Original Article

Lymph node staging with ^{68}Ga-PSMA PET in patients with intermediate and high-risk prostate cancer suitable for radical prostatectomy managed in a prostate cancer unit

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Background: Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is coming up as a superior imaging tool for prostate cancer (PCa). However, its use in primary staging is still debated. The aim of this study was to assess accuracy of ^{68}Ga-PSMA PET/CT in staging patients with intermediate and high risk PCa candidates to radical prostatectomy managed in the Prostate Cancer Unit of our institution.

Methods: We retrospectively evaluated patients with biopsy-proven PCa staged through PSMA PET/CT before undergoing radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND). PET findings were categorized with respect to primary tumor (T), nodal (N) and distant metastasis (M). We analyzed the correspondence between PSMA PET/CT and final histopathological examination.

Results: We evaluated 42 men with high and intermediate risk PCa submitted to RP with ePLND. Mean age was 65.5 years (range, 49–76 years) and median preoperative prostate-specific antigen (PSA) was 13 ng/mL (IQR, 8.1–20 ng/mL). Patients in the high-risk group were 23 (54.7%), and the remainders were in the intermediate risk group. The mean risk of lymph node involvement (LNI) using the Memorial Sloan Kettering Cancer Center (MSKCC)-nomogram was 20%. The most common International Society of Urological Pathology (ISUP) grade was 3 (26.19%) after prostate biopsy. PSMA PET/CT showed focal prostatic uptake in 28 patients [mean value of maximum standardized uptake value (SUVmax) 18.5] and detected pelvic lymph node metastases in 6 cases (14.3%) with a median value of SUVmax 4.5 (IQR, 2–6.9). Histopathological examination detected lymph node metastases in seven patients (16.6%). In the only patient with negative PSMA PET/CT pathology revealed the presence of micrometastasis. After histopathological confirmation, sensitivity, specificity, positive and negative predictive values of pre-operative ^{68}Ga-PSMA PET/CT were 85.7%, 100%, 100% and 97%, respectively.

Conclusions: In our series, ^{68}Ga-PSMA PET/CT holds high overall diagnostic value for lymph node staging in patients with intermediate and high risk PCa. Accuracy may depend on lymph node size.

Keywords: Lymph node; primary staging; prostate cancer (PCa); prostatectomy; prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT)

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Introduction

Prostate cancer (PCa) is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020, with an estimated almost 1.4 million new cases and 375,000 deaths worldwide (1). Radical prostatectomy for the primary treatment of PCa has been increasing in the last years in all risk groups (2). Lymph node metastasis (LNM) were found in about 15% of patients with intermediate and high risk PCa undergoing radical prostatectomy and extended pelvic lymph node dissection (ePLND) for localized disease (3). Nowadays, patients with intermediate risk and Gleason score ≥7 (4+3) or International Society of Urological Pathology (ISUP) grade group ≥3 and patients with high risk PCa require metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan (4). However, pre-operative computed tomography (CT) scan or magnetic resonance imaging (MRI) sensitivity range between 5–94% and 64–79% in detecting lymph node metastasis, respectively, due to variability in patient populations and methodologies in different studies (5). Extended pelvic lymph node dissection is still the most accurate procedure for nodal staging. However, lymphocele/lymphedema, venous thromboembolism and nerve and vascular risk of injuries are present. Furthermore, in the literature, no clear therapeutic effect or improvement in oncological outcomes are reported (6,7). Currently, according to the European Association of Urology (EAU) guidelines, patients who have a risk of nodal metastases over 5% based on validated nomograms (Briganti nomograms, Roach formula, Memorial Sloan Kettering Cancer Center-MSKCC nomograms) should undergo ePLND (4). In recent years, positron emission tomography/computed tomography (PET/CT) with ^{68}Ga-Prostate-specific membrane antigen (PSMA)-2-hydroxy-5-(carboxyethyl) benzyl]-thylenediamine-N, N9-diacetic acid (HBED-CC) has been shown to have higher sensitivity for detecting nodal and distant metastases than conventional imaging and other PET tracers (8). Although most published data concern use of PSMA-based PET/CT in the biochemical recurrence (BCR) setting (9), the high rate of sensitivity and specificity drives increasing use of this technology also in primary staging of PCa. Despite these high sensitivity and specificity values, the use of PSMA PET/CT in primary staging is debated, due to the absence of prospective data on the correct management of patients considered to have a localized disease after conventional imaging (CT scan and bone scintigraphy) and found metastatic after PSMA PET/CT imaging. At present, we do not have the certainty that changes in therapeutic strategy correspond to a survival benefit. This is one reason for the use PSMA PET/CT in an investigative and multidisciplinary setting. We report on our experience in the use of PSMA PET/CT in patients with intermediate and high-risk PCa suitable for radical prostatectomy to evaluate the sensitivity, specificity, positive and negative predictive values of pre-operative ^{68}Ga-PSMA PET/CT in lymph node staging. We present this article in accordance with the STARD reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-10/rc).

