available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Editorial

Use of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Nodal Staging in Prostate Cancer and Tailoring of Treatment: A Continuing Conundrum

Johan Stranne [a,b,*], *Ann Henry* [c], *Daniela E. Oprea-Lager* [d], *on behalf of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel*

[a] *Department of Urology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;* [b] *Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden;* [c] *University of Leeds and Leeds Teaching Hospital, Leeds, UK;* [d] *Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands*

The only way to evaluate pathological lymph node stage (N0 vs N1) in prostate cancer (PCa) is to microscopically examine nodes after extended pelvic lymph node dissection (ePLND) or sentinel node biopsy of a suspicious lesion. The major argument for performing ePLND during radical prostatectomy (RP), despite the lack of evidence of an oncological benefit and the significant risk of morbidity, has been the more accurate N staging achieved than with conventional imaging via computed tomography (CT) or magnetic resonance imaging (MRI) [1]. The sensitivity and specificity of ePLND depend on the extent of the surgical template. Furthermore, ePLND has the inherent drawback of yielding a pathological result for N stage after the prostate has already been removed, so it cannot inform the choice of primary treatment. Radiological nodal staging via CT or MRI is limited by low sensitivity and low specificity [2], so patients with occult N1 disease might only receive local prostate treatment. Nevertheless, local treatments have very good oncological results [3] and there are numerous reports of good long-term results after RP, even in patients with limited N1 disease (<3–4 nodes).

The past few years has seen the emergence of prostate-specific membrane antigen-based positron emission tomography/computed tomography (PSMA-PET/CT) as an imaging modality with 27% greater accuracy than conventional imaging [4]. This has changed the pretreatment staging landscape for patients presenting with high-risk localised or locally advanced disease, as evident in the most recent European Association of Urology guidelines [3]. Updated nomograms that incorporate PSMA-PET/CT improve prediction of the risk of pN1 disease. Negative PSMA-PET/CT findings can have a dramatic effect: for example, for a patient with International Society of Urological Pathology grade group 4 PCa, prostate-specific antigen of 17 ng/ml, and an MRI-visible lesion with a Prostate Imaging-Reporting and Data System (PI-RADS) score of 5, the risk of N1 disease goes from >25% without PSMA-PET/CT to approximately 3% if PSMA-PET/CT findings are negative [5,6]. Pretreatment staging for high-risk localised or locally advanced disease should therefore include PSMA-PET/CT imaging before radical treatment, with ePLND unlikely to alter stage if PET is negative.

The European Association of Nuclear Medicine has proposed a molecular imaging TNM classification (miTNM) that incorporates PSMA-PET/CT findings. Because of earlier diagnosis via PSMA-PET/CT, the prognosis for miN and miM substages is likely to be better than the corresponding CT/MRI N and M substages, but the magnitude of the impact has not yet been defined. The uncertainty now is how to manage miN1 disease, owing to lack of evidence regarding a curative effect, and thus about the benefit of identifying microscopic metastases in patients with a negative scan, which are questions that the current guidelines cannot answer [3].

In addressing these questions, we must define what N1 on PSMA-PET/CT means. The imaging examination will offer an answer in two ways: first, according to the size of the lymph nodes; and second, according to the PSMA

* Corresponding author. Department of Urology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

https://doi.org/10.1016/j.eururo.2024.11.025

expression estimated on PET. Therefore, patients with N1 disease can be assigned to one of three categories: (1) PSMA expression on PET in lymph nodes with a short-axis diameter >10–15 mm; (2) lymph nodes >10–15 mm with no PSMA expression; and (3) PSMA expression in lymph nodes smaller than 10–15 mm. The first two groups would be considered N1 with conventional CT/MRI, and in particular the first group is very likely to have pathological N1 status, for which we already have strategies and guidelines [3]. In the second group, which is probably the smallest, other reasons for enlarged lymph nodes, such as lymphoma or an infectious disease, must be ruled out. If no other cause of lymph node enlargement is found, it is likely that these patients should be treated as N1 according to current guidelines. The third group, with PSMA expression in normal-sized nodes, is challenging, as uptake may vary in intensity and by the number of positive nodes. A change in molecular signal precedes a change in size, and a slight or moderate PSMA expression in lymph nodes smaller than 10–15 mm is often associated with small lymph node metastases that are growing.

