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Clinical-Prostate cancer

68Ga-PSMA PET/CT: Does it predict adverse pathology findings at radical prostatectomy?

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Abstract

Introduction: Data on the accuracy of 68Ga-PSMA positron emission tomography/computed tomography (PET/CT) in patients with intermediate/high-risk prostate cancer are being accumulated. Its role in assessing the extent of local disease has not been fully elaborated.

Aim: To determine the performance characteristics of 68Ga-PSMA PET/CT in identifying local disease extension in patients with intermediate/high risk prostate cancer.

Methods: 68Ga-PSMA PET/CT studies of 61 consecutive patients with intermediate/high-risk prostate cancer who underwent radical prostatectomy were reviewed by nuclear medicine specialists. Tumor location, extraprostatic extension (EPE), seminal vesicle invasion (SVI), and lymph nodes involvement (LNI) were compared to pathological findings. The incremental value of 68Ga-PSMA PET/CT to established nomograms was determined.

Results: Two patients without pathologic uptake of 68Ga-PSMA were excluded. Seventeen patients were diagnosed with EPE (29%), 12(20%) had SVI and 3(5%) LNI. The concordance between tumor location and 68Ga-PSMA PET/CT findings was 48%, and EPE was not indicated by PET in any of the patients. The sensitivity, specificity, positive, and negative predictive value for SVI were 58%, 96%, 78%, 90%, respectively (area under the receiver operating characteristic curve = 0.77) and for LNI 67%, 98%, 67%, 98%, respectively (area under the receiver operating characteristic curve = 0.82). Incorporating imaging findings into the MSKCC-SVI nomogram enhanced the diagnostic accuracy from 0.84 to 0.95 (Integrated Discrimination Increment 0.24, $P = 0.004$).

Conclusion: In patients with intermediate/high-risk prostate cancer, 68Ga-PSMA PET/CT provides information regarding intraprostatic tumor location, SVI and LNI but has no role in assessment for EPE. This information might be useful for pretreatment counseling, decision-making and possibly preoperative planning.

Keywords: Prostate cancer; radical prostatectomy; 68Ga-PSMA PET/CT

1. Introduction

The choice of treatment approach in patients diagnosed with localized prostate cancer is based on various aspects and parameters of the disease. The traditional digital rectal examination, pretreatment prostate specific antigen (PSA) level and biopsy Gleason score are no longer considered sufficient to guide ultimate decision-making, particularly in a high-risk setting. 68Ga-PSMA positron emission tomography/computed tomography (PET/CT), while still not widely available worldwide, is becoming a promising tool used for staging of newly diagnosed patients and tailoring the individual treatment approach. Yet, while most publications focused on the role of this imaging modality in assessment of metastatic and recurrent disease, evidence regarding its diagnostic utility in predicting adverse pathology in radical prostatectomy and lymph node involvement has yet to be determined [1,2].

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Accurate loco-regional staging is cardinal for preplanning the extent of dissection around the neurovascular bundles during radical prostatectomy in high-risk patients as well as the need for extended lymph node dissection. From a different perspective, the application of focal therapy using various modalities depends heavily on the ability to diagnose patients with unilateral/bilateral disease and those with extra prostatic extension (EPE) or seminal vesicle invasion (SVI). While multi-parametric MRI is still considered the most accurate tool for local staging prior to definitive treatment, contemporary data shows great heterogeneity concerning its sensitivity and specificity in evaluating T3a and T3b tumors [3−5].

In the current study we investigated the diagnostic accuracy of 68Ga-PSMA PET/CT in loco-regional staging of surgically treated patients.

2. Methods

After approval from our Institutional review board we retrospectively analyzed a prospectively maintained single-institutional database of 61 consecutive Caucasian men with biopsy proven intermediate/high-risk prostate cancer who underwent 68Ga-PSMA PET/CT prior to robotic assisted laparoscopic radical prostatectomy and pelvic lymph node dissection including the external, hypogastric and common iliac chain bilaterally and obturator lymph nodes. Clinical characteristics of patients included age, pre-treatment PSA, biopsy and pathological Gleason score (GS), clinical and pathological stages. The Partin, Memorial Sloan Kettering Cancer Center (MSKCC) and Briganti nomograms were used to estimate the probability of SVI and lymph nodes invasion (LNI).