Highlight box

Key findings

- In our study, we reported the correlation between ^{68}Ga-PSMA PET findings and pathology results in lymph node staging, in patients with intermediate and high-risk prostate cancer suitable for radical prostatectomy and extended pelvic lymph node dissection.

What is known and what is new?

- PSMA PET is not routinely recommended in primary staging in prostate cancer and in the decision-making process of whether or not to perform pelvic lymph node dissection.
- In our study, we confirm the high overall diagnostic value of PSMA PET for lymph node staging in patients with intermediate and high-risk prostate cancer.

What is the implication, and what should change now?

- PSMA PET in primary staging and in nomograms should be considered to better select the patients suitable for pelvic lymph node dissection.

Methods

We analyzed in a retrospective setting all patients with intermediate and high risk PCa managed in the Prostate Cancer Unit of our hospital between April 2017 and March 2021 that were staged preoperatively through PSMA

PET/CT and submitted to laparoscopic or robotic radical prostatectomy with ePLND. Ethics Committee of Azienda Ospedaliero-Universitaria of Parma approved the protocol study (No. 11033-11/03/2019/AOUPR). Informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Imaging protocol

The PET/CT exams were performed 30–60 days before surgery. Synthesis of ^{68}Ga-PSMA-HBED-CC was performed using a fully automated module (Scintomics GRP®, Fuerstenfeldbruck, Germany) and a pharmaceutical grade ^{68}Ge/^{68}Ga generator (1850 MBq, GalliaPharm® Eckert & Ziegler, Berlin, Germany), as previously described (10). Mean radiochemical purity of the produced radiopharmaceutical was 99.90% and radiochemical yield 68.71%. Whole body PET/CT was acquired, from vertex to medium thigh of the femur 60 min after i.v. injection of ^{68}Ga-PSMA-HBED-CC (150 MBq) on a hybrid scanner Discovery IQ (GE Healthcare®, Chicago, IL, USA). A low-dose non-enhanced CT was performed afterwards for attenuation correction and anatomical correlation. All PET images were corrected for attenuation, dead time, random events, and scatter. Reconstruction of PET images was performed with an iterative algorithm (ordered-subset expectation maximization).

Two experienced (>450 PSMA PET/CT a year) board-certified nuclear medicine physicians (MS, GB) evaluated all the images visually and semiquantitatively. Visual analysis assessed the presence of tracer uptake in the prostate bed (T), pelvic lymph nodes (N), extrapelvic nodes (M1a), and distant metastases (M). Pelvic lymph nodes were defined by side (left, right) and location. Focal tracer uptake was considered suspicious for cancer lesion when higher than surrounding background, according to PROMISE criteria (11). Semiquantitative analysis of tracer uptake was performed using spherical volumes of interest (VOIs) semi-automatically drawn on orthogonal planes. Maximum Standard Uptake Value (SUVmax) was measured in the prostate and in the target nodal or distant lesion considered as the hottest lesion.

