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Research Article

Performance of Ga-68 PSMA PET/CT for diagnosis and grading of local prostate cancer

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ABSTRACT

Background: We aimed to evaluate the utility of prostate-specific membrane antigen (PSMA) PET/CT for the detection of local disease within the prostate.
Methods: This is a retrospective review of a single-center experience evaluating intraprostatic detection rates compared with final histopathology in a radical prostatectomy (RP) population. Seventy-two patients had PSMA PET/CT scan performed as part of their primary staging. Intraprostatic PSMA PET/CT avidity was assessed. PSMA PET/CT uptake was retrospectively correlated with patient characteristics including final histopathology, MRI Prostate Imaging Reporting and Data System (PI-RADS) score, clinical tumor stage, prostate-specific antigen (PSA) level, and patient age.
Results: The sensitivity of PSMA PET/CT for the detection of RP-confirmed prostate cancer was 81.2%. Much higher sensitivity was found within certain subpopulations. The patient characteristics that most strongly correlated with focal intraprostatic PSMA PET/CT uptake were patient age (Kendall's tau coefficient $\tau_b = 0.24$, p < 0.05) and clinical T stage ($\tau_b = 0.21$, p < 0.05).
The International Society of Urological Pathology (ISUP) grade group from final RP was predicted by standardized uptake value (SUV_{max}) and to a lesser extent PSA and the maximal dimension of PET-avid lesions. SUV_{max} monotonically increased with ISUP grade group. If SUV_{max} was above 10 g/mL, the final RP histopathology had a relative risk of 2.3 (95% CI 1.3–4.1) of being ISUP grade group 5.
Conclusion: This trial provides early evidence that PSMA PET/CT assists in the grading of prostate cancer and suggests that the imaging modality is particularly accurate in subpopulations including the elderly and those with palpable disease.

1. Introduction

Prostate cancer diagnosis and treatment can contribute to morbidity [1]. Further, many men are diagnosed with nonclinically significant disease for whom aggressive intervention is not required [2]. Prostate biopsy remains the mainstay of diagnosis and prognostication, but biopsy techniques are invasive and can cause complications, which has led some commentators to suggest that fewer men should be investigated [1]. Consequently, there is scope to develop less invasive tests to diagnose prostate cancer; or at the very least to provide guidance about whether a prostate biopsy is required.

Recent reports have suggested promising results of PET scans based on prostate-specific membrane antigen (PSMA) as a tool for the detection of recurrent prostate cancer. There have been numerous iterations of PSMA inhibitors, but the human experience with small-molecule PSMA inhibitors was in 2008 [3], and the improved ^{68}Ga-PSMA-11 was developed in 2011 [4]. The first large retrospective trials emerged in 2015 [5]. ^{68}Ga-PSMA PET/CT imaging has produced promising early results to the extent that some consider it to be the reference standard for the detection of lymphatic metastases [6]. Specificity for all local and metastasized prostate cancer on a per lesion basis is reportedly very high (97%), but sensitivity is much lower (80%) [7].

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The applications of PSMA PET/CT are diverse, including better detection of new metastases and detection of cancer following biochemical recurrence [8]. However, the evidence examining the use of PSMA PET/CT for assessing the presence of primary intraprostatic tumors is limited, despite its widespread use [9].

The aim of this study is to assess a single-center experience of the utility of PSMA PET/CT in the evaluation of intraprostatic prostate cancer. We examined correlations between clinically relevant variables to ascertain the patients in whom PSMA PET/CT was more sensitive and also to assess the ability of PSMA PET/CT to predict tumor grade.

2. Materials and methods

A search of records from a nuclear medicine imaging provider found a total of 273 PSMA PET/CT scans performed in 204 men who had been referred by a single surgeon between 5 May 2015 and 4 April 2017. The data were extracted retrospectively from their electronic medical records by two collaborating researchers. As a quality assurance exercise, 15 patients were re-entered with no discrepancies found. From these records, patients were selected who (a) underwent PSMA PET/CT for initial staging at the time of diagnosis (post prostate biopsy) and (b) underwent RP within 6 months of their PET scan. Patients were excluded if (c) they had received surgical treatment, chemotherapy, or radiotherapy prior, (d) prostate cancer was not found on histopathological examination or (e) the PSMA PET/CT scan was not their first. A total of 72 patients met all the criteria and were included in the analysis.

