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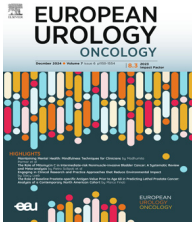

European Association of Urology

The Added Value of Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography to Magnetic Resonance Imaging for Local Staging of Prostate Cancer in Patients Undergoing Radical Prostatectomy

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Abstract

Background and objective: The role of prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET)/computed tomography (CT) in addition to magnetic resonance imaging (MRI) for local staging of prostate cancer (PC) has been poorly addressed so far. Our aim was to assess the diagnostic accuracy of PSMA PET/CT and MRI, alone and combined, for detection of extraprostatic extension (EPE) and seminal vesicle invasion (SVI) in PC.

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Methods: We conducted a multicenter retrospective study evaluating patients undergoing PSMA PET/CT and MRI before radical prostatectomy. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC) for detection of EPE and SVI were calculated for MRI and PSMA PET/CT alone and combined.

Key findings and limitations: We included 550 patients, of whom 2%, had low-risk, 43% had intermediate-risk, and 55% had high-risk PC. Overall, 52% of patients had EPE and 21% had SVI at histopathology. Patient-based comparison of MRI versus PSMA PET/CT for detection of EPE revealed sensitivity of 60% versus 41% ($p < 0.001$), specificity of 77% versus 83% ($p = 0.075$), PPV of 75% versus 73% ($p = 0.6$), NPV of 64% versus 56% ($p < 0.001$), and AUC of 69% versus 62% ($p = 0.01$). Combining the modalities increased the sensitivity (73%; $p < 0.001$) and NPV (69%; $p < 0.001$) and decreased the specificity (67%; $p < 0.001$) and PPV (71%; $p = 0.01$) over MRI alone. Patient-based comparison of MRI versus PSMA PET/CT for detection of SVI revealed sensitivity of 36% versus 44% ($p = 0.2$), specificity of 96% versus 96% ($p > 0.99$), PPV of 71% versus 75% ($p = 0.6$), NPV of 85% versus 87% ($p = 0.2$), and AUC of 66% versus 70% ($p = 0.2$). Combining the modalities increased the sensitivity (60%; $p < 0.001$), NPV (90%; $p < 0.001$), and AUC (76%; $p < 0.001$) and decreased the specificity (92%; $p < 0.001$) over MRI alone. Limitations include the retrospective nature of the study, selection of higher-risk cases for PSMA PET/CT, and lack of central review.

Conclusions and clinical implications: PSMA PET/CT has lower sensitivity for EPE detection in comparison to MRI. However, addition of PSMA PET information to MRI improved the sensitivity for EPE and SVI detection. Thus, the two modalities should be combined to guide treatment selection.

Patient summary: Combining MRI (magnetic resonance imaging) scans with another type of imaging called PSMA PET/CT (prostate-specific membrane antigen positron emission tomography/computed tomography) for patients with prostate cancer leads to better identification of cancer growth outside the prostate in comparison to MRI alone. This could potentially improve the choice of prostate cancer treatment.

1. Introduction

In prostate cancer (PC), accurate assessment of the local tumor extent is essential for determining disease risk and guiding treatment selection [1,2]. Extraprostatic extension (EPE) and seminal vesicle invasion (SVI) are key prognostic factors that often necessitate treatment intensification when present [3,4]. Evaluation of extraprostatic spread is crucial when selecting candidates for radical prostatectomy (RP) and nerve-sparing approaches, particularly as ipsilateral nerve-sparing increases the risk of positive surgical margins, highlighting the need for side-specific EPE assessment in surgical planning [2,5].

Local tumor stage can be assessed via digital rectal examination (DRE), and the European Association of Urology (EAU) guidelines recommend DRE-based cT staging for defining a patient's risk group and TNM classification [2]. However, multiparametric magnetic resonance imaging (mpMRI) outperforms DRE for detection of non–organ-confined disease (stage ≥T3) [6]. Thus, incorporation of MRI information could potentially lead to better assessment of PC prognosis. Novel MRI-based classification systems show promise in improving risk stratification [7,8].

