conjunction with systemic and/or interventional therapies. A recent survey conducted by the DEGRO group revealed that almost all radiation oncology respondents favored MDT for oligometastatic recurrence in PCa patients, with over half considering combining MDT with systemic therapy [4]. Notably, more than half of those surveyed did not differentiate between synchronous and metachronous disease, even though the evidence for MDT in PCa primarily stems from metachronous omPCa [3▪]. Similarly, the recent ESTRO-ACROP Delphi consensus reflected experts' inclination toward offering MDT in all de novo oligometastatic settings (as per ESTRO/EORTC nomenclature [5]), at the same time acknowledging the lack of conclusive evidence [6].

Implementing standardized terminology proved challenging, and the reporting of oligometastatic characteristics often remains partial and insufficient [7]. Therefore, we urge readers to be aware of the specific metastatic disease state where MDT is being assessed within each study. The proper diagnosis and classification depends on the quality of medical imaging, and experts and clinicians consistently endorse prostate-specific membrane antigen (PSMA) positron emission tomography (PET) as the preferred imaging modality for omPCa patients. Despite lack of conclusive comparative evidence, considering the insights from the STOMP trial [2] and the previously mentioned ESTRO-ACROP guidelines [6], the authors agree that PSMA-PET should be regarded as the preferred medical imaging to guide MDT, at least until further evidence suggests an alternative.

The substantial clinical interest in MDT is evident through numerous retrospective cohorts detailed in the literature, outlining treatments of hundreds of cases with MDT. However, the available evidence from prospective trials remains limited, predominantly sourced from small single-arm studies. A recent meta-analysis reported promising outcomes in metastatic PCa patients treated with MDT, indicating a 2-year overall survival (OS) rate of 97%, 2-year local control of 98%, and a favorable 2-year progression-free survival of 46% [3▪]. Notably, the toxicity rates appear to be remarkably low. As few as 0.3% patients experience grade $\geq$3 MDT-related adverse events such as pathologic fractures following radiotherapy, or metastasectomy-related perioperative injuries [3▪]. There is a significant conceptual heterogeneity concerning timing and concurrent therapies, and criteria for the optimal selection of candidates for MDT have yet to be determined. Despite three available phase II RCTs, discussed in detail later in the manuscript, the impact of MDT on OS remains to be determined [1,2,8▪▪].

METASTASIS-DIRECTED THERAPY AS A PART OF MAXIMAL THERAPY WITH CURATIVE MINDSET

The utilization of MDT alongside local curative treatment and systemic therapies for de novo synchronous omPCa presents an enticing idea, rooted in the concept of potentially achieving cure in this early metastatic disease spectrum state. Despite its popularity among clinicians, this approach lacks sufficient

evidence, without any proper prospective comparative studies. For example, Hao *et al.* published the results of a combined therapy approach in 29 patients with de novo hormone-sensitive omPCa, 16 of whom had synchronous oligometastases [9▪]. With an extensive follow-up period, the authors observed comparable OS and even improved progression-free survival (PFS) in patients with synchronous omPCa treated with MDT. Although the median OS almost reached a decade, the median PFS fell just short of two years. Therefore, the long-term survival is likely owing to the significant contribution of modern systemic treatments.

Another publication by Reyes *et al.* detailed the outcomes of two companion studies examining maximal therapy with curative intent for de novo synchronous omPCa or metachronous omPCa postradical prostatectomy in a total of 47 patients [10▪]. Employing an exceptionally aggressive approach, the authors combined MDT with ADT, ARSI, chemotherapy, radical prostatectomy, and even adjuvant prostate bed radiotherapy where applicable. Despite a subset of nonevaluable patients, they reported an impressive 80% rate of PSA control following testosterone recovery at two or three years after treatment.

A similar approach was taken in the study by Chang *et al.* The authors combined neoadjuvant ADT, pelvic radiotherapy, MDT, and subsequent radical prostatectomy in 12 omPCa patients [11▪]. The authors reported 2-year radiological PFS of 83%. Despite very promising results in well selected patients, long-term results and large prospective comparative trials are eagerly awaited to provide further insights in the place for MDT in PCa care.