Patient and disease characteristics included prostate-specific antigen (PSA), age, clinical stage from digital rectal examination, MRI findings, and the International Society of Urological Pathology (ISUP) grade groups from both biopsy and RP specimens. The location within the prostate of any abnormal finding from prostate biopsy and multiparametric MRI were recorded. Biopsy was considered positive if ISUP ≥ 2. MRI was considered positive if PI-RADS≥ 4. The presence of focal uptake on PSMA PET/CT, the standardized uptake value (SUV$_{max}$) and the maximal dimensions of PET-avid lesions were judged by an experienced nuclear medicine physician.

Summary statistics of the aforementioned patient and disease characteristics were calculated with SPSS [10] and MATLAB [11]. Standard statistical methods were used including Kendall's tau-b correlation coefficient and relative risk calculations. Statistical significance was set at $P < 0.05$ for all analysis in this study.

In a pilot study, subpopulations in which PSMA PET/CT was very sensitive were selected by investigators using data from 5 May 2015 to 7 June 2017. Investigators were blinded to any more recent data and suspended the inclusion criteria of requiring RP. Subpopulations were chosen if PSMA PET/CT was 100% accurate for a subpopulation of at least 10 patients. These subpopulations were (a) clinical stage ≥ 2, PI-RADS ≥ 4 and ≥ 70 years old; (b) clinical stage $\geq 2b$ and ≥ 70 years old; and (c) clinical stage ≥ 2 and ≥ 75 years old. These subpopulations were then tested prospectively on all patients who met the more rigorous inclusion and exclusion criteria from 5 May 2015 to 4 April 2017.

Bivariate correlation analysis was used to compare the ISUP grade groups from RP specimens with PSA levels and PSMA PET/CT
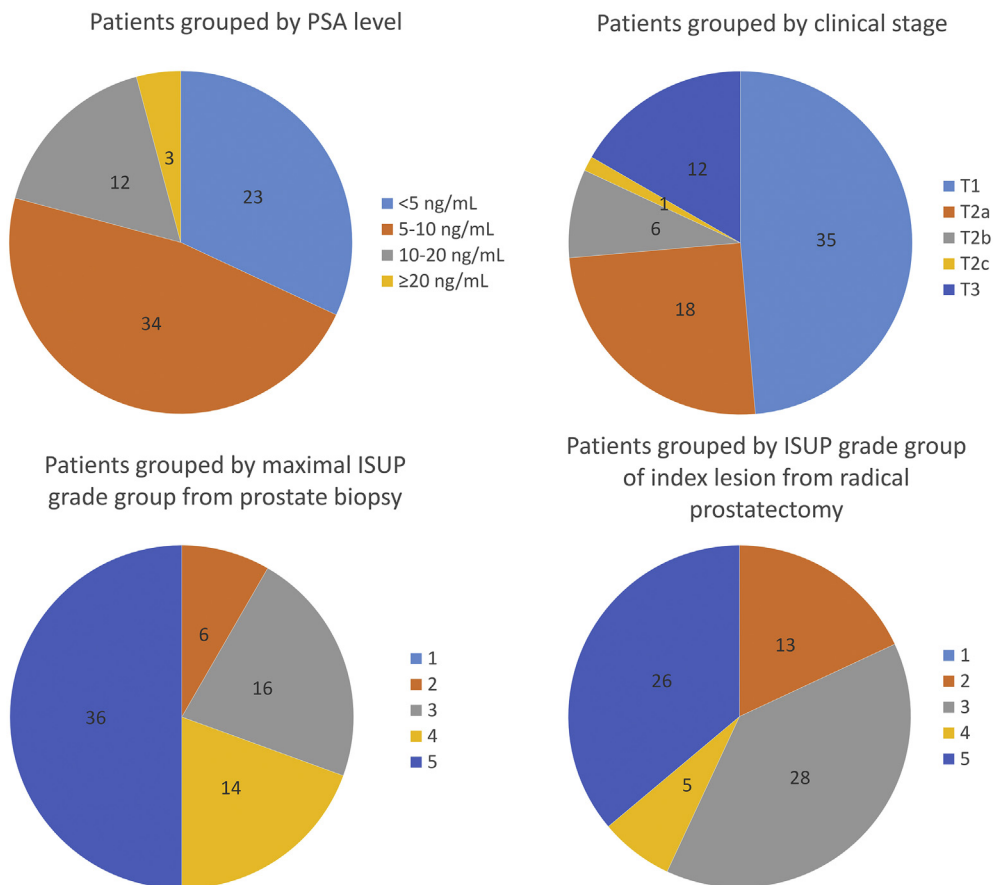

Fig. 1. Patients grouped by patient-specific antigen level, clinical stage, and tumor grade.

parameters. The relative risk of having each ISUP grade group was calculated for patients according to their PSA (<5, 5−10, >10 ng/mL), SUV_{max} (<5, 5−10, >10 g/mL), and maximal dimension of PSMA-avid lesions (<5, 5−10, >15 mm).