Patients and treatment

We discussed all cases with tracer uptake at PSMA PET/CT in our multidisciplinary PCa team. In this analysis, we only considered procedures performed by expert laparoscopic or robotic surgeons. At the beginning extraperitoneal laparoscopic radical prostatectomy was performed by two experienced surgeons (UVM and SF), and since December 2019 a robotic trans-peritoneal radical prostatectomy by a single surgeon (UVM). An extended bilateral PLND was done in all cases in a standard fashion (12). Prostate and lymph node specimens were examined by a dedicated uropathologist (EMS) according to ISUP protocols (13). We considered the following pre-operative variables: age, prostate-specific antigen (PSA), ISUP grade group on prostate biopsy, risk of lymph node involvement (LNI) on MSKCC nomogram and the maximum standardized uptake value (SUVmax) of the pelvic lymph nodes showing tracer uptake on PSMA PET/CT. The final histopathology results (TNM, ISUP group, number of lymph nodes removed and number of positive lymph nodes) were also noted. Conformity between PSMA PET/CT and final histopathological examination was analyzed.

Statistical analysis

Descriptive statistics were performed for total sample and stratified by lymph nodes (LN) positivity (LN–; LN+). Quantitative data [age, initial prostate-specific antigen (iPSA), MSKCC risk of LNI and total LN resected] were synthesized by calculating median and interquartile range (IQR). These measures were compared between groups (LN– *vs.* LN+) using the Mann-Whitney test. Categorical data (Gleason Score, ISUP classification and pathologic TNM staging) were showed as frequencies and percentages. A potential association between these qualitative variables and LN positivity was explored using the Chi-squared test or the Fisher's exact test depending on the expected frequencies. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of PSMA PET/CT for the detection of regional LN metastases were computed considering pathology at radical prostatectomy as standard. Interrater reliability for PSMA PET/CT was measured as percent agreement and Cohen's kappa. For all the analyses a α=0.05 was considered, and the statistical software used was STATA 13.1 version.

Results

Forty-two patients met the inclusion criteria. Mean age was 65.5 years (range, 49–76 years), mean and median preoperative serum PSA were 14.5 and 13 ng/mL (IQR, 8.1–20 ng/mL), respectively. Patients in the high-risk group

