Metastasis Directed Therapy and/or Systemic Therapy in Hormone-Naive Oligometastatic Prostate Cancer Patient: an Emerging Dilemma

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Abstract

The hormone-naive oligometastatic prostate cancer is a challenging setting for the radiation oncology community, as it represents a sort of transition scenario potentially suitable for two different approaches: a local ablative treatment alone vs a metastasis-directed treatment with the addition of hormone therapy. The choice to add androgen deprivation therapy in the oligorecurrent hormone-sensitive patient is a matter of debate, given the detrimental impact on quality of life and the number of adverse events. To date, there is no clear agreement on the optimal management of this subset of patients. As some authors highlight the attractiveness of a local approach alone, as well tolerated, easily repeatable and with very limited costs, on the other hand, other authors focus the need to cover the micrometastatic disease, often not detectable, even with the newly available imaging modalities. In this commentary, we briefly summarize the literature data in support of both therapeutic strategies.

Keywords: Prostate cancer, Oligometastatic cancer, SBRT, Androgen Deprivation Therapy, Radiotherapy

Main text

Since 1995 with the birth of the concept of the oligometastatic disease, as defined by Hellman and Weichselbaum, the spectrum of metastatic tumors has been revised, depending on the timing of onset

(synchronous vs metachronous), or based on the presence/absence of ongoing systemic treatments (oligorecurrent vs oligoprogressive vs oligopersistent metastases).

In the setting of the oligometastatic disease, in the last years, a large amount of

literature studies have supported the beneficial impact of the so-called metastasis-directed therapies (MDT) as a means to gain an advantage in terms of clinical outcomes [1,2].

Specifically for oligometastatic prostate cancer, the administration of stereotactic body radiotherapy (SBRT) has been favorably reported as a safe and effective tool, not only in terms of direct local control, but also as an option to delay the natural history of the disease by postponing the start of systemic therapies [3-6].

Infact, a major concern for this subset of patients is represented by the use of androgen deprivation therapy (ADT), since many patients would avoid the adverse effects and the detrimental impact of hormone therapy in terms of quality of life. In this scenario, the global widespread of metastasis-directed therapy is strictly connected to the availability of new diagnostic tools, such as multiparametric magnetic resonance or newer metabolic tracers for PET-imaging, which have significantly improved the sensitivity and specificity for the identification of the real-oligometastatic patient, who may really benefit from a local approach [7].

The role of newer metabolic tracers for the patient's selection process has been supported also by Fossati et al. [8] in a large multi-center series of patients which were candidate to salvage lymph-node dissection for nodal recurrence. The authors aimed to identify predictive factors of recurrence, in order to refine the accuracy for the

identification of the best fit patient for directed surgical approach.

This has been recently confirmed by the randomized phase II trial ORIOLE, in which a statistically significant advantage provided by SBRT was detected in terms of progression-free survival, when compared to observation in the hormone-sensitive oligometastatic patient. Moreover, the authors reported better progression-free survival rates in patients who reached a complete metabolic response after 6 months. This evidence highlights the need to better focus the patient's selection process, since it is a crucial step in determining the best therapeutic strategy. As recorded by Phillips et al. in their study [9], an incomplete prostate specific antigen (PSA) or absence of metabolic response may suggest the persistence of micrometastatic disease, thus making MDT as a clock reset to the onset of detectable macrometastases. Still, also in this case, MDT remains an attractive option due to the possibility to repeat multiple rounds of local approaches, with no relevant side effects, until a poly-metastatic progression takes place [10]. Furthermore, some authors also hypothesize a SBRT-induced immune effect in affecting the signals promoting the development of the metastatic "iceberg", leading also to potentially overcome, in the next years, the numerical concept of oligometastatic disease in favor of a deeper knowledge of the biological features of the metastatic cells [11].

This has been recently suggested also by Deek et al. [12] in a retrospective study of 269 samples from metastatic castration-sensitive prostate cancer patients with the aim to characterize the biological features of the real oligometastatic disease. The authors focus the need to identify genomic signatures as prognostic factors helpful to delineate the perfect candidates for MDT consolidative approaches. Probably, the combination of the mutational features and of the diagnostic imaging modalities will increase the accuracy in the detection of the real metastatic burden allowing clinicians to perform “sensu stricto” ablative treatments potentially aiming to cure the patient [13].

