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COMMENTARY

Integrating stereotactic body radiation therapy (SBRT) and systemic treatments in oligoprogressive prostate cancer: new evidence from the literature

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Abstract

Recent findings from literature evidenced that metastatic prostate cancer often shows heterogeneous response to therapy, with persistent sensibility to systemic treatments after biochemical, clinical, or radiographic progression. This highlights the advantage of integrated approaches in which local ablative treatments (e.g., stereotactic body radiation therapy) could prolong clinical benefit of systemic therapies beyond oligo-progression. Of course, development of predictive biomarker could be helpful in order to select patients who could much benefit from this treatment strategy. Circulating tumor cell detection and analysis could also have a crucial role in this field. A joint effort of two prospective ongoing trials (ARTO, clinical.gov identifier NCT03449719 and PRIMERA, clinical.gov identifier NCT04188275) might help to improve criteria to select patients in whom a local ablative approach might confer significant benefit. In this commentary, we summarized recent data from literature to support this thesis.

Keywords Integration · Radiation therapy · Systemic treatments · Oligoprogressive · Prostate cancer

Abbreviations

pCa	Prostate cancer
SBRT	Stereotactic body radiation therapy
ADT	Androgen deprivation therapy
PFS	Progression-free survival
mCRPC	Metastatic castrate resistant prostate cancer
CTC	Circulating tumor cells

Newest literature evidence

A recent article entitled "Exploring Spatial–Temporal Changes in 18F-Sodium Fluoride PET/CT and Circulating Tumor Cells in Metastatic Castration-Resistant Prostate Cancer Treated With Enzalutamide", was published in the Journal of Clinical Oncology on September 8, 2020. Briefly, 23 progressive metastatic castration-resistant prostate cancer (mCRPC) patients were treated with enzalutamide 160 mg and underwent 18F-NaF PET/CT staging at baseline, week 13 and at disease progression. Results showed that functional disease burden measured with metabolic imaging decreased during enzalutamide treatment and increased at the time of progression. However, all evaluable patients had at least one responding bone lesion at biochemical, clinical or radiographic progression. Authors concluded that a significant number of lesions showed persistent response, and that treatment benefit could be extended through selective targeting of nonresponding lesions [1].

Existing literature

Kyriakopoulos et al. observation, together with the well-known polyclonal nature of androgen-deprived metastatic prostate cancer (pCa) [2], reinforces the crucial role of integration between systemic treatment and modern ablative treatment techniques, such as stereotactic body radiation therapy (SBRT). Results of this trial perfectly fit with recent data from literature about integration between metastasis

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directed therapy and systemic treatment in metastatic pCa. Indeed, this synergistic approach has been already shown to offer significant benefit both in terms of freedom from palliative androgen deprivation therapy (ADT) [3] and progression-free survival (PFS) [4] in patients affected by oligometastatic disease. Moreover, SBRT significantly improved overall survival within a recent randomized phase II trial testing this treatment strategy in a mixed population including different hystologies [5]. However, in the latter trial only a minority of patients were affected by metastatic pCa, and no data were provided about distinct outcomes by primary. Nonetheless, these results seem to suggest that addition of SBRT to systemic treatment may yield significant benefit in selected patients. A recent systematic review of prospective clinical trials tested the benefit of metastasis directed therapy for oligometastatic prostate cancer. Overall, results showed a 16–60% rate of early PFS, and a local control rate ranging between 93 and 100%. Authors concluded that randomized comparative studies would be required to explore the role and optimal timing of this approach for oligometastatic disease [6]. Therefore, a number of considerations should be taken in account for routine clinical practice and design of prospective trials in this setting.

Considerations for clinical practice and prospective trials design in this setting

First, a growing body of literature, including results from modern prospective trials, supports SBRT for oligorecurrent/oligometastatic patients [3–5], and total consolidation of disease significantly improved distant PFS in patients enrolled in ORIOLE trial [4]. Moreover, SBRT has been shown to be a safe, manageable, and cost-effective approach as compared to standard systemic therapy for metastatic pCa [7]. Thus, advantages of SBRT addition to standard approach plead for the integration of this option in the treatment algorithm of these patients. Second, the timing of local intervention (i.e., upfront versus deferred SBRT treatment) should be addressed. Upfront treatment of all sites of disease in order to ablate active disease foci seems to be favored by SABR-COMET trial results [5]. Up to date, patients with 1–5 lesions, a controlled primary tumor, and all metastatic sites safely treatable seem to be the optimal candidates for this approach [8].