2.1. Imaging methods

PSMA PET/CT results used the radiotracer Ga-68 DKFZ PSMA 11, which was produced initially by Scintomics Gallelut production system and then, after 2 months, an Eckert and Ziegler Modular LabEzy system. High-pressure liquid chromatography was undertaken for quality control. The patients were injected with 120−200 MBq of the PSMA radiotracer 30−40 min prior to the PET/CT scan. Imaging was performed from the level of midthighs to eyes in that direction and provided there was no special indication to include other areas. Patients were scanned with empty bladders as they were able and diuretics were not routinely used. All PET/CT imaging was undertaken using a GE Discovery 690 PET/CT TOF camera. A noncontrast-enhanced CT scan was performed at 120 kV and 200 mA modulated and reconstructed with 0.625 and 3.75 mm slices. Immediately after CT scanning, the PET scan was acquired generally using eight bed positions (bed length 15.7 cm, with overlap of 4 cm, and matrix 128 × 128), at three minutes per bed. The PET emission data were corrected for randoms, scatter, and decay using the GE Vue Point FX reconstruction software, using OSEM iterative reconstruction with 2 iterations and 24 subsets.

The generated images were viewed on a GE Advantage workstation (using Volumeshare software version 4.6) and interpreted by a single experienced nuclear medicine physician who was not blinded to any clinically relevant data. The location, three-dimensional size and SUV_{max} value were reported on a per lesion basis with a sextant scheme: apex, midgland, and base each split into left and right. Other areas of focal avidity including possible lymph nodes were also reported. The scan was regarded as positive if the nuclear medicine physician could see focal avidity within the prostate.

2.2. Ethics

The study was approved by the Adventist HealthCare Limited Human Research Ethics Committee (HREC ID 2016-006).

3. Results

The average age of the 72 patients who fulfilled the inclusion and exclusion criteria was 68 (range, 50−83, SD 7). The PSMA PET/CT occurred a maximum of 99 days (average 39, SD 26 days) prior to RP. The average pre-operative PSA level was 8.7 ng/mL (SD 9.5 ng/mL). There were 23% of patients with a PSA below 5 ng/mL and 21% above 10 ng/mL. From the 72 patients, 35 were stage T1, 18 were T2a, 6 were T2b, 1 was T2c and 12 were T3. The average ISUP grade group by radical prostatectomy (RP) was 3.6 (SD 1.15) with 36% ISUP grade group 5. The ISUP grade groups from biopsy were slightly higher (average 4.1, SD 1.0). These data are shown in Fig. 1.

MRI scans occurred on average 45 days prior to PSMA PET/CT (SD 29 days), and all scans occurred within 6 months. Eleven patients had no MRI data available. Three MRI scans occurred prior to biopsy. No lymphatic or metastatic disease was detected on any MRI scan. MRI detected RP-confirmed cancer in 95% of cases (Table 1).

PSMA uptake within the prostate was found with 81.2% sensitivity. The spread of local and systemic focal uptake detected by PSMA PET/CT is summarized in Table 1. The average intraprostatic SUV_{max} for all patients was 9.0 g/mL (SD 12.7 g/mL) and the average maximal intraprostatic tumor dimension was 14.3 mm (SD 12.4 mm).

The highest correlation with PSMA PET/CT (i.e., highest sensitivity) was found in older patients and those with higher clinical stage (palpable disease). The ISUP grade group correlated with SUV_{max} and the maximal dimension of PSMA-avid lesions, but ISUP grade group from RP was not significantly correlated with the overall positivity of PSMA PET/CT. Overall, most features that are predictive of prostate cancer severity were found to correlate with the findings from PSMA PET/CT (Table 2).

Lesions were effectively localized by PSMA PET/CT because locations of focal avidity strongly correlated with the specific location of the lesion discovered by both biopsy and a clinically significant MRI (Table 3).

