Editorial Commentary

To see clear is not enough; it is the action that counts

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In 2020, professor Hofman and coworkers published the proPSMA trial (1). The trial is a prospective randomized controlled trial (RCT) of patients with high-risk prostate cancer (PCa). It compared staging with [^{68}Ga]Ga-prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) of 150 patients against conventional staging of 152 patients. 87 of 295 patients had metastases in lymph nodes or bones. Staging with [^{68}Ga]Ga-PSMA PET/CT had a higher accuracy than conventional imaging (92% *vs.* 65%). A recent study has reproduced the findings in staging with PSMA PET/CT (2). Now international guidelines recommend the new staging modality.

However, the annual European Association of Urology (EAU) conference in Milan 2023 led to the warning regarding the implications for treatment: treatment should not be changed based on PSMA PET/CT findings (3). Gelardi and coworkers supported the recommendation and commented: "*Therapeutic decision should be made with caution until we have more data from prospective studies that incorporate upfront staging PSMA-ligand PET/CT*".

The statement seems like a paradox. Three findings favor staging with PSMA PET/CT. The scans have an impressively high sensitivity and specificity (1). PSMA PET/CT detects positive sites in lymph nodes and bones that are not detected with conventional imaging. Up to half of the patients with PCa have staging with PSMA PET/CT that motivates changes in treatment (4). Our editorial uses miN1/miM1 for positive N/M findings with PSMA PET/CT according to a classification based on staging PET/CT, PROMISE, now version 2, to differentiate against standard TNM staging that is based on staging with conventional imaging modalities.

Our editorial comments on a recent multicenter prospective phase 3 study by Djaïleb and coworkers (protocol registered in ClinicalTrials.com, NCT03368547/02611882/02919111) (5). Indirectly the study elucidated the paradox. The study reported 240 patients who underwent staging with [^{68}Ga]Ga-PSMA PET/CT before radical prostatectomy (RP) and pelvic lymph node dissection and who were followed up clinically. None of the patients had undergone neoadjuvant treatment before RP or adjuvant treatments after the RP. Eighty patients (33%) had prostate biopsies with the International Society of Urological Pathology (ISUP) grade 5. Staging PSMA PET/CT showed that 199 patients (83%) did not have metastases (miN0/miM0), and 41 patients (17%) had miN1/miM1 PCa.

None of the patients had a change in treatment due to the preoperative staging PSMA PET/CT. The patients were followed median 32.4 (interquartile range,

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23.3–42.9) months. Ninety-one patients (38%) developed prostate-specific antigen (PSA) relapse [PSAR; previously denoted biochemical recurrence (BCR), as in the Djaïleb publication] (5).

The study had an overall relatively high frequency of PSAR. It reflected the patient selection with intermediate- and high-risk PCa as the largest subgroup of patients (80 patients, 33%) in the preoperative setting who had prostate biopsy results with ISUP grade 5 (5). The authors state that miN1/miM1 was a significant predictor of PSAR on a univariate basis. Djaïleb *et al.* concluded that preoperative PSMA PET was a strong predictive biological indicator that increased PSAR risk assessment (5).

Other studies reported that staging PSMA PET/CT gave a similar or slightly higher frequency of patients with miN1/miM1 (6-14). Zheng *et al.* showed that staging PSMA PET/CT gave pathological upgrading for 27% of the patients and a downgrading for 23% of the patients (6). In a study by Donswijk and coauthors, an upstaging for N/M status was found in 23%/13% while downstaging was found in 9%/23% (15). Comparison with histopathology, apart from correct staging, PSMA PET/CT also has a few patients with false positive findings and slightly more patients with false negative findings (16).

The high frequency of patients with PSAR in patients with staging PSMA PET/CT before the initial treatment pointing to metastatic lesions is a strong counterargument against the recent EAU recommendation of not to treat patients based on PSMA PET/CT. The recommendation is based on a concern of a (supposed) risk for overtreatment, and supports a doctor's delay for treatment. But in real life, the implicit delay looks like a preplanned undertreatment, especially of patients who have positive metastatic lesions on PSMA PET/CT that conventional imaging has not detected.

