

Editorial

PSMA-PET for Lymph Node Detection in Recurrent Prostate Cancer: How do we use the Magic Bullet?

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Currently, there is a surge in imaging in prostate cancer due to the recent advances in PET imaging using the prostate-specific membrane antigen as target structure. In their article, Jilg *et al.* [8] add significant knowledge on the true capability of this new imaging technique for the detection of lymph node metastases in patients with recurrent disease.

In the past, imaging in patients with biochemically recurrent prostate cancer did not play a major role. Especially at low prostate specific antigen (PSA) values, conventional imaging modalities like computed tomography (CT) or magnetic resonance imaging (MRI) or bone scintigraphy often cannot reliably detect and localize recurrent disease and therefore lack impact on treatment decisions. However, since the recent introduction of novel positron emission tomography (PET) tracers targeting the prostate-specific membrane antigen (PSMA), the role of imaging is changing rapidly [1]. These (almost) prostate cancer specific tracers are able to reveal sites of recurrence in a clarity clearly superior to still most commonly used agents like ¹⁸F-fluoroethylcholine or ¹¹C-choline [2].

Thus, increasing numbers of urologists, radiation physicians and oncologists perceive PSMA-based PET as the long-desired magic bullet to detect recurrent prostate cancer [3]. In turn this has led to a surge of imaging in these patients – despite the still limited experience with this novel technology. Furthermore, histological proof of detected lesions is

only reported in a subset of publications and reported sensitivity and specificity rates differ significantly [4-7].

In the presented study, Jilg *et al.* provide additional data on the value (and limitation) of this new imaging technology in patients with biochemical recurrence. In this well-conducted analysis positive findings on ⁶⁸Ga-HBED-CC-PSMA PET were validated by detailed histopathological assessment. [8]. Most importantly, it shows that a certain size of metastatic lesions within lymph nodes is needed (50% and 90% detection rate at short axis diameters of ≥ 2.3 mm and ≥ 4.5 mm) to be picked up by ⁶⁸Ga-HBED-CC-PSMA PET – reminding us that also this method is not perfect and fails to detect microscopic lesions mainly due to limited spatial resolution of PET as well as insufficient tracer accumulation. However, ⁶⁸Ga-HBED-CC-PSMA PET detects metastatic lymph node lesions significantly earlier than conventional CT or MRI that usually requires a size of at least 8 mm [9]. Certainly, the true sensitivity of ⁶⁸Ga-HBED-CC-PSMA PET in biochemical recurrence cannot be calculated from this study since only patients with positive findings were considered for salvage lymph node dissection (and that in part might explain the slightly different results to previously published studies in patients with primary prostate cancer where also PET-negative patients underwent surgery). On the contrary, this study also demonstrates the high accuracy for

detection of lymph node metastases by this novel imaging technology. This is further underlined by the successful development of radioactively labeled PSMA-targeted molecules for intraoperative surgical guidance *via* gamma detectors [10-12].

But where do we proceed from here? Where is the manual on how to use the PSMA-targeted magic bullet? The perspicuity of ⁶⁸Ga-HBED-CC-PSMA PET might suborn us to treat patients without considering the limitations of this evolving imaging (*e.g.* still missing microscopic disease). When offering patients currently considered experimental localized therapies like salvage lymph node dissection we should bear in mind the most important rule in medicine: “Primum nihil nocere, secundum cavere, tertium sanare”.

Offering patients localized targeted strategies we have to be aware that we might miss sites of disease and that we impose certain morbidity on patients. We must always remember to treat patients and not their images, and in doing so need to account for the patients' clinical condition, the prostate cancer specific history and risk stratification as well as the outcome of standard conservative or observational treatments [13]. Careful patient selection, adequate and balanced counselling as well as thorough investigation of follow-up is mandatory. Here, prospective studies must be undertaken to provide the answers and the evidence needed for implementation into guidelines.

Once again, the authors have to be congratulated for their dedicated work-up of imaging as well as histological evaluation that in detail describes the diagnostic capability of ⁶⁸Ga-HBED-CC-PSMA PET as well as its limitations for lymph node staging. As PSMA-based PET imaging is currently increasingly utilized such critical evaluation with direct histological comparison is important.

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