EDITORIAL

Chasing the Culprit: targeting metastatic index lesions in oligometastatic hormone-sensitive prostate cancer

Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-025-01052-w

In the last decade, the widespread use of prostate-specific membrane antigen positron emission tomography (PSMA PET) has revolutionized metastatic staging in prostate cancer, offering unprecedented sensitivity and specificity even at very low PSA levels [1]. By enabling earlier detection of oligometastatic hormone-sensitive prostate cancer (omHSPC), PSMA PET has fueled growing interest in metastasis-directed therapy (MDT) as a potentially curative approach [2, 3]. Although MDT has gained traction in clinical practice, mostly based on observational studies and small non-randomized trials, its role in de novo omHSPC remains investigational. Critical questions remain unanswered: when to treat and for which clinical goal, whether all detectable lesions should be targeted upfront or at progression, and how PSMA PET can be integrated for response monitoring and guiding salvage strategies.

In this context, the recent study by Verma et al. [4] provides valuable insight into the natural history progression of de novo omHSPC managed with standard of care systemic therapy, including androgen deprivation therapy (ADT), frequently combined with androgen receptor pathway inhibitors (ARPI) or docetaxel, and prostate-directed radiotherapy, but without MDT. In their retrospective cohort study, including 79 patients with de novo omHSPC (1–5 lesions, 72% M1b) on PSMA PET, after a median follow-up of 39 months, 19% of patients experienced biochemical or clinical progression, with a median time to progression of 28 months. Among those who progressed, restaging PSMA PET demonstrated that 73% relapsed at the original (index) metastatic site, and in 27% of cases, progression was confined exclusively to that site, without the development of new metastatic lesions. Disease PSMA-detected progression in the index site with new metastatic lesions was observed in 7 patients (46.6%).

This finding carries important clinical implications. If most patients relapse at previously PSMA-identified but untreated metastatic foci, it strongly supports the hypothesis that such untreated hormone-sensitive lesions can act as reservoirs for disease progression and clonal evolution. In this context, untreated metastases may persist over time and ultimately evolve into castration-resistant disease (CRPC), potentially becoming the dominant sites of progression in the CRPC phase. Moreover, the observation that some patients progressed exclusively at a single site suggests that comprehensive local control of all PSMA-positive disease may delay or even prevent systemic dissemination [3]. Notably, no baseline prognostic factors, including ISUP grade, nodal status, number of metastases, or prostate-specific antigen (PSA) nadir, were significantly associated with progression at the index lesion, underscoring the unpredictability of metastatic behavior in the absence of local intervention.

Although Verma's study is limited by its retrospective nature and relatively small sample size [4], uniform PSMA-based staging and restaging, standard of care treatment approaches, and expert central review of imaging strengthen its findings. To our knowledge, this is the first report that directly characterizes patterns of failure in de novo omHSPC staged with PSMA PET imaging and treated without MDT. These results raise questions about the current treatment paradigm for de novo omHSPC, which, based on level I evidence, supports systemic therapy combined with prostate irradiation while omitting local treatment of metastatic lesions.

The rationale for MDT in this *de-novo* setting is threefold (4). First, ablative radiotherapy achieves high local control rates, often exceeding 90%, with minimal additional toxicity. Second, retrospective studies suggest MDT may delay disease progression, defer the need for next-line systemic therapies, and potentially improve survival [2]. Third, targeting oligometastatic sites early at diagnosis could potentially prevent polyclonal seeding and reduce the emergence of treatment-resistant clones. These arguments, while compelling, remain hypothesis-generating and have yet to be validated in randomized phase III trials.

The treatment landscape, however, is evolving. The phase II prospective SOLAR trial study explored a multimodal comprehensive approach of local primary treatment, MDT, and intensified systemic therapy of fixed duration, showing a durable remission off therapy after testosterone recovery in the majority of selected patients with de novo omHSPC disease [5]. Ongoing large randomized trials such as STAMPEDE-2 (NCT06320067), OLIGO-PRESTO (NCT04115007), PLATON (NCT03784755), and STARMET (NCT05209243) are actively investigating whether MDT of all disease sites can improve clinical outcomes when added to standard systemic therapy and prostate RT, potentially shaping future clinical practice and guideline recommendations [3, 6].

Nevertheless, the optimal timing for MDT in the *de-novo* setting remains an open issue. An alternative strategy is to defer MDT until evidence of disease progression at restaging PSMA, as investigated in retrospective and prospective randomized trials such as ARTO and GROUQ-PCS 9 [7]. This approach may rely on close monitoring of PSA kinetics and restaging with PSMA PET to selectively guide salvage MDT in patients with oligoprogressive disease, while avoiding upfront MDT in those omHSPC patients who are likely to progress rapidly to a polymetastatic state. The findings of Verma's study add nuance to this debate by showing that, in some cases, progression remains confined to the original lesions, allowing for delayed yet still potentially effective salvage MDT. These observations raise the hypothesis that an adaptive strategy guided by serial PSMA imaging might potentially achieve outcomes comparable to upfront MDT while reducing the risk of overtreatment. This approach may be particularly relevant for high-volume metastatic patients who are traditionally excluded from MDT but could benefit from targeted intervention of residual PSMA active disease lesions. Whether this strategy confers a

Received: 3 October 2025 Revised: 16 October 2025 Accepted: 27 October 2025
Published online: 25 November 2025

survival benefit remains uncertain and should be evaluated in prospective clinical trials.