Moreover, the use of MDT approaches may have a favorable impact from a socio-economic point of view, given the possibility to delay the administration not only of conventional ADT drugs but also for second generation antiandrogens [14].

On the contrary, the early activation of ADT is a matter of debate, with some studies reporting an OS advantage compared to delayed strategies [15]. Also, the optimal management of ADT is controversial, although continuous ADT in the metastatic setting has been proved to be superior to intermittent administration in terms of clinical outcomes, still at the price of a worse impact on quality of life [16, 17].

Moreover, the logistics for intermittent ADT are controversial, especially for the criteria for stopping or resuming the treatment [18].

In a recent literature review by Carrasquilla et al., the authors hypothesize a risk-adapted intermittent ADT strategy for the management of lymph-node oligorecurrent hormone-sensitive prostate cancer also including an involved field SBRT in order to ablate the potential castration-resistant clones, thus prolonging the efficacy of intermittent hormone therapy [19].

In a recent manuscript by Chaw et al. [20], a randomized phase II study measured the impact of immediate ADT + SBRT vs SBRT + delayed ADT in a cohort of 88 patients with up to 3 oligometastases. The authors observed better clinical outcomes in the arm with immediate ADT suggesting a potential synergistic effect of the combined treatment. However, major concerns remain both in terms of survival benefits, and adverse events due to long-term systemic therapy. Moreover, the delay of ADT may also delay the transition to the castration-resistant phase, as also supported by Studer *et al* [21].

Furthermore, specifically in the case of lymph-node oligometastases, the optimal management remains controversial, as in opposition to MDT, some authors also support elective nodal irradiation, being associated with a lower rate of recurrence, despite only retrospective studies to date are available, still reporting an increased incidence of toxicity compared to MDT [22].

Of note, lymph-node metastases are associated to a higher median OS as compared to other anatomic sites. As also highlighted by Tran et al. [23], probably the

choice between a focal approach versus an elective treatment may be guided not only by appropriate imaging (i.e. Choline or PSMA-PET/CT) but also by PSA doubling time (PSADT); longer PSADT may suggest a more indolent natural history of the disease, thus more suitable for focal and potentially curative approaches. Otherwise, in the case of shorter PSADT, an elective nodal irradiation may cover also the occult micrometastatic disease, which may not be detected even by the newer metabolic tracers. Of note, also the number of metastatic lymph-nodes is another parameter that must be taken into account for the choice of the best tailored approach [24].

As far as bone oligometastases, given the lack of prospective data, a wide range of variability remains between institutions, and the use of ADT remains a matter of debate, as some authors hypothesize the applicability of the same MDT strategy such as for lymph-nodal oligometastases [25]. Probably, also in this setting, the same indicators mentioned for lymph-nodes (PSADT, number of metastases) are helpful tools to guide clinicians in the choice of the best therapeutic management. Of course, the retrospective nature of the currently available evidence limits the power of our conclusions. Surely, stronger evidence concerning the role of MDT in metastatic

prostate cancer will be provided by the ongoing randomized trials PEACE V (NCT03569241), STEREO-OS (NCT03143322), ADOPT (NCT04302454), RADIOSA (NCT03940235) and CORE (NCT02759783) [14, 26].

Conclusions

The management of the hormone-naive oligometastatic prostate cancer patient represents a real challenge for the radiation oncologist. New imaging modalities are leading to increase the accuracy in detecting the real disease burden, aiming to refine the features of the true oligometastatic patient, potentially curable with ablative metastasis-directed treatments. Promising data are derived from the literature, to date, and in our opinion, in light of the current lack of robust evidence, the addition of immediate ADT must be guided by the assessment of other parameters such as PSA doubling time, number and sites of oligometastases, life expectancy, etc. Probably in the next years, the growing availability of more mature data and the deeper knowledge of the intrinsic biological features of the metastatic disease will provide further elements to help clinicians in the choice of the best tailored treatment.

Abbreviations:

ADT – androgen deprivation therapy
MDT – metastasis-directed therapies
PET – positron emission tomography
PSA – prostate specific antigen
PSADT – doubling time
PSMA – prostate specific membrane antigen
SBRT – stereotactic body radiotherapy

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