Brief Correspondence

Prostate-specific Membrane Antigen–radioguided Surgery Facilitates Pelvic Lymph Node Dissection During Radical Prostatectomy for the Treatment of Locally Advanced Prostate Cancer with Regional Lymph Node Metastases

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The emergence of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has substantially improved the accuracy of primary staging in high-risk prostate cancer (PC) [1]. The use of more sensitive imaging techniques has introduced a stage shift, with more patients classified as having positive lymph node (LN) status at diagnosis [2].

During radical prostatectomy (RP), even with an extended template, LN removal in the pelvic region may prove challenging and affected LNs may be missed [3]. Data on sentinel node biopsies have demonstrated the varying draining sites of the prostate and the feasibility of targeted LN resection in the pelvis [4]. More recently, PSMA-radioguided surgery (RGS) in the setting of recurrent PC has been introduced to facilitate targeted resection of PSMA-avid LN metastasis (LNM) as a viable option to defer systemic treatment [5]. Currently, PSMA-RGS during robotic RP is being investigated in a phase 2 trial. Preliminary results from this trial [6] and from the small prospective DETECT study [7], each involving 12 patients, confirmed the feasibility of PSMA RGS during RP. Here we retrospectively report on the use and postoperative outcomes of PSMA RGS in 35 consecutive patients undergoing open RP for primary treatment of locally advanced PC with locoregional PSMA-positive LNs on preoperative PSMA PET. The patient population and methods are summarized in the Supplementary material.

We analyzed data for six patients (17%) with intermediate-risk PC and 29 (83%) with high-risk PC [2] (Table 1). Preoperative PSMA PET showed 78 LNMs (median 2 LNMs per patient, interquartile range [IQR] 1–3), of which 20 (26%) were located outside the extended pelvic LN dissection (ePLND) field. Seven patients (20%) had LNMs exclusively outside the standard ePLND template, 21 patients (60%) had LNMs exclusively inside the template, and seven (20%) had LNMs both inside and outside the template (Fig. 1). An example of patient imaging is shown in Supplementary Figure 1.

Postoperative histopathology showed 153 LNMs in 950 resected LNs, corresponding to a median of 3 LNMs (IQR 1–6) and a median of 23 resected LNs (IQR 20–33) per patient. Overall, 20 histopathologically confirmed LNMs (13%) were located outside the ePLND template in 11 patients (31%).

Overall, RGS successfully facilitated resection of 70/78 (90%) PSMA-positive LNs, confirming pN1 status in 33/35 patients (94%). Postoperative follow-up indicated false-positive PSMA PET for five of 78 LNs (6%). The three LNMs that were missed were located in the paravesical and pararectal regions. A detailed description of these LNs and the corresponding patients is included in the Supplementary material. The median maximum standardized uptake value on preoperative PSMA PET was 3.0 (IQR 2.1–3.6) for false-positive LNMs and 8.3 (IQR 4.3–17.3) for true-positive LNMs. In addition, comparison between PSMA PET and histopathology showed that 22 patients (63%) harbored LNMs within the ePLND field that were not seen on PSMA PET, underlining the necessity of performing ePLND.

Adjuvant androgen deprivation therapy (ADT) ± radiation therapy was administered in five patients (Supplementary Table 1). Overall, 25 patients experienced biochemical recurrence (BCR), of whom underwent postoperative PSMA PET imaging. The median follow-up for the ten patients without BCR was 14 mo (95% confidence interval [CI] 8–20). The median survival time was 3 mo (95% CI not applicable) for BCR-free survival (bRFS), 5 mo (95% CI 4–7) for treatment-free survival (TFS), and 6 mo (95% CI 5–7) for metastasis free survival (MFS). On univariable analysis, the only variable associated with postoperative outcomes was LNM presence on preoperative PET. Risk increased with the number of LNMs: bRFS, HR 1.30 (95% CI 1.02–1.67); TFS, HR 1.23 (95% CI 0.98–1.53); and MFS, HR 1.31 (95% CI 1.03–1.66). In this small sample of patients, detection of more than two PSMA-positive LNMs on PET was significantly associated with higher risk of BCR (HR 2.59, 95% CI 1.07–6.23), initiation of further treatment (HR 2.56, 95% CI 1.15–5.70), and the appearance of metastases (HR 3.11, 95% CI 1.23–7.45). Results for the Cox regression analyses are shown in Supplementary Tables 2–4.