To compare outcomes and harmonise treatments, there is an urgent need for universal agreement on a PSMA positivity scale, such as PI-RADS for MRI. The Standardized PSMA-PET Analysis and Reporting Consensus (SPARC) initiative is aiming to harmonise interpretation criteria from multiple guidelines, including the E-PSMA guidelines, PSMA-RADS v2.0, and PROMISE v2 [7–9].

When consensus is achieved, the next steps are to decide what treatment to offer and demonstrate how this impacts patient outcomes, and how to interpret equivocal lesions, which can be positive or negative (such as a PI-RADS 3 lesion on MRI). Patients with low risk of N1 disease on such a PSMA scale should be treated as N0 according to their risk group. For those with a higher likelihood of N1 disease, but who still have M0 status, treatment may depend on the number of positive nodes. The exact cutoff for the number of positive nodes is unknown, and trials will be crucial. If the number of positive nodes is high (more than 5) it is likely that additional systemic treatment with androgen deprivation therapy, with or without an androgen receptor pathway inhibitor, may be beneficial. For patients with fewer positive nodes (up to 5), there is a lack of knowledge regarding the best treatment option [10]. These are the patients who may benefit from a combination of local and lymph node treatment via either radiotherapy or RP + ePLND, in addition to systemic treatments. To evaluate treatment options, clinical trials should randomise or include stratification by the modality used for staging, including the number of positive lesions and the level of PSMA expression. Some trials are addressing this issue, such as the PEACE V (STORM) trial [11] and the AVIDITY trial in the UK, but more trials are of outmost importance.

Even before such clinical trials are completed, especially when there is agreement on universal PSMA-PET/CT scales, PSMA-PET/CT can be of great value in the clinic. It helps both to indicate N0 disease, avoiding unnecessary lymph node treatments, and to identify patients with a high metastasis burden, thereby avoiding both undertreatment and overtreatment. The remaining group, with a few small positive nodes, must be discussed and managed individually in a multidisciplinary team setting to decide on the best available treatment option for each patient.

Conflicts of interest: The authors have nothing to disclose.

Funding/Support and role of the sponsor: This work was sponsored by the European Association of Urology. The sponsor played a role in collection and management of the data, and preparation and review of the manuscript.

References

[1] Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2021;79:243–62.
[2] Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008;63:387–95.
[3] Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2024;86:148–63.
[4] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.
[5] Gandaglia G, Barletta F, Robesti D, et al. Identification of the optimal candidates for nodal staging with extended pelvic lymph node dissection among prostate cancer patients who underwent preoperative prostate-specific membrane antigen positron emission tomography. external validation of the Memorial Sloan Kettering Cancer Center and Briganti nomograms and development of a novel tool. Eur Urol Oncol 2023;6:543–52.
[6] Vis AN, Meijer D, Roberts MJ, et al. Development and external validation of a novel nomogram to predict the probability of pelvic lymph-node metastases in prostate cancer patients using magnetic resonance imaging and molecular imaging with prostate-specific membrane antigen positron emission tomography. Eur Urol Oncol 2023;6:553–63.
[7] Ceci F, Oprea-Lager DE, Emmett L, et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 2021;48:1626–38.
[8] Werner RA, Hartrampf PE, Fendler WP, et al. Prostate-specific Membrane Antigen Reporting and Data System version 2.0. Eur Urol 2023;84:491–502.
[9] Seifert R, Emmett L, Rowe SP, et al. Second version of the Prostate Cancer Molecular Imaging Standardized Evaluation framework including response evaluation for clinical trials (PROMISE v2). Eur Urol 2023;83:405–12.
[10] Oprea-Lager DE, MacLennan S, Bjartell A, et al. European Association of Nuclear Medicine focus 5: consensus on molecular imaging and theranostics in prostate cancer. Eur Urol 2024;85:49–60.
[11] De Bruycker A, Spiessens A, Dirix P, et al. PEACE V – salvage treatment of oligorecurrent nodal prostate cancer metastases (STORM): a study protocol for a randomized controlled phase II trial. BMC Cancer 2020;20:406.