In the paper by Kyriakopoulos et al. [1], authors underlined that the degree of early resistance resulted in higher burden of disease at time of progression. Thus, ablating initial foci of disease might influence patients' prognosis and following PFS. From this point of view, a prospective randomized phase II trial (ARTO, clinical.gov identifier NCT03449719) is currently ongoing, randomizing mCRPC patients to receive a first line with abiraterone acetate (control arm) or abiraterone acetate plus SBRT on all sites of disease (experimental arm). This trial aims to catch the benefit of an upfront local approach in this specific setting. A pragmatic example of how SBRT may be integrated in oligometastatic disease is summarized in Fig. 1. Third, clinicians should be aware that definition of oligometastatic disease should not be exclusively based on lesions number. Indeed, the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) consensus classification of oligometastatic patients is based more on patient clinical history (e.g., previous polymetastatic disease, ongoing systemic treatment, oligoprogressive status at current evaluation) rather than

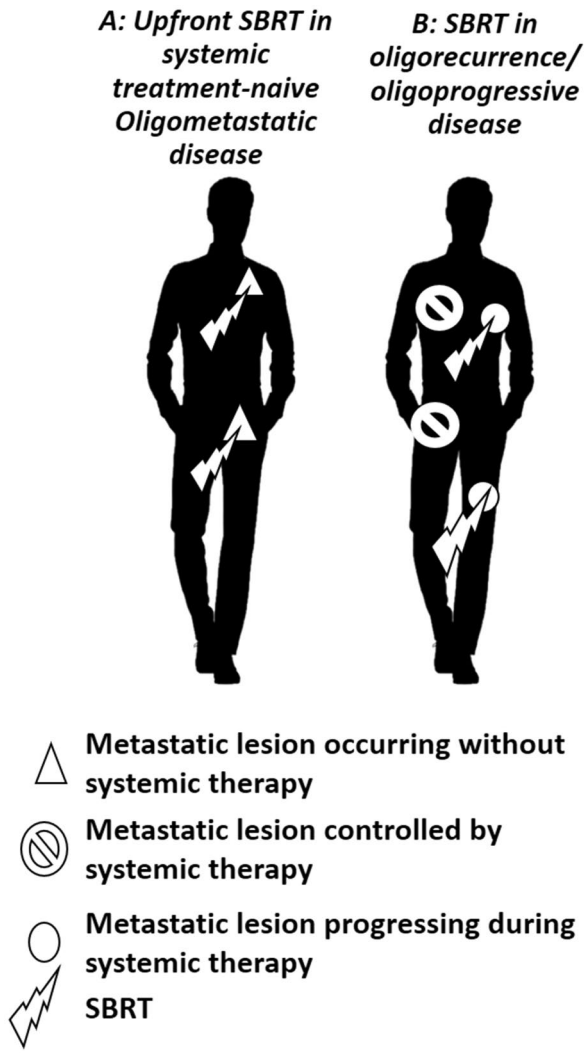

Fig. 1 Examples of local therapy management. Stereotactic Body Radiation Therapy (SBRT) approach could be used upfront to treat oligometastatic disease occurring in the absence of systemic therapy (**a**) or at progression to restore stable disease during systemic treatment (**b**)

the burden of disease [9]. Moreover, site of disease should influence definition of oligometastatic disease more than number of lesions. For example, the Italian Association of Radiotherapy and Clinical Oncology (AIRO) excluded patients with visceral metastasis from all clinical scenarios referring to oligometastatic disease [10]. Of course, novel imaging due to its increased sensitivity, may induce significant upstaging and radically change our definition of burden of disease in clinical practice. However, data from ORIOLE trial showed that total consolidation of prostate-specific membrane antigen (PSMA) radiotracer-avid disease significantly decreased the risk of distant progression at 6 months [4]. These data suggest that sensitivity of modern imaging should be exploited for early detection and treatment of disease rather than to withhold local therapy. Indeed, metastasis directed therapy may maintain its benefit also after sensitive imaging, and treatment de-escalation is not currently justified [11]. Kyriakopoulos et al. experience provides additional data in support of ablative treatment for oligoprogressive patients despite their initial disease burden, given the intra-individual heterogeneity in terms of treatment response at progression detected in this cohort. Finally, an increase in the expression of androgen receptor (AR) splicing variants on circulating tumor cells was detected, confirming the effect of treatment on polyclonal selection of treatment-refractory cells: progressive adaptation of disease to androgen deprivation may entail a systemic disease progression and a reduced benefit from local approaches. Biomarker-driven patient selection in this setting is not available [12], although a substantial percentage of patients included in the ARTO trial will be enrolled also in a prospective observational trial (PRIMERA, clinical.gov identifier NCT04188275) just preliminarily presented [13]. PRIMERA trial will explore the predictive value of circulating micro-RNA and AR-V7 mutational status in mCRPC patients treated with abiraterone or enzalutamide in first line setting. A joint effort of these two trials could help to improve criteria to select patients in whom a local ablative approach might confer significant benefit.

Conclusions

In summary, progressive disease is a heterogeneous entity composed of mixed cell populations with distinct sensitivity to treatments. The potential for systemic and local treatment integration prompts to improve selection criteria and develop clinical trials focused on this issue.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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