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Letter to the Editor - Reply

Reply to Alessia Cimadamore, Antonio Lopez-Beltran, Liang Cheng, and Rodolfo Montironi's Letter to the Editor re: Francesca Ambrosini, Nataniele Piol, Matteo Bauckneht, et al. Immunohistochemical Prostate-specific Membrane Antigen (PSMA) Expression Patterns of Primary Prostate Cancer Tissue as a Determining Factor for Prostate Cancer Staging with PSMA Positron Emission Tomography/Computed Tomography. Eur Urol Oncol. In press. https://doi.org/10.1016/j.euo.2025.02.012

We thank Professor Montironi and colleagues for their constructive comments on our recent publication on immunohistochemical (IHC) expression of prostate-specific membrane antigen (PSMA) in primary prostate cancer in relation to staging via PSMA positron emission tomography (PET)/computed tomography (CT) [1].

As the authors rightly point out, PSMA is a complex transmembrane glycoprotein whose subcellular localisation varies, especially in response to therapeutic interventions [2]. Their discussion of the internalisation mechanisms and differential distribution of PSMA between membrane and cytoplasmic compartments is consistent with our clinical findings and supports the rationale for integration of IHC data with PSMA-targeted imaging.

Our study investigated whether PSMA IHC in biopsy specimens can predict PSMA PET/CT imaging results, particularly the maximum standardised uptake value. We demonstrated a statistically significant correlation between PSMA immunoreactive scores in both prostate biopsy cores and index lesions from whole-mount specimens and PET/CT signal intensity. These results support the concept that PSMA expression can serve as a surrogate marker for tracer uptake.

We are particularly pleased that the authors emphasised the importance of interdisciplinary collaboration between pathologists and clinicians. While our study focused on a subset of treatment-naïve patients, the increasingly complex therapeutic landscape for prostate cancer presents additional challenges in interpreting PSMA expression. This underscores the need to consider treatment status and tissue-level expression when evaluating PSMA PET/CT imaging to avoid potential diagnostic pitfalls. Importantly, this consideration extends beyond androgen deprivation therapies, as PSMA expression can be modulated by androgen receptor pathway inhibitors [3] and taxanes [4]. A deeper understanding of PSMA localisation—whether membranous or cytoplasmic—may not only serve as a diagnostic tool but could also help in identifying the patients who are most likely to benefit from PSMA-targeted therapies.

We hope that our study will provide a rationale for integrating PSMA IHC into preoperative diagnostics and represent a first step towards patient-specific therapeutic decision-making in the context of PSMA-targeted approaches. Standardisation of IHC interpretation and a better understanding of PSMA biology—including internalisation pathways—are crucial next steps to achieve these aims. Our prospective design and relatively large cohort provide a solid foundation, but we recognise the limitations of our study, including manual IHC scoring. Therefore, we welcome the call for expanded studies and multicentre collaboration.

Finally, we are grateful for the opportunity to clarify and strengthen the clinical implications of our findings. We fully support the proposal to promote more integrated dialogue between uropathologists and clinicians to further elucidate the role of PSMA in the treatment of prostate cancer. Together, these efforts can lead to a more personalised, biologically based diagnostic pathway.

***Conflicts of interest*:** Matteo Bauckneht reports personal fees from AAA and GE Healthcare outside the submitted work. The remaining authors have nothing to disclose.

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***Data sharing statement*:** The raw data supporting the conclusions are available on request. The data will be provided to researchers who meet the criteria for access to confidential information and agree to the terms of use.

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