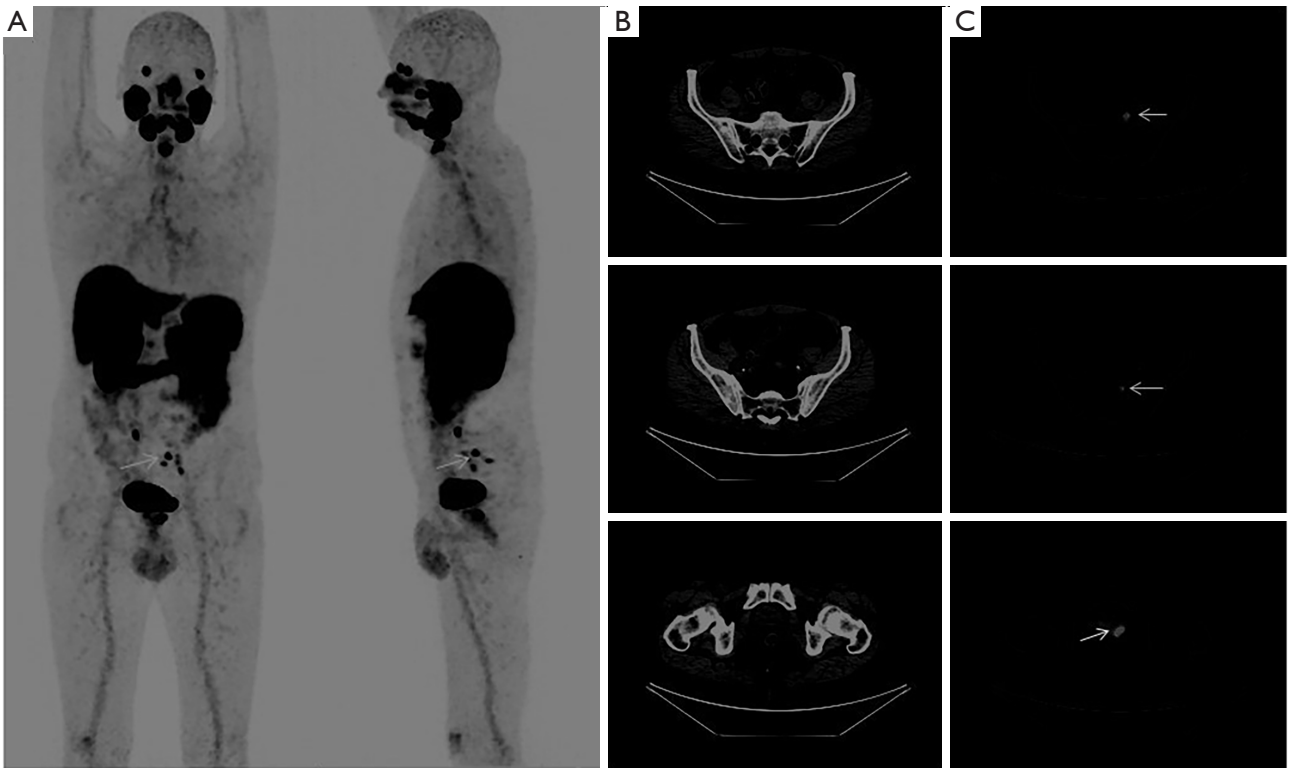

Figure 1 ^{68}Ga-PSMA PET/CT in the primary staging of PCa. Male patient of 62 years old with prostate cancer pGS7 (3+4), ISUP grade 2 at biopsy, iPSA 8 ng/mL. MIP images (A), CT axial sections (B) and fused PET/CT axial sections (C). PSMA PET/CT showed focal increased uptake in left internal iliac and presacral LNs with SUVmax 8.5 (white arrows) (A). Focal uptake was also found in the left peripheral zone of the prostate gland (white arrow) corresponding to primary tumor (C). PSMA, prostate-specific membrane antigen; PCa, prostate cancer; ISUP, International Society of Urological Pathology; MIP, Molecular Insight Pharmaceuticals; CT, computed tomography; PET, positron emission tomography; iPSA, initial prostate specific antigen; LNs, lymph node; SUVmax, maximum standardized uptake.

were 23 (54.7%). The remainders were in the intermediate risk group (45.3%). The mean risk of LNI using the MSKCC-nomogram was 20%. The most common ISUP grade was 3 (26.19%) after prostate biopsy. PSMA PET/CT showed focal prostatic uptake in 28 patients with a mean value of SUVmax 18.5 (range, 3.8–75.3) and weak diffuse uptake in 9 patients. In 6 cases (14.3%) PSMA PET/CT showed tracer accumulation in pelvic lymph nodes defined as metastases (an example is presented in *Figure 1*), with a median value of SUVmax 4.5. The correct value is IQR (2-6.9). All of them presented focal uptake in the prostate (mean SUVmax 12.3). In 5 patients PET/CT was completely negative for tracer uptake in the prostate, LNs or distant lesions. The median number of removed lymph nodes was 11 (IQR, 5–17). At the histopathological examination, lymph node metastases were detected in 7 patients (16.6%) and the median percentage of lymph nodes involvement was 16% in patients with LNM. Six patients with PSMA PET/CT uptake at pelvic lymph node had metastases at the histopathological examination. Only one patient with negative PSMA PET/CT had LNI. This patient had a high-risk PCa with a PSA value of 20 ng/mL, and an ISUP grade 3. In this case, only one metastatic lymph node out of 10 removed lymph nodes was found and pathology examination disclosed micrometastasis. In patients with LNM and positive PSMA PET/CT mean preoperative PSA was 17.9 ng/mL, ISUP group was 2, 4 and 5 in 2, 2 and 2 cases, respectively, with a LNI median risk of 25%. The only difference between LN– and LN+ was the pathological T stage, which was higher in LN+ patients, as reported in *Table 1*. In our series, following pathology confirmation, sensitivity, specificity, positive and negative predictive values of pre-operative ^{68}Ga-PSMA PET/CT were 85.7%, 100%, 100% and 97.2%,

