EDITORIAL COMMENT

Hope et al.[1] report on the impact of pretreatment ^{68}Ga-PSMA-PET/CT or PET/MRI in the management of 45 patients with high-risk prostate cancer (PCA). Results of PSMA-PET/CTs were compared to the findings of CT scans and skeletal scintigraphy. Based on their data, PSMA-PET imaging resulted in changes of radiation therapy (RT) dose and volumes in 47% of the patients due to newly diagnosed N1/M1a disease. RT changes resulted in the extension of clinical target volume (CTV) covering the small pelvis and even the retroperitoneum or a RT boost to avid lymph nodes. Noteworthy, 82% of the patients received long-term androgen deprivation therapy (ADT). No data for oncological or functional outcome are given and no data with regard to the treatment associated toxicity of extended RT protocols are reported.

The data transported by the paper are important for several reasons. Firstly, we know from previous studies that whole body MRI detects systemic or extrapelvic metastases in 20%-30% high-risk PCA.[2] Secondly, previous prospective evaluations did not show any benefit of diffusion weighted MRI or ^{11}C-choline-PET/CT to improve the preoperative identification of lymph node metastases.[3] Although Hope et al[1] add some more data to the literature with regard to the clinical usefulness of ^{68}Ga-PSMA-PET/CT in staging and subsequent therapy of men with high-risk PCA, a variety of issues have to be considered carefully prior to the implementation of new imaging modalities in clinical routine.

Although not described in detail, the patient cohort included in this report is quite heterogenous: 31 (69%) patients underwent RT for curative intent whereas 14 (31%) patients underwent radical prostatectomy (RP) followed by adjuvant RT. It needs to be emphasized that all patients underwent PSMA-PET/CT prior to RT or RP but not prior to adjuvant RT. Those patients treated in an adjuvant approach need to be analyzed separately: Based on the data given, we even do not know if the lymph nodes depicted on the preoperative PSMA-PET/CT scans have been dissected at time of RP. In this scenario, preoperative PSMA-PET/CT would not have given clinically useful additional information with regard to the presence of locoregional lymph nodes metastases (LNM) as compared to a properly performed extended pelvic lymphadenectomy.[4,5] It would have been quite interesting to receive some more information about those patients such as the number of retrieved lymph nodes, number of positive lymph nodes, PSA at time of adjuvant RT. In addition, the level of evidence with regard to adjuvant RT of the whole pelvis is rather low and current guidelines do recommend this approach only in a highly selected group of patients[4] reflecting that the natural history of pN+ patients with 1-2 positive lymph nodes results in a 5- and 10-year CSS rate of 94% and 72%.[6]

When it comes to the identification of pelvic lymph node or systemic metastases, additional metastatic foci were identified in 21 (47%) men indicating a clinically important diagnostic benefit of ^{68}Ga-PSMA-PET/CT.

The authors used the Roach formula to predict lymph node involvement and to include pelvic lymph nodes in the CTV. It has to be remembered that the Roach formula was calculated based on the Partin nomograms which rely on a limited pelvic lymphadenectomy only.[7] The Roach formula will overpredict the risk of lymph involvement in clinically organ confined disease and it might underpredict the risk of LNM in high risk disease.[8] There are numerous nomograms which have been proven to result in a higher reliability[9] and which should be used in daily routine.

The diagnostic accuracy of pretherapeutic PSMA-PET/CTs is still discussed controversially even in the studies cited by Hope et al[1] Cantiello et al[10] used ^{64}copper which is not the standard radiotracer of choice. Herlemann et al[11] comprised only 34 patients of whom only 20 did undergo primary RP and, Gorin et al[12] used ^{18}fluoride so that already these 3 studies are heterogenous. In a recent systematic meta-analysis of 298 patients pretherapeutic PSMA-PET/CT demonstrated a modest sensitivity and specificity to identify LNM.[13]

Furthermore, therapeutic implications of ^{68}Ga-PSMA-PET/CT are unclear when it comes to RT since the standard of care in high-risk PCA would be RT plus ADT.[4] If there is any oncological benefit when pelvic or even extrapelvic lesions are included in the CTV is completely unknown. Even the subgroup analysis of 173 pN1 patients treated in the RTOG 85-31 study reported on a significantly improved outcome in terms of 5 year (54% vs 33%, $P < .0001$) and 9 year (10% vs 4%, $P < .0001$) if RT was combined with ADT as compared to RT alone.[14] The extension of RT to oligometastatic foci in the retroperitoneum or skeletal system represents an experimental and individual therapy.