2.1. PET technique and analysis

68Ga-PSMA-11 (68Ga-HBED-CC) was used as the PSMA ligand and injected intravenously as a bolus dose of 148−166.5 MBq (4−4.5 mci) 45−60 minutes before image acquisition. Patients were instructed to void immediately prior to study initiation. PET/CT acquisition was performed from the tip of the skull to mid-thigh using the Discovery 690 PET/CT system (GE Healthcare). First, a diagnostic noncontrast CT was performed, followed by a PET scan with an acquisition time of 4 minutes per bed position. PET images were reconstructed by means of an ordered-subsets expectation maximization algorithm. CT data were used for attenuation correction. The studies were read on a XELERIS workstation (GE Healthcare) equipped with fusion software that enables the display of PET images (with and without attenuation correction), CT images, and the fused data of both modalities. Maximal standardized uptake values (SUV) were obtained for the various lesions detected within the prostate using 1 cm volume-of-interest sphere.

For study purposes, PET/CT data were analyzed visually by nuclear medicine readers who were blinded to any previous MR results or pathological findings and resolved any disagreements by a consensus meeting. Lesions with increased tracer uptake above background were considered positive. As the criteria used to identify EPE on 68Ga-PSMA PET/CT are not well-established, we applied comparable criteria for EPE used in MRI, namely, angulated contour of the prostate gland and obliteration of rectoprostatic angle. Tumor location on 68Ga-PSMA PET/CT and the maximal standardized uptake value (SUV-max) were recorded.

2.2. Histopathological evaluation

All specimens were evaluated by experienced uro-pathologists using a predetermined protocol in accordance with the 2014 International Society of Urological Pathology Consensus Conference guidelines [6]. Tumors were further characterized by side (right/left lobe) and location (apex, base, midgland). Positive surgical margins were defined as tumor on ink and the Gleason score at the margin site was indicated.

2.3. Statistical analysis

Descriptive statistics were used to summarize patients' characteristics. The Student's *t*-test was used for comparison of means. Pearson correlation coefficient was used to compare the correlation between PSA and SUV and a 1-way analysis of variance was used to compare the correlation between SUV and tumor GS. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic performance of 68Ga-PSMA PET/CT, Partin, MSKCC and Briganti estimates and the areas under the ROC curves were obtained to compare the diagnostic capacity of the models. Logistic regression models were built to assess whether the addition of 68Ga-PSMA PET/CT findings to existing nomograms can enhance its ability to detect SVI using the Integrated Discrimination Increment (IDI) [7,8]. All tests were 2-tailed and statistical significance was defined as a $P < 0.05$.

3. Results

A total of 61 patients underwent 68Ga-PSMA PET/CT prior to robotic assisted laparoscopic radical prostatectomy, and 2 patients were excluded due to negative PET study. Characteristics of the remaining 59 men are presented in Table 1. Twelve patients (20%) had a biopsy GS 3+4 (GG 2), 23 (39%) had GS 4+3 (GG3), 18 (31%) had GS 8 (GG 4), and 6 patients (10%) were diagnosed with GS 9 (GG 5). Twenty-nine men (49%) were categorized as high-risk, and 25 (42%) were considered unfavorable-intermediate risk [9,10]. On final pathology, 10 patients (17%) had unilateral disease and 49 (83%) had a bilateral disease. Seventeen patients had extraprostatic tumor extension (29%) and in another 10 men (20%) SVI was detected. Three (5%) were diagnosed with LNI.

Table 1
Patients' characteristics ($n = 59$)

Age (y)	
Mean (SD)	65.35(6.99)
PSA (ng/dl)	
Mean (SD)	12.97(11.88)
Biopsy Gleason Score (no., %)	
Gleason 3+4 (group 2)	12(20%)
Gleason 4+3 (group 3)	23(39%)
Gleason 8 (group 4)	18(31%)
Gleason 9 (group 5)	6(10%)
Clinical stage(no., %)	
T1c	34(57%)
T2a	3(5%)
T2b	6(10%)
T2c	11(19%)
T3	5(9%)
Prostate SUV max	
Mean (SD)	8.36(5.83)
Risk group(no., %)	
Favorable intermediate	5(9%)
Unfavorable intermediate	25(42%)
High risk	29(49%)
Pathologic Gleason score(no., %)	
Gleason 3+4 (group 2)	22 (37%)
Gleason 4+3 (group 3)	21(36%)
Gleason 8 (group 4)	10(17%)
Gleason 9 (group 5)	6(10%)
Pathologic Stage(no., %)	
T2	30(51%)
T3a	17(29%)
T3b	12(20%)
Lymph node invasion(no., %)	
	3(5%)
Positive surgical margins(no., %)	
	10(17%)

PSA = prostate specific antigen; SUV max = maximal standardized uptake values.