Table 1 Patients' characteristics

Characteristics	Total sample (n=42)	N		P value*
		N– (n=35)	N+ (n=7)	
Age, years	–	67.5 [59.5–71.5]	70 [68–71]	0.28
iPSA	–	12.5 [8.1–19.9]	16 [8.3–20]	0.46
MSKCC risk of LNI	–	12 [5–45]	25 [5–45]	0.55
Total LN resected	–	11 [5–14], 10.2±5.8	14.5 [10–18], 14±7.3	0.227
GS biopsy				0.5
6 (3+3)	7 (16.7)	7 (20.0)	0 (0)	
7 (3+4)	8 (19.1)	7 (20.0)	1 (14.3)	
7 (4+3)	11 (26.2)	9 (25.9)	2 (28.6)	
8 (4+4)	10 (23.8)	8 (22.8)	2 (28.6)	
9 (4+5)	5 (11.9)	3 (8.5)	2 (28.6)	
9 (5+4)	0 (0)	0 (0)	0 (0)	
10 (5+5)	1 (1.4)	1 (2.8)	0 (0)	
ISUP biopsy				0.547
1	7 (16.7)	7 (20.0)	0 (0)	
2	8 (19.1)	7 (20.0)	1 (14.3)	
3	11 (26.2)	9 (25.9)	2 (28.6)	
4	10 (23.8)	8 (22.8)	2 (28.6)	
5	6 (14.3)	4 (11.3)	2 (28.6)	
Pre-operative risk group				0.76
Favorable IR	9 (21.4)	7 (20.0)	2 (28.6)	
Unfavorable IR	10 (23.8)	9 (25.7)	1 (14.3)	
High risk	23 (54.8)	19 (54.3)	4 (57.1)	
pGS				0.12
6 (3+3)	3 (7.1)	3 (8.5)	0 (0)	
7 (3+4)	12 (28.6)	10 (28.6)	2 (28.6)	
7 (4+3)	12 (28.6)	11 (31.5)	1 (14.3)	
8 (4+4)	8 (19.1)	7 (20.0)	1 (14.3)	
9 (4+5)	6 (14.3)	3 (8.5)	3 (42.8)	
9 (5+4)	1 (2.4)	1 (2.8)	0 (0)	
10 (5+5)	0 (0)	0 (0)	0 (0)	
pISUP				0.14
1	3 (7.1)	3 (8.5)	0 (0)	
2	12 (28.6)	10 (28.6)	2 (28.6)	
3	12 (28.6)	11 (31.5)	1 (14.3)	
4	8 (19.1)	7 (20.0)	1 (14.3)	
5	7 (16.7)	4 (11.4)	3 (42.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total sample (n=42)	N		P value*
		N– (n=35)	N+ (n=7)	
pT				0.016
T2	17 (40.5)	17 (48.5)	0 (0)	
T3a	14 (33.3)	11 (31.5)	3 (42.8)	
T3b	11 (26.2)	7 (20.0)	4 (57.2)	

Values are presented as n (%), mean ± SD or median [IQR]. *, P value is significant (<0.05). iPSA, initial prostate specific antigen; MSKCC, Memorial Sloan Kettering Cancer Center; LNI, lymph node involvement; LN, lymph node, GS, Gleason score, ISUP, International Society of Urological Pathology; IR, intermediate risk, IQR, interquartile range; SD, standard deviation; N, node.

respectively. All patients were re-evaluated 4–6 months after surgery and all of them tested negative for biochemical or clinical recurrence of disease.

Discussion

A more precise lymph node staging is the way to avoid unnecessary lymphadenectomy. Nowadays all the patients with more than 5% risk of LNI on nomogram must undergo extended pelvic lymph node dissection. However, this cut-off value overestimates the real risk of LNI, as reported by a study of the EAU Young Academic Urologist-Robotic Section. In this paper the authors, by analyzing the results of five high volume European centers, reported a rate of 77.8% of ePLND in patients with LNI >5% with only 4.1% of nodal metastasis detected (14). Moreover, 85% of negative lymph nodes specimens after PLND in patients with intermediate and high risk PCa reported by other authors (3) suggest that most pelvic lymphadenectomies performed during radical prostatectomy may be not necessary. Recently, PET/CT imaging with PSMA-based radioligands has been showed in several retrospective and prospective studies to be superior compared to CT and MRI exams (15,16), bone scintigraphy (17,18) and PET/CT with ^{18}F-fluciclovine (15,19-21) or radiolabeled choline (22,23). Application of PSMA PET/CT in the primary staging of PCa have recently emerged due to the essential role of imaging for risk stratification and treatment decisions (15,24,25). In the proPSMA randomized control study the use of PSMA PET/CT as first-line imaging changed treatment in 28% of patients (compared to 15% following conventional imaging) with a lower radiation burden (15). Moreover, a recent analysis based on the proPSMA Trial results has demonstrated that PSMA PET/CT is less costly than conventional imaging for initial staging (26). However, diagnostic accuracy of PSMA PET/CT varies across different series, as shown in a recent systematic review on 27 studies including 2,832 patients. The variations may be related to technical aspects of the PET/CT tomograph and image reconstruction methods, to the reader and urologist experience, to the surgical procedure and to handling of pathology specimens (27).

