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EDITORIAL

European guidelines update on PSMA PET/CT for prostate cancer staging—snap back to reality

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Since the discovery of PSMA as a specific target for prostate cancer (PCa) cells, PSMA-binding radiopharmaceuticals gradually revolutionised the management of patients, getting a salient place in the spotlight of a florid scientific debate and academic activity over the past decade [1]. In particular, the lack of significant PSMA expression in healthy prostate tissue raised high expectations on the development of a potential "magic bullet" for prostate cancer theranostics. Indeed, the introduction of PSMA-ligand PET/CT was undoubtedly a milestone, as this technique demonstrated an excellent diagnostic accuracy in most stages of PCa. The most notable example is the setting of biochemical relapse following radical treatment. The high sensitivity and specificity of the method, even at low PSA levels, in comparison with existing tools led to its rapid inclusion in the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines [2]. The modality is currently experiencing a steady growth in several other clinical settings, including pre-operative staging [3], restaging after systemic treatments, and assessment of treatment response. As a matter of fact, clinicians often request this examination even beyond the indications given by current clinical guideline. Moreover, PSMA-targeted radioligand therapy represents one of the most relevant breakthroughs in modern medicine, with the exciting results of trials such as VISION [4] and TheraP [5] leading to FDA and EMA approval and its inclusion in the last update of the guidelines [6].

In this evolving framework, the setting of preoperative clinical staging is of particular interest. For decades, before the advent of PSMA, European guidelines have exclusively recommended abdomen-pelvis CT/MRI and bone scintigraphy as the standard work-up [7]. However, the poor accuracy of CT and MRI for lymph node involvement (approximately 0.40 sensitivity and 0.80 specificity for both) and bone scintigraphy for skeletal metastases (0.59 sensitivity and 0.75 specificity) is well known [8, 9] and limits their use in staging to selected patients with intermediate to high-risk disease. Over the years, a great deal of effort has gone into the development of radiopharmaceuticals for PET/CT imaging to overcome these hurdles, and choline-based agents gained some attention. However, even the sensitivity of choline PET/CT in detecting lymph node involvement remains rather low, despite a very high specificity (0.43 sensitivity and 0.95 specificity) and good levels of accuracy in skeletal assessment (0.83 sensitivity and 0.95 specificity) [9, 10]. Given all these limitations, extended pelvic lymph node dissection (ePLND) is still considered the gold standard for PCa nodal staging. Preoperative risk assessment tools, i.e., nomograms, combining clinical, imaging, and biopsy findings, are recommended to estimate the risk of patients with pathological lymph nodes and to identify the most appropriate candidates for ePLND [11].

Such scenario has changed significantly when PSMA-ligand PET entered the scene, in particular, following the publication of proPSMA, the first prospective, randomised, multi-centre trial comparing [^{68}Ga]Ga-PSMA-11 PET/CT with standard-of-care imaging in the staging setting [12]. In this study, PSMA-ligand PET/CT showed very high levels of sensitivity (0.85) and specificity (0.98), fewer questionable findings in both lymph nodes and bone, as well as less radiation exposure, decisively outperforming conventional imaging. Subsequent studies have also confirmed PSMA-ligand

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PET/CT as the current most sensitive and specific imaging technique for lymph node staging, identifying pathological lymph nodes up to approximately 5 mm, with even better performance as the PCa risk increases [13, 14]. This generated a great deal of excitement in the urology and nuclear medicine communities and PSMA-ligand PET/CT was included alongside conventional modalities in the EAU guidelines for preoperative staging in high-risk patients in 2022 despite the lack of data on the impact of PSMA PET/CT findings on patient outcomes [15]. This led to a growing demand for PSMA-ligand PET/CT and, consequently, to a growing interest in the development of ^{18}F-labelled radiopharmaceuticals, bearing advantages such as longer half-life, cost-saving cyclotron large-batch production, improved spatial resolution, and reduced urinary excretion in some compounds.