Findings of 68Ga-PSMA PET/CT studies were compared to pathology. Of the 49 patients with bilateral tumor involvement, 32 (65%) were detected accurately by 68Ga-PSMA PET/CT while in 17 (35%) the extent of disease was underestimated being categorized as unilateral on PET/CT. Among the latter, in 13/17 patients (76%), the dominant lesion was in fact detected by the 68Ga-PSMA PET/CT whereas the contralateral Gleason 3 pattern tumor was overlooked.

SUV-max was calculated (median 6.6 range 3.1−18.9 interquartile range 6.2), we found a significant linear association between the intensity of 68Ga uptake (reflected by SUV-max) and preoperative PSA level (Pearson correlation coefficient, 0.34, $P = 0.008$). SUV max was also associated with the Gleason score, the largest mean difference (6.43) noted between GS 3+4 and 4+3 ($P = 0.02$). The concordance between the specific anatomical tumor location (stratified as apex /midgland/base) and 68Ga-PSMA PET/CT findings was 48% (Table 2).

By using imaging criteria for extraprostatic extension reported elsewhere [11], namely angulated contour of the prostate gland and obliteration of rectoprostatic angle, we could not ascertain the presence of EPE in any of the 17 men diagnosed with pathological T3a.

Table 2
Diagnostic accuracy of 68Ga-PSMA PET/CT in detecting tumor location

Tumor side	68Ga-PSMA PET/CT accuracy (%)
Right	4/4(100%)
left	5/6(83%)
Bilateral	32/49(65%)
Total	41/59(69%)
Index lesion* side	
Right	11/11(100%)
Left	11/12(92%)
Bilateral	32/36(89%)
Total	54/59(91%)
Tumor location	
Right apex	14/24(58%)
Right midgland	32/50(72%)
Right base	15/20(75%)
Left apex	14/25(56%)
Left midgland	41/53(77%)
Left base	12/17(71%)

* The dominant tumor focus within the prostate according to size and/or Gleason score.

The sensitivity, specificity, positive and negative predictive value for detection of SVI by 68Ga-PSMA PET/CT were 58%, 96%, 78% and 90% respectively and the area under the ROC curve was 0.77 (95% confidence interval, 0.59−0.95; $P = 0.004$). The area under the ROC curve for detection of SVI using the Partin and MSKCC predictive models were 0.84 and 0.89, respectively, and incorporating the 68Ga-PSMA PET/CT results into the MSKCC nomogram increased the area under the ROC curve to 0.95 (Fig. 1). To further evaluate the diagnostic value of 68Ga-PSMA PET/CT in predicting SVI we calculated the IDI for the MSKCC nomogram with and without 68Ga-PSMA PET/CT results. With an IDI of 0.24 ($P = 0.004$) we showed a significant increase of 83% in the discrimination ability for SVI using the combined score. Figure 2 illustrates the distribution of probabilities produced with this model.

Lymph node dissection was performed in all patients, 3 (5%) of whom were diagnosed with LNI. The sensitivity, specificity, positive and negative predictive value for detection of LNI by 68Ga-PSMA PET/CT were 67%, 98%, 67% and 98% respectively and the area under the ROC curve was 0.82. The areas under the ROC curve for predicting LNI using the Partin, MSKCC and Briganti nomograms were 0.87, 0.71 and 0.72 respectively (Fig. 3).

Two patients who were excluded due to negative PET study had GS 4+3 (GG3) and 8 (GG 4) prostate cancers with EPE on final pathology.