Staging PSMA PET/CT transfers some N0/M0 and miN1/miM1 patients from the non-metastatic group of patients to the group of patients with metastatic lesions. Thereby the survival for both the non-metastatic and the metastatic group of patients will increase, despite the survival for the whole cohort remains unchanged. Feinstein called the consequence of the stage migration for a Will-Rogers phenomenon (17). Nevertheless, the Djaïleb study showed that the ignoring of the metastatic sites of PCa detected with staging PSMA PET/CT dominated for the risk of PSAR (5).

We hypothesize that adequate treatment based on the PSMA PET/CT improves survival compared with standard treatment based on conventional imaging. The ongoing Danish RCT PRISMA-PET (NCT05123300, ClinicalTrials.gov) evaluates the hypothesis (18). The trial aims to recruit 448 patients with high-risk PCa and will randomize 1:1 for staging with [^{18}F]PSMA-1007 against conventional imaging. The trial plans a follow-up for 20 years. The trial intends to report the impact of staging on stage migration and treatment, the diagnostic accuracy of [^{18}F]PSMA PET/CT, and the impact of the treatment on PSAR and progression-free survival. Another endpoint is the OS (18).

^{18}F-based PSMA is a valid alternative to ^{68}Ga-based PSMA PET/CT (14).

Many studies, described in a PSMA-specific review, show that patients benefit from treatment based on PSMA PET/CT-positive metastatic lesions such as salvage radiation therapy (19). As illustration, a patient with PSAR underwent a restaging PET/CT. The scan showed a metastatic lymph node lesion, so treatment was changed from surveillance to metastasis-directed therapy (MDT). At a new relapse, restaging PSMA PET/CT showed positive metastatic lesions (20), so the patient, still taxane-naïve, fulfilled the criterion for PSMA-based radioligand therapy (PRLT).

PRLT has also been used as first-line treatment of oligometastatic PCa detected with PSMA PET/CT. Other patients with oligometastatic recurrent PCa detected with PET/CT have been treated with MDT (21). Two RCTs (TheraP and VISION) evaluated the outcome after third-line PRLT for patients with PSMA PET/CT-positive metastatic castration-resistant PCa (mCRPC) (22,23). The trials excluded patients with heterogeneous PSMA expression in the PCa lesions. For 98 and 529 patients treated with third-line treatment with PRLT, PSA more often was reduced >50% than PSA was for 85 and 205 patients in the control groups given the alternative treatments, cabazitaxel or best standard of care. In the TheraP trial, the rates of PSA reductions were 65% *vs.* 37%. Both trials prospectively documented the survival after treatment based on restaging PSMA PET/CT in a setting of preplanned treatment (22,23). In consequence, the US Federal Drug Agency (FDA) and the European Medical Agency (EMA) have approved PRLT as third-line treatment of patients with mCRPC.

An ongoing RCT, PSMAddition, an international, prospective, open-label, randomized, phase 3 trial (NCT04720157) (24), plans to include 1,100+ PSMA-PET/CT positive patients with metastatic hormone-sensitive PCa. The study evaluates a doublet of androgen deprivation

therapy (ADT) + androgen receptor pathway inhibitor (ARPI) with or without PRLT. The result of the trial may further contribute to integration of nuclear medicine in multidisciplinary teams for the management of PCa.

Before PSMA PET/CT, D'Amico developed a risk classification based on initial PSA, cancer grade, and extent of the primary PCa. Many subsequent studies have validated the prognostic value of the risk score. In the Djaïleb and coworkers study, multivariate statistical analyses might be undertaken to evaluate whether staging PSMA PET/CT has an added value to this well-known risk score (5).

In conclusion, PSMA PET/CT is the best imaging modality to point to positive sites of PCa. Staging PSMA PET/CT of high-risk PCa patients detects lymph node metastases for almost a third of the patients and bone metastases for a sixth of the patients, as reported in a recent review (25). The estimates fit with recent literature (6-14). So staging PSMA shows metastatic PCa for half of the high-risk patients. This large subgroup of patients needs a more aggressive treatment than only local treatment of the primary PCa.

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