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# The use of PSMA-PET/CT for nodal staging and tailoring treatment – a continuous conundrum

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The only ways of pathological lymph node staging (N0 vs. N1) in prostate cancer (PCa) are to evaluate the nodes microscopically after an extended pelvic lymph node dissection (ePLND), or potentially after sentinel node biopsy of a suspicious lesion. More accurate N-staging than conventional imaging with Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) has been the major argument for performing an ePLND at the time of radical prostatectomy (RP), despite lack of evidence for an oncological benefit and significant morbidity risk[1]. The sensitivity and specificity of ePLND is dependent on the extent of the surgical template. Furthermore, it has the inherent drawback of giving the pathological N-stage result *post festum*, when the prostate is already removed, therefore not informing the primary treatment choice. Nodal radiological staging using CT or MRI, is limited by both low sensitivity, and specificity [2], resulting in patients with occult N1 disease receiving local prostate treatment only. Despite this, local treatments have very good oncological results [3], and there are numerous reports on good long-term results after RP, even in patients with limited N1 disease (< 3-4 nodes).

In the past few years, Prostate-Specific Membrane Antigen (PSMA)-PET/CT has been introduced, as an imaging modality with a 27% greater accuracy than conventional imaging [4]. This has changed the pre-treatment staging landscape for patients presenting with high-risk localised and locally advanced disease, evident in the most recent EAU guidelines [3]. Updated nomograms which incorporate PSMA-PET/CT improve the prediction of risk of pN1 disease. A negative PSMA-PET/CT can have a dramatic effect (e.g., an ISUP GG 4 patient with PSA 17 and a PIRADS 5 lesion goes from > 25 % risk of N1 disease without PSMA-PET/CT, to approximately 3 % with a negative PSMA-PET/CT) [5, 6]. Pre-treatment staging for high-risk localised and locally advanced disease should therefore include a PSMA-PET/CT prior to radical treatment, with ePLND unlikely to alter stage if PET is negative.

The EANM proposed a molecular imaging TNM ('miTNM') classification, incorporating PSMA-PET/CT findings. Due to earlier diagnosis, the prognosis of miN and miM substages is likely to be better than their CT/MR imaging N and M counterparts, but the magnitude of the impact is yet undefined. The uncertainty now is both how to manage miN1 disease, due to a lack of evidence for curative effect, and consequently uncertainty about the benefit of identifying microscopic metastases, in those with a negative scan, questions the guidelines of today cannot answer [3].

To answer, we must define what N1 on PSMA-PET/CT means. The imaging examination will offer the answer in two ways: firstly, based on the size of the lymph nodes; secondly, based on the PSMA expression estimated on the PSMA-PET. Therefore, a patient may have N1 disease in three different ways: (i) by having PSMA expression on the PET-scan in lymph nodes with the short-axis diameter greater than 10-15 mm; (ii) by having lymph nodes greater than 10-15 mm, with no PSMA expression; (iii) by having PSMA expression in lymph nodes smaller than 10-15 mm. The first two groups would be considered N1 with conventional CT/MRI-imaging, and especially the first group is very likely pathologically N1, for which we already have strategies and guidelines [3]. In the second group, which is likely the smallest one, other reasons for enlarged lymph nodes, such as lymphoma or infectious diseases, 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 number of positive nodes. Molecular signal change precedes change in size, and a slight/moderate PSMA expression in lymph nodes smaller than 10-15 mm does often mean small, growing lymph node metastases. To compare outcomes and harmonize treatments there is an urgent need for a universal agreement on a PSMA positivity scale, like the PI-RADS scale for MRI. The Standardized PSMA-PET Analysis and Reporting Consensus–SPARC initiative is aiming to harmonise interpretation criteria of multiple guidelines, e.g., E-PSMA Guidelines, PSMA-RADS version 2.0 and PROMISE v2 [7-9].

When consensus is finalized, the next step is 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 (like a PI-RADS 3 lesion on MRI). Patients with low risk of N1 on such a scale should be treated as N0, and according to risk group. For those with higher likelihood of being N1, but still M0, treatment may depend on the number of positive nodes. The exact cut-off on the number of positive nodes is unknown, and trials will be crucial. If the number of positive nodes is high (exceeding 5) it is likely that additional systemic treatment with ADT, +/- ARPI, may be beneficial. For the patients with few positive nodes (up to 5) there is a lack of knowledge of the best treatment option [10]. These are the patients that may benefit from combination of local and lymph node treatment, either by RT

(or RP + ePLND) in addition to systemic treatments. To evaluate treatment options clinical trials should randomise or include a stratification by type of staging used, including varying number of positive lesions and degree of PSMA expression. There are some trials addressing the issue, eg 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 completed, especially when universal PSMA-PET/CT-scales are agreed upon, 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 high burden of metastases, thereby avoiding both under- and over-treatment. The remaining group, with few and small positive nodes, must be discussed and managed individually in multi-disciplinary teams to decide the best available treatment option for each patient.

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