4. Discussion

Accurate local staging of prostate cancer, particularly in the high-risk setting remains a challenge. Its critical role in

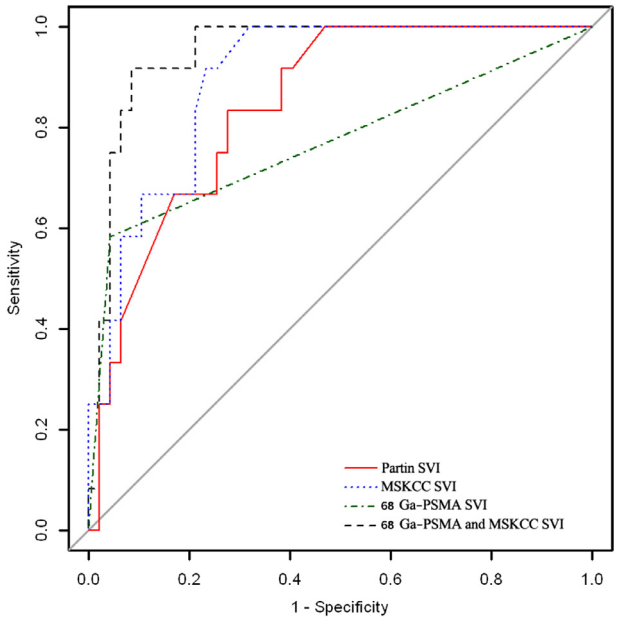

Fig. 1. The areas under the ROC curves comparing diagnostic capacities of seminal vesicle invasion on 68Ga-PSMA PET/CT, Partin and MSKCC nomograms and a combined score incorporating the MSKCC nomogram and 68Ga-PSMA PET/CT. Abbreviations: ROC = Receiver operating characteristic; PET/CT = positron emission tomography/computed tomography; MSKCC = Memorial Sloan Kettering Cancer Center.

preoperative planning of nerve sparingallowing comprehensive discussion with patients on their anticipated postoperative erectile dysfunction as well as the potential need for multimodal therapy cannot be overstated. Likewise, there is growing interest in the accurate identification of unilateral tumors amenable to focal therapy. While prostate MRI remains the standard of care in this context, the emerging role of 68Ga-PSMA PET/CT is under intense scrutiny.

Our study demonstrates that 68Ga-PSMA PET/CT may add useful information regarding local characterization of the cancer. Specifically, PET/CT had incremental value in predicting SVI on final pathology over available models such as the Partin and MSKCC nomograms. Corroborating prior results, we also found that the intensity of 68Ga uptake (reflected as SUV max) correlated with pathological Gleason score, the largest difference noted between GS 3 +4 (GG2) and 4+3 (GG3) [12,13]. Whether these findings can be incorporated into routine clinical practice, deferring the option of active surveillance in those deemed at low risk, is a topic for further investigation. Our study, however, suggests that 68Ga-PSMA PET/CT can add useful information in characterizing the primary lesion, and may enhance the diagnostic accuracy of prostate biopsies in patients in whom MRI is contraindicated [14]. In our cohort only 10 patients had unilateral disease; hence the true value of PET/CT in identifying tumors amenable to focal therapy should be further investigated. Much like