ADDITION OF METASTASIS-DIRECTED THERAPY TO STANDARD OF CARE TO INTENSIFY THERAPY

In exploring MDT as means to intensify hormone therapy, Deodato *et al.* examined the application of MDT targeting bone metastases in 37 omPCa patients treated with ADT [12▪]. The majority of these men had oligometastatic hormone-sensitive prostate cancer (HSPC), whereas a smaller subset had castration-resistant prostate cancer (CRPC). Employing a dose-escalation approach up to 24 Gy, the authors reported 51% next-line systemic treatment-free survival, minimal toxicity, and no RT-induced bone fractures. Although promising, achieving similar outcomes might be possible with modern combination systemic therapy (e.g. ADT with ARSI ± docetaxel chemotherapy).

Kwan *et al.* combined stereotactic body radiation therapy (SBRT) MDT with immunotherapy in heavily pretreated CRPC patients [13▪]. It remains challenging to discern the specific benefit of MDT due to the simultaneous introduction of experimental immunotherapy. Instead of treating all visible disease sites, which might not be beneficial in advanced CRPC, MDT was administered to 1–2 metastases before the first and second cycle of Avelumab to boost the immune response, with the hope of adding an abscopal effect. Although uncommon in PCa treatment, the upregulation of tumor neoantigens with SBRT could help to overcome resistance to immune therapies, potentially opening another line of treatment. Investigating molecular biomarkers, as done by the authors, is a high research priority to identify optimal candidates for MDT.

Pan *et al.* introduced an intriguing concept of early treatment escalation in CRPC patients [14▪]. The authors used MDT to eradicate up to five metastases in 29 patients initially diagnosed with nonmetastatic PCa but who experienced disease progression on ADT. With a >90% PSA response in 84% of cases and the median metastasis-free survival still not reached at a median follow-up of 21 months, the results appear notably positive. However, the stringent inclusion and selection criteria limit generalizability, and verifying survival benefit through an RCT remains necessary.

The largest trial on treatment escalation with MDT was recently published by Francolini *et al.* [8▪▪]. The authors randomized patients to receive either ARSI alone or in combination with MDT targeting all visible disease sites as first-line treatment for oligometastatic CRPC. This substantial trial involving 157 patients showed positive results in terms of the primary biochemical endpoint. Importantly, patients who received MDT demonstrated improved radiologic progression-free survival (PFS), providing pivotal evidence supporting the combination of MDT with ARSI in the first-line treatment of oligometastatic CRPC. The nonsignificant difference in OS, however, questions the clinical meaningfulness of MDT in this setting.

Lastly, local treatment aimed at preventing adverse events was investigated in the PROMPTS trial by Dearnaley *et al.* [15]. The study evaluated whether systematic screening with magnetic resonance imaging (MRI) reduced the incidence of clinical spinal cord compression (SCC) in CRPC patients with spinal bone metastases. Patients received RT or surgical decompression upon radiologic symptoms of SCC. However, at a median follow-up of 22 months involving 420 patients, no statistically significant improvement in time to clinical SCC was observed. This RCT concluded that routine screening and preemptive treatment of bone lesions in the spinal cord area are not warranted in asymptomatic patients. While not exclusively pertaining to omPCa, this trial

underlines that MDT does not provide a significant clinical benefit for patients in every setting.

METASTASIS-DIRECTED THERAPY TO DEFER ANDROGEN-DEPRIVATION THERAPY

MDT remains a valuable option for hormone-naive patients seeking to defer or avoid side effects from ADT. Recently, Deek *et al.* provided updated long-term results from the STOMP and ORIOLE trials, emphasizing that MDT continues to serve as a means to circumvent or delay ADT-related toxicity [16▪]. The authors also explored genetic mutations associated with response to MDT, signaling a promising and crucial direction toward refining patient selection. However, the updated results from these trials did not reveal improvements in OS, radiologic PFS, or CRPC-free survival.