In addition to MRI, prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET) is increasingly being used for primary staging of PC [9]. The proPSMA trial demonstrated that PSMA PET/computed tomography (CT) outperforms conventional CT and bone scans in detecting pelvic nodal and distant metastases in patients with high-risk PC [10]. PSMA PET/CT may also enhance PC detection, and favorable sensitivity and specificity for detection of clinically significant lesions have been reported [11–13]. However, studies have reported conflicting results on PSMA PET/CT detection of EPE and SVI in comparison to mpMRI [12,14–17]. Recent results from a prospective trial showed that [^{18}F]PSMA-1007 PET/CT outperformed mpMRI regarding correct identification of final pathological stage [18]. Given the potential added value of PSMA PET/CT in local staging before treatment, additional large multicenter studies are needed to validate these findings.

Although randomized trials have shown that PSMA PET/CT has better accuracy than conventional imaging for detection of nodal and distant metastases, its role in local staging has been poorly addressed so far [2]. Additional data are urgently needed to clarify the role of PSMA PET/CT in local staging and its impact on medical decision-making. The aim of our multicenter study was to assess the accuracy of PSMA PET/CT, MRI, and their combination in detecting EPE and SVI in patient-level and side-specific analyses.

2. Patients and methods

2.1. Patient population

After local institutional review board approval, data were collected. Written informed consent was waived because

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of the retrospective nature of the study. Men with histopathologically proven PC selected for curative treatment using RP with or without pelvic lymph node dissection and preoperatively staged with PSMA PET/CT and either biparametric MRI (bpMRI) or mpMRI from 2016 to 2022 at seven tertiary referral centers worldwide (The Netherlands, Germany, Italy, USA, and Hong Kong, China) were included. Patients were excluded if they had received prior systemic, radiation, or focal therapy for PC.

2.2. MRI procedures and interpretation

Radiological reporting was performed by dedicated uroradiologists according to the Prostate Imaging-Reporting and Data System v2.1 guidelines [19]. Both mpMRI (including anatomic T1-weighted, T2-weighted [T2W], and functional sequences, diffusion-weighted imaging [DWI], and dynamic contrast-enhanced [DCE] imaging) and bpMRI (DWI and T2W sequences without DCE) were allowed. Radiologist-reported information on the local stage and the presence of EPE and SVI was extracted from the reports and documented in a side-specific manner.

2.3. PSMA PET/CT protocols and procedures

All PSMA PET/CT scans were performed at tertiary centers according to local protocols, including external scans for referred patients [20]. PET images were acquired from the mid-thigh to the skull base and were combined with low-dose or diagnostic CT for anatomic correlation. Scans were re-evaluated by an experienced nuclear medicine physician (>5 yr and/or >500 studies) or a trained research fellow, blinded to MRI and histopathology. Local staging was reassessed in accordance with the PROMISE guidelines, with missing side-specific data collected [21]. Radioligands used included [^{68}Ga]Ga-PSMA-11, [^{18}F]PSMA-1007, [^{18}F]DCF-PyL, and [^{18}F]-JK-PSMA-7. Images were acquired in accordance with European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging criteria [22,23]. EPE (miT3a) was defined as tumor activity extending beyond the prostate contour as visualized on concurrent CT and/or the presence of morphological criteria on CT (eg, angulated contour of the prostate gland or obliteration of the rectoprostatic angle). SVI (miT3b) was defined as PET tumor activity extending into the seminal vesicle and/or separate focal activity in the seminal vesicle [24].

2.4. Histopathological reference standard

Histopathological reporting of whole-gland and side-specific tumor stage for RP specimens served as the reference standard. Specimens were processed according to the EAU/International Society of Urological Pathology (ISUP) PC guidelines [2] using either conventional or whole-mount sections, depending on the local protocol. Histopathological evaluation and grading were performed by local uropathologists according to the ISUP guidelines [25]. EPE (pT3a) was defined as a tumor extending beyond the prostate contour invading periprostatic fat, posterolateral connective tissue, or the neurovascular bundle, or with microscopic bladder neck invasion. SVI (pT3b) was defined as tumor invasion into the seminal vesicle muscular wall [26]. The EPE and SVI locations (left, right, or bilateral) were reported by the pathologist as standard practice and were extracted from the reports.

2.5. Statistical analysis

Results are reported as the median value for continuous variables and the frequency and proportion for categorical variables. Diagnostic accuracy measures (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were calculated for detection of EPE (defined as stage $\geq$T3a) and SVI (defined as stage T3b) for MRI and PSMA PET/CT alone and in combination, with the highest T stage used per analysis. Sensitivity and specificity results were compared using McNemar's test [27]. PPV and NPV results were compared according to Moskowitz and Pepe [28]. The area under the receiver operating curve (AUC) was calculated and results were compared using the DeLong test [29]. Missing data were handled via complete case analysis. A p value of <0.05 was considered significant. Statistical analyses were performed using R v4.2.1 (R Foundation for Statistical Analysis, Vienna, Austria).