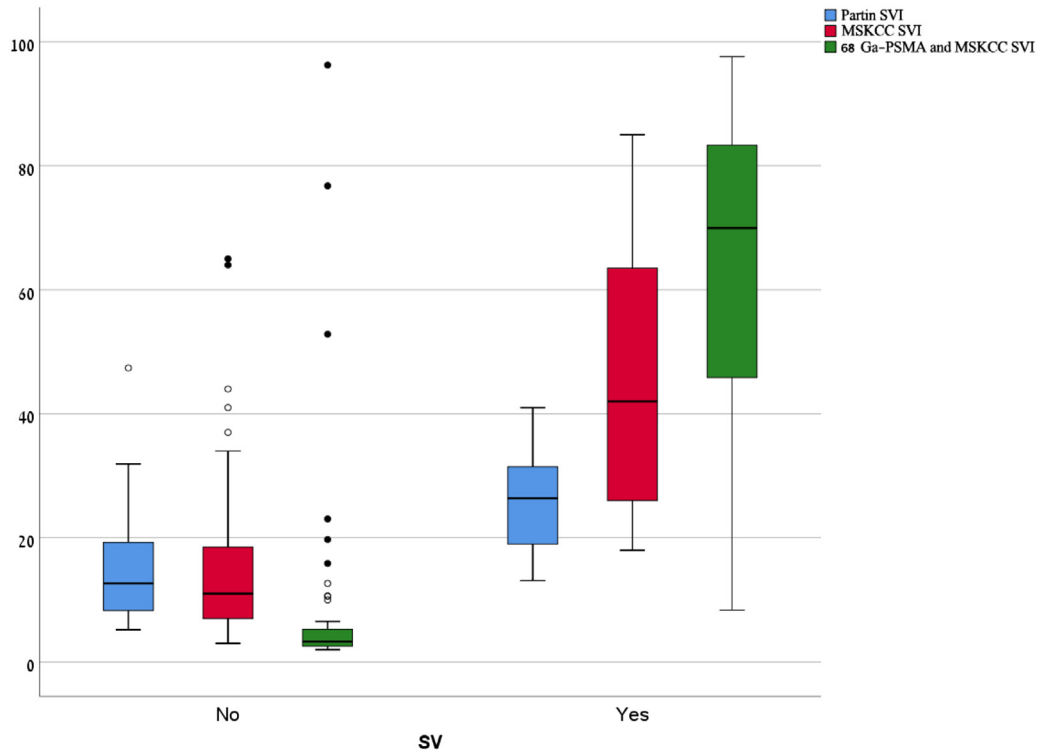

Fig. 2. Box-and-whisker plot shows probability for presence of seminal vesicle invasion, with and without 68Ga-PSMA PET/CT results. Bottom and top of boxes indicate 25th and 75th percentiles, respectively. Horizontal lines inside boxes indicate median values. Abbreviations: PET/CT = positron emission tomography/computed tomography; MSKCC = Memorial Sloan Kettering Cancer Center.

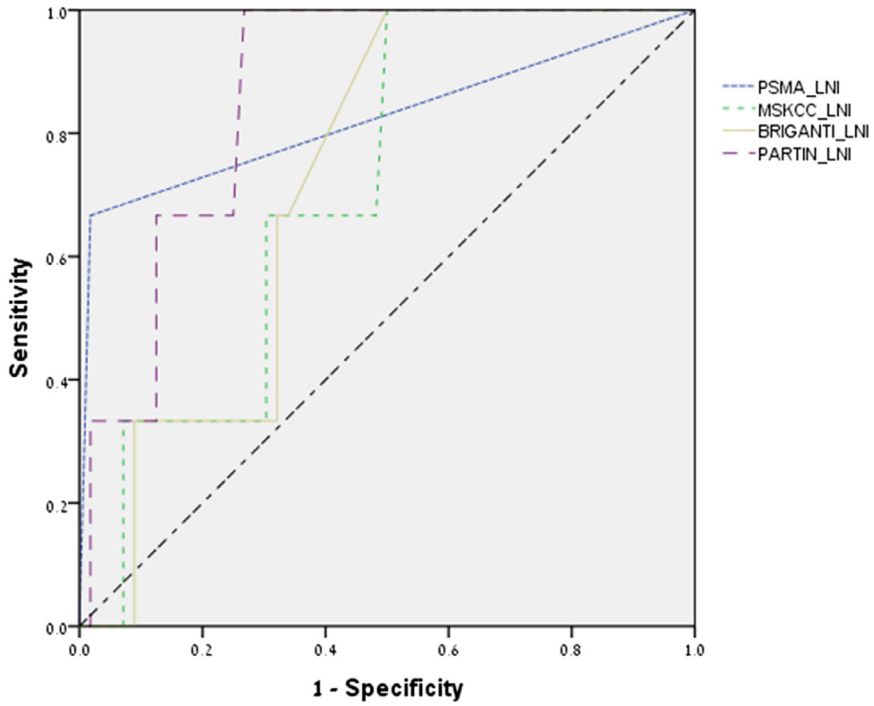

Fig. 3. The areas under the ROC curves comparing the diagnostic capacities of lymph nodes invasion on 68Ga-PSMA PET/CT, Partin, MSKCC and Briganti nomograms. Abbreviations: ROC = Receiver operating characteristic; PET/CT = positron emission tomography/computed tomography; MSKCC = Memorial Sloan Kettering Cancer Center.