In primary PC, natural lymphatic drainage varies substantially between patients. As a result, a high proportion of patients present with LNMs outside the ePLND template [3]. Here, we report on the use of PSMA RGS in 35 patients undergoing RP with ePLND for PC with suspected LNMs on preoperative PSMA PET. LNMs outside the ePLND field were seen on preoperative PSMA PET in 40% of patients. Without preoperative PSMA PET imaging and subsequent PSMA RGS, these LNMs would have been missed. Large, palpable LNMs might have been found by simple extension of the ePLND template to the proposed area on PSMA PET; however, small-volume LNMs might still have been missed without

Table 1 – Patient characteristics (*n* = 35)

Parameter	Result
Median age, yr (interquartile range)	66 (64–69)
Median initial prostate-specific antigen, ng/ml (interquartile range)	18 (9–35)
Preoperative D'Amico risk group, *n* (%)	
Intermediate risk	6 (17)
High risk	29 (83)
Preoperative clinical staging via PSMA positron emission tomography	
Median time from clinical staging to surgery, d (interquartile range)	36 (18–42)
Patients with metastatic lymph node metastases, *n* (number of nodes)	35 (78)
Median number of metastatic lymph nodes, *n* (interquartile range)	2 (1–3)
Postoperative nodal and metastasis status on histopathology	
pN1 patients, *n* (number of pN1 lymph nodes)	33 (153)
pM1a patients, *n* (number of pM1a lymph nodes)	9 (19)
Postoperative margin status, *n* (%)	
R0	12 (34)
R1	23 (66)
Median postoperative Gleason score (range)	8 (7–9)
Postoperative Gleason category, *n* (%)	
Gleason 7	14 (40)
Gleason 8–10	21 (60)
Postoperative tumor histopathology, *n* (%)	
≤pT2c	6 (17)
pT3a	5 (14)
pT3b	23 (66)
pT4	1 (3)

PSMA = prostate-specific membrane antigen.