The sensitivity of PSMA PET/CT differed depending on patient and disease characteristics (Fig. 2). For example, it was higher in those with at least clinical stage 2 (86%) or with an age over 70 (94%).

Further subpopulations are reported in Table 4. These groupings were selected based on data prior to 7 June 2017. Subpopulations from all 72 patients who satisfied the inclusion and exclusion criteria were analyzed prospectively, which included 55 patients

Table 1
Summary of local and systemic findings of PSMA PET/CT and MRI.

	Location of focal uptake	Proportion of patients (%)
Local disease from PSMA PET/CT	Intraprostatic	82
	Right side of the prostate	61
	Left side of the prostate	40
	Left and right side of the prostate	19
	Apex (lower 1/3) of the prostate	38
	Base (upper 1/3) of the prostate	38
Lymph nodes from PSMA PET/CT	Any nodes	11
	External iliac nodes	6
	Internal iliac nodes	3
	Elsewhere within the pelvis	3
	Adjacent to the stomach	1
Osseous from PSMA PET/CT	Ribs	3
Non-osseous from PSMA PET/CT	Thyroid	1
Overall from PSMA PET/CT	Any evidence of nodal or metastatic disease	14
Local disease from MRI	Intraprostatic with ISUP≥4	95
	Right side of the prostate	70
	Left side of the prostate	61
	Left and right side of the prostate	36
	Apex (lower 1/3) of the prostate	51
	Base (upper 1/3) of the prostate	51

Table 2
Correlation between maximal SUV_{max} from PSMA PET/CT and other patient and disease characteristics.

	Maximal intra-prostatic SUV_{max}	
Age	0.30	(<0.001)
Patient-specific antigen	0.30	(<0.001)
Clinical stage	0.25	(0.008)
Maximum International Society of Urological Pathology (ISUP) from biopsy	0.39	(<0.001)
ISUP of index lesion from radical prostatectomy	0.32	(0.001)
MRI PI-RADS	0.15	(0.16)

Table 3
Correlation of positive PSMA PET/CT positivity with positive MRI and positive biopsy within specific zones of the prostate.

Location	Correlation of PSMA PET/CT with MRI		Correlation of PSMA PET/CT with biopsy	
Right apex	0.61	(<0.001)	0.45	(<0.001)
Right mid	0.38	(0.003)	0.40	(0.001)
Right base	0.32	(0.01)	0.36	(0.002)
Left apex	0.40	(0.001)	0.06	(0.61)
Left mid	0.48	(<0.001)	0.32	(0.007)
Left base	0.32	(0.01)	0.10	(0.41)

There has been a wide variety in detection rates of intraprostatic tumors by PSMA PET/CT from 77% to 100% (Table 6). These studies were collected from a systematic search of the literature (Supplementary Data). Such heterogeneity may be explained by (a) difficulty in discerning diffuse cancers, particularly with possible background avidity in the prostate [12]; (b) the variety of PSMA inhibitors that have been used; (c) the lack of accepted clinical indications for PSMA PET/CT with heterogeneous study populations; and (d) radiologists' different thresholds to report focal uptake as standardized protocols are only recently established [13].

Table 4
Patient groups in whom PSMA PET/CT was 100% sensitive for prostate cancer.

Group	Clinical stage	PI-RADS	Age (years)	Proportion of patients who fit criteria (%)
1	≥2	≥4	≥70	23
2	≥2b	Any	≥70	18
3	≥2	Any	≥75	13
Group 1, 2, or 3				27

known prior to 7 June. From all 72 patients, the subpopulations were 100% sensitive for prostate cancer.

Correlations were found between the RP ISUP grade group, and the maximum local SUV_{max} (0.322, p = 0.003), maximal dimension of PET-avid lesions (0.237, p = 0.026), the latest PSA (0.259, p = 0.014) but not the doubling time (p = 0.602), age (p = 0.39), clinical stage (p = 0.112), or MRI PI-RADS score (p = 0.801). The likelihood of a patient having ISUP grade group at least 4 can be predicted based on PET findings, including SUV_{max} (Table 5). There was a dose response in the relationship between SUV_{max} and ISUP grade group (table S1). Only five patients had ISUP grade group of four; therefore, these confidence intervals are relatively wider.

4. Discussion

This study demonstrated novel correlations between the findings of PSMA PET/CT and recognized clinical parameters for prostate cancer by comparing PSMA PET/CT with final RP specimens.