In summary, the data presented by Hope et al[1] add clinically important data to the literature concerning the role of modern imaging techniques to detect locoregional or systemic metastases in newly diagnosed high-risk PCA. A high percentage of patients will undergo treatment changes based on a PSMA-PET/CT. However, due to the lack of large patient cohorts and prospective clinical trials as well as the known pitfalls of PSMA-PET/CT it still does not represent a routine imaging study and we still need to do our homework to initiating cooperative research projects which shed some light on the pros and cons of modern, likely sensitive but also expensive and restrictive imaging studies.

Axel Heidenreich, MD, PhD, Department of Urology, Uro-Oncology, Robot-Assisted and Reconstructive Urologic Surgery, University Hospital Cologne, Germany

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AUTHOR REPLY

We greatly appreciate the thoughtful comments in regards to our manuscript, which highlight a number of important issues about the use of PSMA-PET. It should be noted at the outset that PSMA-PET should not be considered a standard imaging modality. In the United States, PSMA-PET is investigational and is not FDA approved. Although PSMA-PET may be considered standard of care in a few countries, its use in the United States is limited to clinical trials. Nonetheless, the prevalence of PSMA-PET is likely to increase in the next few years, as we should be close to approval of this agent in the coming year. Our hope is that the preliminary data presented in our manuscript may help guide the use of PSMA-PET imaging.

PSMA-PET scans were available to patients meeting certain high-risk criteria prior to definitive treatment (as outlined in the manuscript) or in the setting of biochemical recurrence. We do not routinely obtain repeat PSMA-PET scans following radical prostatectomy (RP) prior to adjuvant radiation; unfortunately we are not able to verify if all PSMA-avid lymph nodes were removed at the time of lymph node dissection (LND) in our cohort. However, from our data we can tell that patients with PSMA-avid lymph nodes had more extensive LNDs (median 31 vs 17 lymph nodes removed, $p = 0.009$).

Table 1 demonstrates the cohort of patients who underwent prostatectomy prior to salvage RT. Four of the patients had negative PSMA-PET scans and negative nodes at surgery. In our cohort, median PSA after RP was 0.14 ng/mL (interquartile range 0.09-0.43). The estimated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in this cohort was 63%, 83%, 80%, and 56% respectively. Other institutional series with histopathologic correlates have estimated higher sensitivity and NPV[1-3], though lower sensitivity has also been reported.[4] One reason for the difference between our small cohort and the literature is that there is a bias in our study, as patients with PSMA-avid nodes that were not removed at time of

Table 1. Nodal status on PSMA-PET, postop PSA, and pathologic characteristics of the 14 patients who underwent radical prostatectomy after PSMA-PET scan

Patient Number	Nodal Status Based on PSMA-PET (Number of Nodes Identified)	Pathologic Nodal Status	Number of Pathologically Involved Lymph Nodes	Number of Lymph Nodes Removed	Max Dimension of Pathologically Involved Nodes (NA if pN0)	Postop PSA
1	–	+	3	21	9 mm	0.15
2	–	–	0	18	NA	0.04
3	–	+	1	27	4 mm	0.09
4	+ (2)	+	2	39	10 mm	0.16
5	–	–	0	11	NA	0.77
6	+ (4)	+	5	28	7 mm	0.50
7	–	–	0	14	NA	0.08
8	–	–	0	10	NA	0.04
9	–	+	5	29	6 mm	0.13
10	–	–	0	6	NA	0.11
11	–	+	2	17	6 mm	0.09
12	+ (2)	+	3	31	18 mm	0.41
13	+ (4)	–	0	34	NA	1.84
14	+ (2)	+	2	22	3 mm	0.40