PSMA-ligand PET/CT emerged as a light at the end of the tunnel, achieving a goal that was considered impossible only a few years ago. Nonetheless, the widespread use of this technique has inevitably raised various challenges that will need to be tackled soon. Despite the initial momentum, the scientific community has realised that this paradigm shift was probably a flight too close to the sun. This culminated at the recent EAU annual congress in Milan, with the release of the latest update to the European interdisciplinary guidelines that include a strong statement, curbing the enthusiasm regarding PSMA in prostate cancer staging: "Treatment should not be changed based on PSMA PET/CT findings, in view of current available data" [6].

The main concern is stage migration and the still not accurately defined impact on patient management and selection of the best available treatment [16, 17]. The high sensitivity of PSMA-ligand PET/CT may have the potential to reveal occult disease and upstage a significant percentage of patients (approximately 20%). This clearly increases the number of oligo- and polymetastatic patients denying appropriate radical intervention to selected patients previously eligible [12, 18]. In medicine this is nothing new, as the so-called Will Rogers phenomenon occurs cyclically with the development of new technologies. In 1985, Dr. Feinstein first used this expression—borrowed from a famous sketch by the eponymous American performer—to describe the stage migration observed in lung cancer patients following the introduction of CT scan. The phenomenon describes an epidemiological paradox whereby patients from the group with a better prognosis crossover to the group with the worse prognosis. Upstaging a subset of patients increases survival in both groups, with this apparently miraculous improvement derived from imaging only but not related to any real change in individual outcomes [19]. The early integration of PSMA-ligand PET/CT into clinical algorithms based on the less accurate conventional imaging could therefore lead to misinterpretation of survival data. Currently, there is a lack of data-driven evidence to support a survival benefit from switching management in patients upstaged from localised to metastatic disease on PSMA-ligand PET/CT. We need to be aware that any therapeutic decision should be made with caution until we have more data from prospective studies that incorporate upfront staging PSMA-ligand PET/CT with adequate follow-up to estimate the impact on overall survival. Several randomised clinical trials are ongoing to assess the impact on clinical decision-making and outcomes in PCa patients staged with PSMA-ligand PET/CT [20–23].

Additionally, some aspects of the diagnostic performance of the ever-more-widely used fluorinated compounds are yet to be fully elucidated, in particular, the significantly higher frequency of equivocal bone findings with [^{18}F]PSMA-1007. The interpretation of areas of skeletal focal uptake is often challenging, especially when no underlying alterations are visible on the co-registration CT. These findings are clinically irrelevant in most cases, but they may result in treatment delays or mis-staging. The underlying pathophysiological reasons for this non-specific focal deposition remain unknown, with several studies focussing on the topic and some hypotheses such as the role of free, unbound fluorine, and concomitant malignant bone marrow conditions still under investigation [24–28]. To ensure correct interpretation, it is essential to keep in mind the wide spectrum of physiological, benign, or pathological conditions expressing PSMA [29], to be conscious of the potential for false positives and to read the images critically, including an evaluation of the patient's baseline clinical data.

In conclusion, we believe that the seemingly pessimistic update of the European guidelines on the role of PSMA-ligand PET/CT in PCa staging should be regarded as another—albeit unconventional—milestone in the successful history of this technology. Clinicians are already striving towards the integration of this methodology in the clinical management of PCa patients. The scientific community of nuclear medicine should be able to step up, focussing on paradigm-shifting prospective clinical trials thoroughly evaluating the prognostic and predictive impact of PSMA-ligand PET/CT, contributing to a definitive and standard-defining evidence.

Comparing PSMA-ligand PET/CT to any other previous imaging technique is akin to juxtaposing images from the new James Webb telescope to the old Hubble's, as uncountable new stars emerge from the dark depths. But, as these space telescopes can teach us: *to see clearly is not enough, we need to look farther*.

Declarations

Ethical approval Institutional review board approval was not required because the paper is an editorial.

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Conflict of interest The authors declare no competing interests.

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