Table 5
Prediction of ISUP grade group ≥ 4 by SUV_{max}, maximal tumor dimension and PSA levels

Condition	Relative risk of ISUP ≥ 4 (95% CI)
SUV < 5	0.4 (0.2–0.9)
SUV > 10	1.9 (1.1–3.1)
Length < 5	0.8 (0.4–1.6)
Length > 15	1.7 (1–2.8)
PSA < 5	0.9 (0.5–1.6)
PSA > 10	1.7 (1–2.8)

SUV = SUV_{max} in g/mL.
IUSP = International Society of Urological Pathology
Length = maximal dimension of PET-avid lesions in mm.
PSA = prostate-specific antigen in ng/mL.

On the issue of standardization, we did not use a specific SUV_{max} threshold to define a positive scan as there exists no current evidence for specific thresholds [14].

From a theoretical standpoint, PSMA PET/CT is limited by the 5% of prostate cancers with less than a hundredfold overexpression of PSMA, making focal avidity more difficult to detect [12]. There is a limitation on size since PSMA PET/CT is theoretically unable to detect tumors less than 2 mm in diameter and empirically unsuccessful under 2.4 mm [15]. A strength of our study is that our results were compared to final histopathology as biopsy alone is less accurate and could obscure the potential of PSMA PET/CT [16].

The present study provides early evidence of patient groups, which have a higher sensitivity for prostate cancer (Table 4). The main contribution to this diagnostic accuracy was from clinical staging and age. The relative importance of clinical staging was surprising, since digital rectal examination has lower accuracy than many other tests for prostate cancer [17]. Nevertheless, it is reasonable that a larger displacing tumor would be more apparent on a scan. The second most important feature was age, which was an unexpected result, given that age is not a prognostic factor for prostate cancer [3]. It may be hypothesized that indolent and more differentiated prostate cancer associated with age expresses PSMA more strongly.

One surprising finding was that MRI was overall more sensitive than PSMA PET/CT. This is contrary to other studies [18]. Heterogeneous sensitivities have been described in a systematic review, but our sensitivity of 95% exceeded the average 82% [19]. Confining the analysis to the 18% of our patients who had a negative PSMA PET/CT did not change the sensitivity. The discrepancy with literature values may suggest different reporting standards as well as an observer bias since the nuclear medicine physician was not blinded to biopsy results. As there were few negative MRI scans, it was difficult to find statistically significant correlations between PSMA PET/CT and MRI.
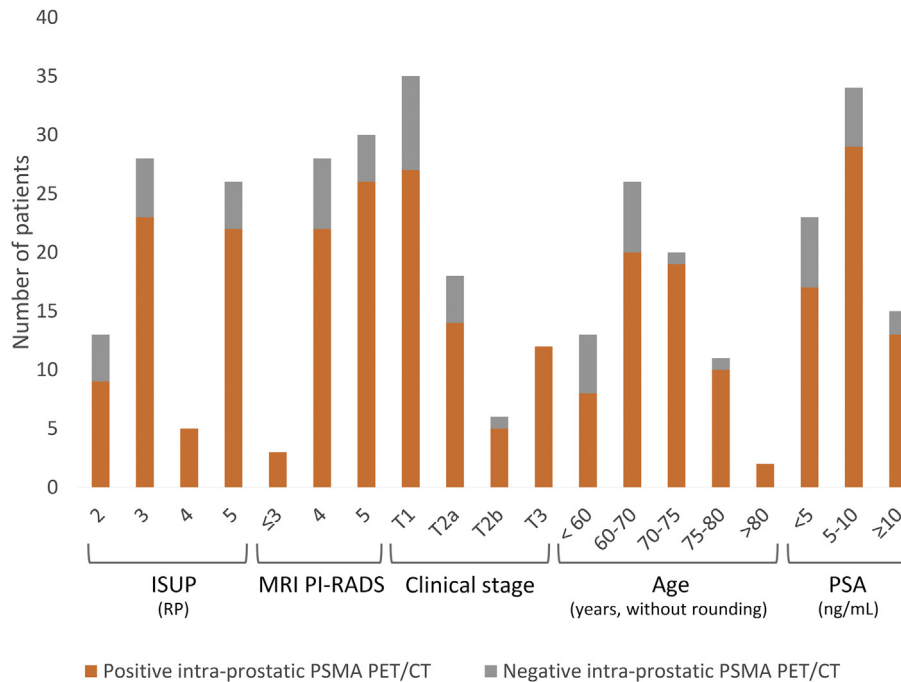
Fig. 2. Sensitivity of PSMA PET/CT within subpopulations.