Glicksman *et al.* administered MDT to 74 patients experiencing early biochemical failure and omPCa following definitive local treatment. Notably, due to regulatory constraints, a major part of the cohort comprised patients who were non-metastatic on conventional imaging. The study achieved an impressive 70% of patients being ADT-free at the 2-year mark [17▪]. The findings from Glicksman *et al.*, alongside those by Pan *et al.* and Francolini *et al.* discussed earlier, suggest that timing could be paramount for the success of MDT, with early disease patients along the metastatic biological and clinical spectrum being those to derive the largest benefit from MDT.

Finally, Holscher *et al.* reported on the outcomes of 63 omPCa patients treated with MDT targeting 1–5 disease sites visible on PSMA-PET [18▪]. Approximately 47% of these patients remained free from ADT at the two-year mark, confirming the efficacy of MDT in postponing the initiation of ADT.

SURGERY IN THE SETTING OF OLIGOMETASTATIC PROSTATE CANCER

MDT predominantly relies on radiotherapy; however, several studies described surgical interventions performed for visceral or bone lesions [19], which could be especially valuable in case of symptomatic metastases. As aforementioned, authors have also explored the possibility of comprehensive treatments combining radical prostatectomy with MDT and systemic therapy to potentially achieve cure [10▪,11▪]. These treatments are also sometimes performed in high-volume centers outside of clinical trials [20]. Overall, while radiotherapy is significantly more popular, there are instances in which surgery can play an important role in omPCa care.

RETROSPECTIVE SERIES

Numerous retrospective studies have surfaced in recent years exploring MDT in omPCa, many of which introduce investigational approaches. A few studies were chosen arbitrarily to provide a glimpse into the breadth of data.

Bianchi *et al.* conducted a retrospective analysis involving 113 patients with recurrent omPCa postlocal radical treatment, diagnosed using PSMA-PET. Their comparison of MDT plus standard of care (SOC) with SOC treatment indicated significantly improved metastasis-free survival (MFS) and CRPC-free survival in patients receiving MDT. However, interpreting these findings requires caution due to the lack of propensity score matching and potential confounding inherent in nonrandomized treatment allocation [21].

Mercier *et al.* reported on the association between MDT and short-term ADT, observing improved outcomes. They found that combining MDT with short-term ADT ($n = 18$) led to enhanced biochemical PFS compared to MDT alone ($n = 30$) [22]. In contrast, Pastorello *et al.* studied 95 patients with 150 nonspinal bone metastases diagnosed via PSMA-PET. Their findings suggested a negative trend for polymetastatic disease-free survival with concomitant systemic therapy. While not explicitly stated by the authors, it's plausible that the unfavorable outcomes were linked to the selection of patients with more aggressive disease for combined treatment with ADT [23].

The majority of these retrospective trials share methodological challenges, including potential selection bias and confounding factors. Consequently, RCTs are imperative to comprehensively guide the utilization of MDT in the ever-evolving landscape of modern omPCa treatment.

CONCLUSION

While evidence on MDT remains limited, ongoing data from well designed prospective trials continues to emerge. Notably, phase II trials such as the STOMP and the ORIOLE trials, along with their pooled extended results, provide substantial support for employing MDT to delay the initiation of ADT in oligometastatic HSPC patients. Recent meta-analysis of prospective trials highlights the remarkable local control of metastatic sites achieved by MDT, alongside favorable PFS rates and notably low toxicity. The groundbreaking ARTO trial set the stage for integrating MDT with ARSI in the first-line treatment of oligometastatic CRPC. Such a trial is likely to have even a larger effect in mHSPC, allowing potentially for deep prolonged responses empowering an intermittent therapy interval in some patients, resulting in better health-related quality of life (HR-QoL).

Undoubtedly, MDT stands as a promising treatment strategy, and its indications are gradually emerging. Considering the uncertainty surrounding its impact on major oncologic outcomes, patients should be consistently counseled about available systemic therapies that have demonstrated proven survival benefits. Nevertheless, this concept makes so much sense that there is a risk of overuse and misuse. Therefore, the radiation therapy community is called upon to design a large, prospective, controlled trial with meaningful disease (i.e. OS) and patient (i.e. HR-QoL) endpoints.

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Conflicts of interest

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- ■■ of outstanding interest

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