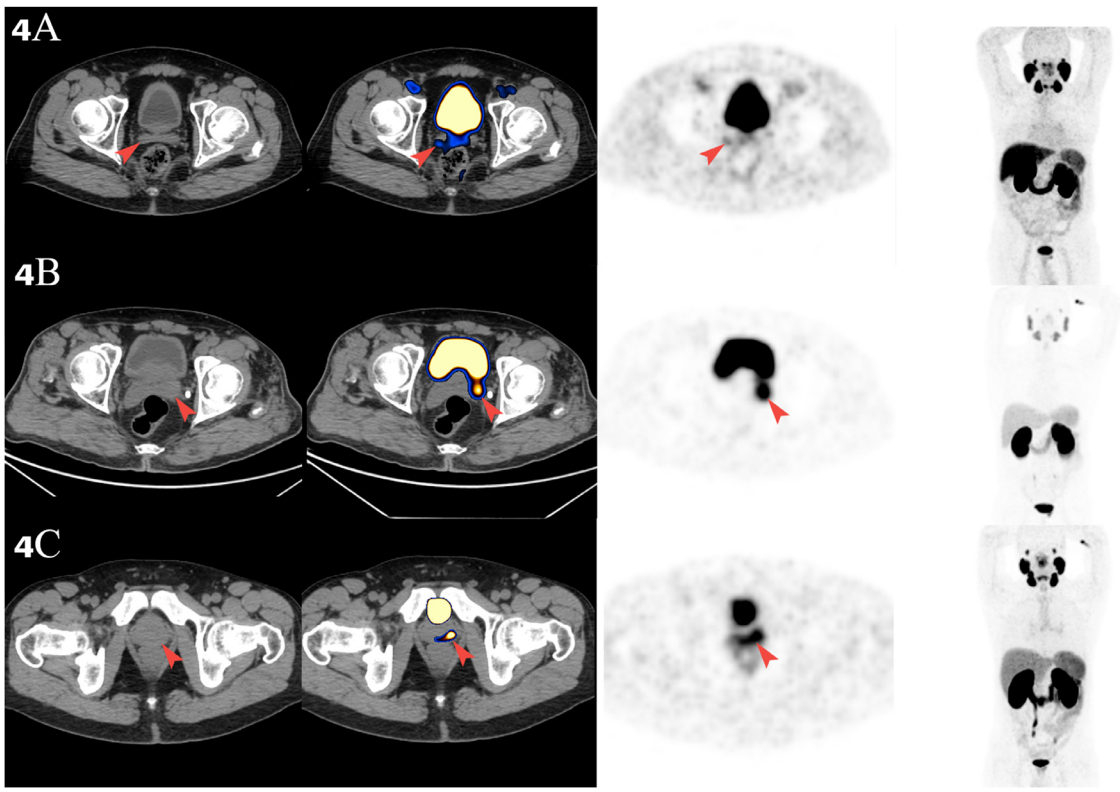

Fig. 4. (A), False positive 68Ga-PSMA-11 focal uptake in the right seminal vesicle. (B), True positive 68Ga-PSMA-11 focal uptake in the left seminal-vesicle. (C), Extraprostatic extension on final pathology; could not be determined accurately on 68Ga-PSMA PET/CT.

MRI, we did notice that PET is less efficient in detecting Gleason 3 patterns [15,16].

Two patients were excluded from our cohort due to negative PET studies. In most of the large PSMA series, roughly 5% of the patients with pathologically confirmed prostate cancer show no uptake in the primary lesion. [17]. Among these patients 68Ga-PSMA PET/CT cannot be used for local staging.

While several studies evaluated the incremental value of multi-parametric MRI to well-established nomograms [18,19] there is paucity of information pertaining to the ability of 68Ga-PSMA PET/CT to detect accurately the local extent of the disease. Von klot et al. evaluated 21 patients with prostate cancer and showed high PPV and NPV for detection of SVI (100% and 97%, respectively) [11]. Using angulated contour of the prostate gland and obliteration of rectoprostatic angle as criteria for EPE, they were also able to demonstrate a high detection rate of pT3a disease. In contrast, as the latter subtle findings could not be demonstrated unequivocally in any of our high-risk patients, our data suggest that PET/CT studies cannot be used reliably to assess extraprostatic involvement, highlighting the inexorable role of MRI in this setting. Whether it can accurately predict the presence of LNI should be further investigated.

In conclusion, 68Ga-PSMA PET/CT, particularly when added to existing validated risk stratification tools, may enhance the ability to predict the intraprostatic location of the dominant tumor and determine the presence of SVI and LNI in patients diagnosed with intermediate/high-risk prostate cancer. It is of a limited value in assessment of EPE.

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