3. Results

3.1. Patient characteristics

A total 563 consecutive patients fulfilling the inclusion criteria were identified. Thirteen patients (2%) were excluded because of missing data (no DRE performed in eight patients, and side-specific MRI or pathology information missing for 5 patients; Fig. 1). This resulted in a final population of 550 patients, of whom 2% had low-risk, 43% had intermediate-risk, and 55% had high-risk PC. Median age and prostate-specific antigen at the time of surgery were 66 yr and 9.7 ng/ml, respectively. The PSMA PET/CT radioligands most frequently used were [^{68}Ga]Ga-PSMA-11 (59%) and [^{18}F]PSMA-1007 (35%; Table 1).

Overall, EPE was diagnosed via DRE, PSMA PET/CT, and MRI in 13%, 30%, and 43% of patients, respectively. Final histopathology revealed EPE in 52% of patients and SVI in 21% (Table 1). According to side-specific analysis, EPE and SVI were identified in 25% and 7% lobes via MRI and in 17% and 7% of lobes via PSMA PET/CT, respectively. Final histopathology revealed EPE in 35% of prostate lobes and SVI in 14%.

3.2. Diagnostic accuracy of DRE versus MRI and PSMA PET/CT for detection of EPE

DRE identified 55/288 (19%) EPE cases, while MRI detected 174/288 (60%) and PSMA PET/CT detected 118/288 (41%) cases (both $p < 0.001$). DRE failed to detect 233/288 (81%) EPE cases, compared to 114/288 (40%) missed by MRI and 170/288 (59%) missed by PSMA PET/CT. Regarding specificity, DRE correctly excluded EPE in 245/262 (94%) cases, in comparison to 203/262 (77%) with MRI and 218/262 (83%) with PSMA PET/CT (both $p < 0.001$; Supplementary Table 1).

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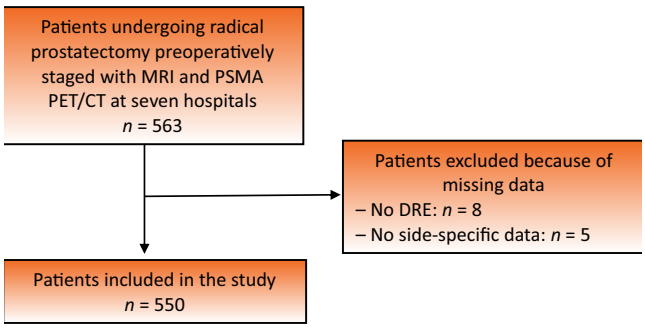

Fig. 1 – Flowchart of patient inclusion in the study. CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

3.3. *Diagnostic accuracy of MRI versus PSMA PET/CT and the combined modalities for detection of EPE*

MRI correctly identified 174/288 (60%) EPE cases, while PSMA PET/CT detected 118/288 (41%) cases ($p < 0.001$). MRI correctly ruled out EPE in 203/262 cases (77%), compared to 218/262 cases (83%) with PSMA PET/CT ($p = 0.075$). Combining MRI and PSMA PET/CT led to correct identification of an additional 37 EPE cases (13%) in comparison to MRI alone. However, this was countered by 28 fewer cases (10%) for which EPE was accurately ruled out (Tables 2 and 3).

After stratification into intermediate-risk and high-risk subgroups, the results for patient-level sensitivity and specificity remained consistent (Supplementary Tables 4 and 5). Side-specific analysis results were concordant with the patient-level analysis, except for AUC, for which addition of PET/CT to MRI resulted in a significant increase (from 69% to 72%; $p = 0.011$; Table 2).

3.4. *Diagnostic accuracy of MRI versus PSMA PET/CT and the combined modalities for detection of SVI*

MRI identified 42/116 (36%) SVI cases, while PSMA PET/CT detected 51/116 (44%) cases ($p = 0.19$) (Tables 4 and 5). Combining MRI with PSMA PET/CT led to detection of an additional 28 cases (24%), countered by 15 fewer cases (3%) in which SVI was accurately ruled out (Tables 4 and 5). The AUC increased from 66% with MRI to 76% with MRI + PET/CT ($p < 0.001$; Table 4). After stratification into intermediate-risk and high-risk subgroups, results for the comparative analyses remained consistent (Supplementary Tables 4 and 5). Side-specific analysis resulted in findings concordant with the patient-level analysis.