To reduce the potential bias linked to the retrospective nature of our study, we chose to analyze patients handled by skilled urologists/pathologists in the context of the Prostate Cancer Unit of our hospital. Moreover, PET/CT readers of our institution are highly confident in PSMA-based imaging with more than 450 scans/year (10) and reporter agreement was very high for both nodal side and pelvic location (kappa 1, 100%). The increasing interest for the application of PSMA PET/CT in primary staging is related to the high specificity and negative predictive value for local lymph node metastases (28-35), as confirmed in our study. Results of different series about specificity are similar, but there are great differences about sensitivity, ranging from 33% to 100% (36), due to the small sample size, heterogeneity of risk groups, limited number of lymph nodes removed, and presence of lymph nodes micrometastasis.

In the review by Stabile *et al.*, the authors suggest that due to the high NPV of PSMA PET/CT in men with a lower risk of LNI might be employed to reduce the number of ePLND. Instead, ePLND should be performed in high-risk patients, even with a negative PSMA PET/CT (27).

In our experience PSMA PET/CT revealed optimal specificity but also good sensitivity (83%) and the presence of lymph node PSMA uptake has appeared as a strong indication to perform ePLND. However, a negative ^{68}Ga-PSMA PET/CT does not exclude microscopic lymph

node metastasis at all. Indeed, in our experience pathology demonstrated the presence of micrometastasis in the only case of false negative PSMA PET/CT, who is a patient with high-risk disease. The retrospective nature and the enrollment of selected patients with intermediate and high risk Pca represent limitations to this study. Moreover, the sample size was relatively small (42 patients submitted to radical prostatectomy) with LNI in 7 patients (16.6%) and only one case of false negative PSMA PET/CT.

In one of the large prospective primary staging series of intermediate and high-risk PCa with PSMA PET/CT undergoing Radical Prostatectomy (RP) and ePLND (262 patients), the authors reported a 41% sensitivity, which is lower than ours (85.7%) (37). This aspect may be explained by the difference in sensitivity and NPV in high-risk patients, as reported by Stabile *et al.* (27), due to the presence of a higher number of patients in the high-risk group (81%) compared to our series (54.7%). Nowadays, compared to conventional imaging, PSMA PET/CT provides superior assessment of patients' risk, and it should be considered as a tool to guide treatment. The future aim will be to integrate PSMA PET/CT with PSA levels, histopathological and mpMRI results, to improve selection of candidates to ePLND. The study by Franklin *et al.* (31) suggested that patients with a negative preoperative ^{68}Ga-PSMA PET/CT, ISUP grade <5 and Prostate imaging-reporting and data system (PI-RADS) <5 on mpMRI or ISUP Grade 5 with PI-RADS <4 have a risk of LNI <5% than predicted with nomograms and in these cases an ePLND is not necessary. Finally, the increasing accessibility to PSMA-based imaging due to the approval of ^{68}Ga-PSMA-11 injection by Food and Drug Administration (FDA) (38) and the publication of the specific Monograph in the European Pharmacopeia (39), may allow larger validation studies in the setting of primary staging.

Conclusions

In our Prostate Cancer Unit's experience, ^{68}Ga-PSMA PET/CT demonstrated high overall diagnostic value for lymph node staging in intermediate and high-risk PCa. Staging accuracy may depend on lymph node-size. PSMA positive lymph nodes have to be included in the dissection field.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-10/coif). DC serves as an unpaid editorial board member of *Chinese Clinical Oncology* from August 2022 to July 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics Committee of Azienda Ospedaliero-Universitaria of Parma approved the protocol study (No. 11033-11/03/2019/AOUPR). Informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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