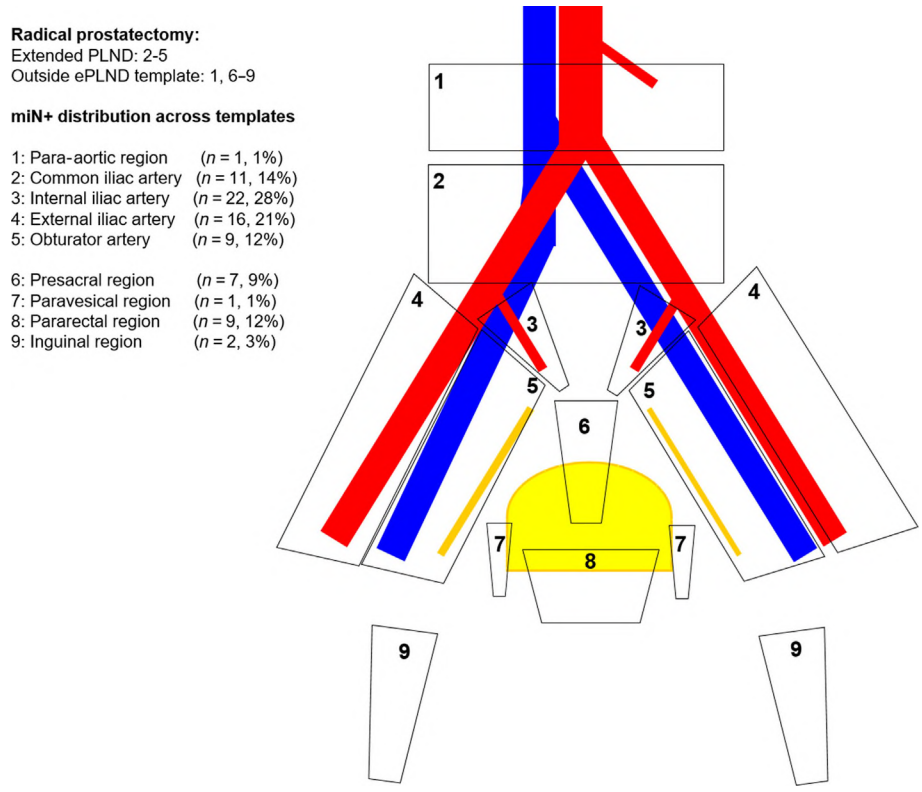

Fig. 1 – Distribution of suspected LN metastases on preoperative prostate-specific membrane antigen positron emission tomography across LN dissection regions. ePLND = extended pelvic LN dissection; LN = lymph node.

the use of RGS, whether inside or outside the ePLND template. Comparison between PSMA PET and histopathology showed that 22 patients (63%) harbored LNMs within the ePLND field that were not seen on PSMA PET. This confirms that a thorough ePLND cannot be omitted [6,8].

Overall, PSMA RGS facilitated the resection of PET-positive LNs in 33/35 patients (94%). PSMA RGS did not facilitate the resection of two pararectal LNMs with weak PSMA expression and one paravesical LNM owing to a diffuse background signal from the bladder because of renal clearance of ^{99m}Tc-labelled PSMA-I&S, which represents a limitation of this method.

In the current analysis, a lower LNM burden on preoperative PET was associated with a lower risk of BCR, initiation of further therapy, and the appearance of metastases. Although the analysis is limited by the small sample size, a threshold of up to two LNMs appeared to be beneficial. Similar associations of lower LN burden with better postoperative outcomes have been reported for PSMA RGS at PC recurrence [5]. An association between a postoperative low volume of up to two LNMs on histopathology and favorable bRFS and cancer-specific survival has been described in several retrospective studies [9–11]. Here, we did not observe an association between histopathology and worse postoperative outcomes (bRFS, TFS, MFS), which may be because of the small sample size.

To the best of our knowledge, this is the first report on PSMA RGS during RP and ePLND for positive LNs on preoperative PSMA PET with postoperative outcomes. However, several limitations are noteworthy, including the small cohort size and the retrospective study design. PSMA RGS remains an experimental approach and large-scale prospective data are warranted to assess its clinical use. In addition, the decision to administer adjuvant therapy was not standardized in this cohort. However, to account for the potential confounding effect of adjuvant ADT on survival outcomes, patients with adjuvant ADT were excluded from all survival analyses. From a technical point of view, PSMA RGS lacks visual feedback (eg, via fluorescence), making it prone to interfering background noise; addressing this issue could improve RGS, especially in robotic surgery. Furthermore, the PSMA PET LNM thresholds associated with better outcomes on univariable analysis should be interpreted with caution and warrant investigation in larger studies. Given the small sample size in our study, these analyses are prone to overfitting.

Taken together, our results show that RGS reliably facilitated resection of LNMs seen on preoperative PSMA PET. Localization and removal of affected LN tissue were possible in most cases otherwise missed by an ePLND template. Here, a lower number of LNMs on preoperative PSMA PET was associated with lower risk of biochemical recurrence, initiation of further therapy, and the appearance of metastases. However, prospective trials are warranted to determine the therapeutic and prognostic impact of PSMA RGS during RP, especially in patients with LNMs outside the ePLND field.

Author contributions: Matthias M. Heck had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Heck.
Acquisition of data: Steinhelfer, Korn, Büchler.
Analysis and interpretation of data: Lunger, Korn, Heck.
Drafting of the manuscript: Lunger, Steinhelfer, Korn, Heck.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2022.12.001.

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