There has been limited investigation into the ability of PSMA PET/CT to predict tumor grade; however, these results have been inconclusive [20, 21]. Our study has shown that the localized intraprostatic SUV_{max} is predictive of the ISUP grade group. The precise relative risks are significant (Table 5, Table S1), but larger populations will need to be studied to ensure precision.

A major limitation of the present study was the absence of PSMA PET/CT data in patients without prostate cancer. Consequently, the specificity and other summary statistics regarding the diagnostic accuracy of PSMA PET/CT for the detection of prostate cancer could not be ascertained. The lack of data on true negatives or false positives is difficult to overcome, as prospective trials will typically require biopsy proven prostate cancer as an inclusion criterion [22]. A prospective trial of PSMA PET/CT prior to histopathology would definitively assess the utility of PSMA PET/CT in men without prostate cancer, but this trial is unlikely to occur. Past trials have used lesion-specific analysis to evaluate the accuracy of PSMA PET/CT in disease-free zones of the prostate; however, this is not the same as evaluating prostate cancer negative patients [23].

The current study is subject to various biases due to its retrospective methodology. Consequently, the selection of subpopulations in whom PSMA PET/CT was more sensitive was biased by overfitting. The prospective component of the study did minimize the effect of overfitting, as the parameters used to predict a positive PSMA PET/CT were chosen when blinded to data acquired after 7 June 2017. Nevertheless, the conclusions of this study ought to be treated with caution due to the small sample size. For example, the classification algorithm we generated for our prospective trial had a small component that separated clinical stage T2a and T2b, but it is questionable whether this subtle difference would be reproducible.

These results challenge the widespread view that PSMA PET/CT has limited use for primary staging [9]. Previous literature has shown that despite the high specificity of PSMA PET/CT for detecting individual lesions in diverse settings (97%) it has a lower sensitivity (80%) [7]. Indeed, in the context of primary staging, the sensitivity for detecting any cancer was only 40%, or 27% if studies with less than 10 patients were excluded [7]. Similarly, low sensitivity and high specificity was reported in the only prospective trial

Table 6

Intra-prostatic sensitivity of PSMA PET/CT prior to any surgical or medical treatment in the past literature

Study (year)	N	Sensitivity for intra-prostatic cancer (%)	Comment
[24] (2016)	30	93	
[25] (2015)	28	77	
[26] (2017)	34	100	
[23] (2016)	20	49	Only prospective study. This sensitivity was per specific histopathological detection lesion (n = 50). MRI was combined with PSMA PET/CT.
[27] (2017)	20	95	
[28] (2016)	24	96	This number included metastases (in 38% of patients)
[6] (2016)	130	92	
[7] (2016)	1309	40	Meta-analysis of overall detection rate of prostate cancer for primary staging, including lymph nodes
[29] (2016)	66	92	
[30] (2018)			
Present study	72	82	

that analyzed primary intraprostatic tumors [23]. Nevertheless, this study has suggested that for certain patient groups, there is a much higher sensitivity for the detection of prostate cancer.

Another application of this study is to predict the grade of prostate cancer from PSMA PET/CT without a biopsy. There is strong evidence that the results of PSMA PET/CT have prognostic value owing to the correlation of SUV_{max} and maximal tumor dimension with the ISUP grade group. The PSMA PET/CT results are a clinical tool for estimating the ISUP grade group. The small sample sizes cannot exclude some stochastic variation, so further studies with larger populations will be needed to improve precision. However, these early results do indicate that PSMA PET/CT reporting should minimally include SUV_{max} and lesion size due to the implications on tumor grade. This has been suggested but not mandated by recent guidelines [13].

PSMA PET/CT appears to have a role in the assessment of local prostate cancer. In certain groups of patients defined mainly by clinical stage and age, the sensitivity of PSMA PET/CT scan may approach 100%. In addition, SUV_{max} and size of focally avid lesions were found to be good predictors of ISUP grade group. Further prospective investigation into whether PSMA PET/CT may obviate the need for biopsy in specific groups appears to be justified.

Conflicts of interest

No conflicts of interest to disclose for any author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2020.07.008.

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