The present study also highlights an additional important point of discussion: the use and interpretation of PSMA PET imaging for restaging of omHSPC, particularly at low rising PSA values. Careful consideration of scan timing and the biological heterogeneity of metastatic lesions is essential, as persistent PSMA uptake may reflect either early resistant disease or post-treatment changes such as inflammation or pseudo-progression [8, 9]. Notably, PSMA uptake was observed in the prostate gland in 5 of 79 patients included in this study, despite prior irradiation of the primary tumor [4]. Conversely, repeated PSMA imaging in patients with low PSA values could allow interception of progression before it becomes biochemically or clinically apparent, identifying early sites of disease that may benefit from preemptive MDT [10]. Structured integration of PSMA imaging with PSA kinetics and, potentially, genomic profiling is therefore expected to help refine patient selection and optimize the timing of MDT in future studies.

In conclusion, the study by Verma et al. provides valuable evidence suggesting that untreated PSMA-positive metastatic sites may be the principal drivers of progression in de novo omHSPC. These findings support the exploration of comprehensive MDT strategies and raise paramount questions regarding timing, sequencing, and patient selection. These data also indicate that untreated PSMA-positive lesions may not only drive early progression, but could potentially persist and evolve into dominant castration-resistant disease sites, underscoring the importance of early local control. While randomized evidence is still awaited, this study enhances our understanding of disease biology and the evolving role of PSMA-guided therapy in the omHSPC setting.

Salvatore Cozzi[1] and Thomas Zilli[1,2,3]✉

[1]Radiation Oncology, Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale, Bellinzona, Switzerland. [2]Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland. [3]Faculty of Medicine, University of Geneva, Geneva, Switzerland. ✉email: Thomas.Zilli@eoc.ch

REFERENCES

1. Mazzone E, Cannoletta D, Quarta L, Chen DC, Thomson A, Barletta F, et al. A comprehensive systematic review and meta-analysis of the role of prostate-specific membrane antigen positron emission tomography for prostate cancer diagnosis and primary staging before definitive treatment. Eur Urol. 2025;87:654–71.
2. Miszczyk M, Rajwa P, Yanagisawa T, Nowicka Z, Shim SR, Laukhtina E, et al. The efficacy and safety of metastasis-directed therapy in patients with prostate cancer: a systematic review and meta-analysis of prospective studies. Eur Urol. 2024;85:125–38.
3. Zilli T, Achard V, Dal Pra A, Schmidt-Hegemann N, Jereczek-Fossa BA, Lancia A, et al. Recommendations for radiation therapy in oligometastatic prostate cancer: An ESTRO-ACROP Delphi consensus. Radiother Oncol. 2022;176:199–207.
4. Verma P, Maitre PKG, Murarka N, Choudhury S, Ghosh S, Agrawal A, et al. Progression of index metastases in oligometastatic hormone-sensitive prostate cancer: Implications for metastases directed therapy?. Prostate Cancer Prostat Dis. 2025. https://doi.org/10.1038/s41391-025-01056-6.
5. Nickols NG, Tsai S, Kane N, Tran S, Ghayouri L, Diaz-Perez S, et al. Systemic and tumor-directed therapy for oligometastatic prostate cancer: the SOLAR Phase 2 trial in De Novo oligometastatic prostate cancer. Eur Urol. 2024;86:190–3.
6. Gillessen S, Turco F, Davis ID, Efstathiou JA, Fizazi K, James ND, et al. Management of patients with advanced prostate cancer. Report from the 2024 Advanced Prostate Cancer Consensus Conference (APCCC). Eur Urol. 2025;87:157–216.
7. Le Guevelou J, Cuccia F, Flippot R, Ferrera G, Terlizzi M, Zilli T, et al. The current landscape of stereotactic body radiation therapy for metastatic castration-resistant prostate cancer. Prostate Cancer Prostat Dis. 2025;28:546–56.
8. Mesci A, Ahmadi E, Ali A, Gouran-Savadkoohi M, Evelyn Tsakiridis E, Biziotis OD,et al.(18)F-DCFPyL (PSMA) PET as a radiotherapy response assessment tool in metastatic prostate cancer. Clin Transl Radiat Oncol. 2023;39:100583.
9. Hotta M, Nguyen K, Thin P, Armstrong WR, Sonni I, Farolfi A, et al. Kinetics of PSMA PET signal after radiotherapy in prostate cancer lesions: A single-center retrospective study. Radiother Oncol. 2025;207:110869.
10. Beaufils M, Meynard L, Bernard-Tessier A, Brenot-Rossi I, Guerin M, Tauty A, et al. PET imaging for metastatic castration sensitive prostate cancer (mCSPC) for patients with PSA response after systemic therapy: A multicentric ambispective analysis. J Clin Oncol 2025;43 (suppl 5; abstr 37).

AUTHOR CONTRIBUTIONS

SC: Writing – Original Draft; TZ: Conceptualization, Writing – Review & Editing.

FUNDING

This study was not funded.

COMPETING INTERESTS

The authors declare no competing interests.