3.5. *Detection of EPE and SVI via PSMA PET/CT among MRI-negative and MRI-positive cases*

Among EPE cases with negative MRI findings, PSMA PET/CT had sensitivity of 32% (95% confidence interval [CI] 24–42%) and NPV of 69% (95% CI 63–75%) for EPE detection Supplementary Table 6. Among EPE cases with positive MRI findings, PSMA PET/CT had specificity of 73% (95% CI 60–84%) and PPV of 84% (95% CI 75–90%) for EPE detection. According to side-specific analysis, PSMA PET/CT detected EPE in 43/195 (22%) positive lobes with negative MRI findings (Supplementary Table 6).

Among SVI cases with negative MRI findings, PSMA PET/CT had sensitivity of 38% (95% CI 27–50%) and NPV of 90% (95% CI 87–92%) for SVI detection Supplementary Table 7. Among SVI cases with positive MRI findings, PSMA PET/CT had specificity of 76% (95% CI 50–93%) and PPV of 85% (95% CI 66–96%) for SVI detection Supplementary Table 7). According to side-specific analysis, PSMA PET/CT detected SVI in 28/101 (28%) positive lobes with negative MRI findings (Supplementary Table 7).

Table 1 – Baseline characteristics of the 550 patients included in the study

Parameter	Result [a]
Median age, yr (IQR)	66 (62–71)
Median PSA, ng/ml (IQR)	9.7 (6.5–16.2)
Clinical T stage (DRE), *n* (%)	
cT1c	269 (48)
cT2a	165 (30)
cT2b	37 (7)
cT2c	8 (2)
cT3	71 (13)
Biopsy ISUP grade group, *n* (%)	
1	27 (5)
2	138 (25)
3	162 (29)
4	148 (27)
5	75 (14)
EAU risk group, *n* (%)	
Low risk	10 (2)
Intermediate risk	237 (43)
High risk	303 (55)
MRI T stage, *n* (%)	
No suspicious lesion	17 (3)
T2a	210 (38)
T2b	23 (4)
T2c	67 (12)
T3a	173 (32)
T3b	58 (11)
T4	2 (0)
PET/CT T stage, *n* (%)	
miT0	26 (5)
miT2	362 (66)
miT3a	91 (17)
miT3b	61 (11)
miT4	10 (2)
PET/CT N stage, *n* (%)	
miN0	489 (89)
miN1	37 (7)
miN2	24 (4)
Radioligand used, *n* (%)	
[^{68}Ga]Ga-PSMA-11	326 (59)
[^{18}F]PSMA-1007	194 (35)
[^{18}F]-JK-PSMA-7	21 (4)
[^{18}F]DCFPyL	6 (1)
Unknown	3 (0)
Pathological T stage, *n* (%)	
pT2	262 (48)
pT3a	172 (31)
pT3b	114 (21)
pT4	2 (0)
Pathological N stage, *n* (%)	
pN0	384 (70)
pN1	86 (16)
pNx	80 (15)

IQR = interquartile range, PSA = prostate-specific antigen, DRE = digital rectal examination, ISUP = International Society of Urological Pathology, EAU = European Association of Urology; MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography; PSMA = prostate-specific membrane antigen.
[a] Percentages may not add up to 100 because of rounding.

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Table 2 – Sensitivity and specificity of MRI and PSMA PET/CT alone and in combination for detection of extraprostatic extension

Parameter	MRI		PET/CT		*p* value	MRI + PET/CT [a]		*p* value [b]
	n/N	Result, % (95% CI)	*n/N*	Result, % (95% CI)		*n/N*	Result, % (95% CI)	
Patient-level analysis								
Sensitivity	174/288	60 (55–66)	118/288	41 (35–47)	<0.001	211/288	73 (68–78)	<0.001
Specificity	203/262	77 (72–82)	218/262	83 (78–88)	0.075	175/262	67 (61–72)	<0.001
PPV	174/233	75 (69–80)	118/162	73 (65–80)	0.6	211/298	71 (65–76)	0.011
NPV	203/317	64 (58–69)	218/388	56 (51–61)	<0.001	175/252	69 (63–75)	<0.001
AUC	–	69 (65–73)	–	62 (58–66)	0.006		70 (66–74)	0.4
Side-specific analysis								
Sensitivity	190/385	49 (44–54)	123/385	32 (27–37)	<0.001	233/385	61 (55–65)	<0.001
Specificity	636/715	89 (86–91)	653/715	91 (89–93)	0.10	590/715	83 (80–85)	<0.001
PPV	190/269	71 (65–76)	123/185	66 (59–73)	0.27	233/358	65 (60–70)	<0.001
NPV	636/831	77 (74–79)	653/915	71 (68–74)	<0.001	590/742	80 (76–82)	<0.001
AUC	–	69 (66–72)	–	62 (59–64)	<0.001	–	72 (69–74)	0.011

MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography; CI = confidence interval; PPV = positive predictive value, NPV = negative predictive value, AUC = area under the receiver operating characteristic curve.
[a] Highest stage from both modalities used.
[b] Comparison of MRI versus MRI + PSMA PET

Table 3 – EPE cases missed and detected via MRI and PSMA PET/CT alone and combined

Modality	Patient-level analysis			Prostate side-specific analysis		
	Patients with EPE	EPE detected, *n* (%)	EPE missed, *n* (%)	Lobes with EPE	EPE detected, *n* (%)	EPE missed, *n* (%)
MRI	288	174 (60)	114 (40)	385	190 (49)	195 (51)
PSMA PET/CT	288	118 (41)	170 (59)	385	123 (32)	262 (68)
MRI + PSMA PET/CT	288	211 (73)	77 (27)	385	233 (61)	152 (39)

EPE = extraprostatic extension; MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography; PSMA = prostate-specific membrane antigen.

Table 4 – Sensitivity and specificity of MRI and PSMA PET/CT alone and in combination for detection of seminal vesicle invasion

Parameter	MRI		PET/CT		*p* value	MRI+ PET/CT [a]		*p* value [b]
	n/N	Result, % (95% CI)	*n/N*	Result, % (95% CI)		*n/N*	Result, % (95% CI)	
Patient-level analysis								
Sensitivity	42/116	36 (27–46)	51/116	44 (35–53)	0.19	70/116	60 (51–69)	<0.001
Specificity	417/434	96 (94–98)	417/434	96 (94–98)	>0.99	402/434	93 (90–95)	<0.001
PPV	42/59	71 (58–82)	51/68	75 (63–85)	0.6	70/102	69 (59–77)	0.5
NPV	417/491	85 (81–88)	417/482	87 (83–89)	0.19	402/448	90 (87–92)	<0.001
AUC	–	66 (62–71)	–	70 (65 – 75)	0.20	–	76 (72–81)	<0.001
Side-specific analysis								
Sensitivity	50/151	33 (26–41)	56/151	37 (29–45)	0.4	78/151	52 (43–59)	<0.001
Specificity	926/949	98 (96–98)	926/949	98 (96–98)	>0.99	906/949	95 (94–96)	<0.001
PPV	50/73	68 (57–79)	56/79	71 (60–81)	0.7	78/123	64 (55–73)	0.25
NPV	926/1027	90 (88–92)	926/1021	91 (89–92)	0.4	906/979	93 (91–94)	<0.001
AUC	–	65 (62–69)	–	67 (63–71)	0.4	–	74 (70–78)	<0.001

MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography; CI = confidence interval; PPV = positive predictive value, NPV = negative predictive value, AUC = area under the receiver operating characteristic curve.
[a] Highest stage of both modalities used.
[b] Comparison of MRI versus MRI + PSMA PET.

4. Discussion

The role of PSMA PET/CT in conjunction with MRI for local PC staging remains unclear, so further evidence from large multicenter studies is required. In our study, MRI outperformed PSMA PET/CT for EPE detection. Combining the modalities improved the sensitivity and NPV for EPE and SVI detection but reduced the specificity. These results suggest that from a clinical perspective, combining MRI and PSMA PET/CT can enhance detection and exclusion of EPE and SVI, and could potentially improve treatment selection. While higher sensitivity and NPV may improve the safety of nerve-sparing surgery, the combined approach risks overstaging, especially for EPE, for which the specificity

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Table 5 – SVI cases missed and detected via MRI and PSMA PET/CT alone and in combination

Modality	Patient-level analysis			Prostate side-specific analysis		
	Patients with SVI	SVI detected, *n* (%)	SVI missed, (%)	Lobes with SVI	SVI detected, *n* (%)	SVI missed, *n* (%)
MRI	116	42 (36)	74 (64)	151	50 (33)	101 (67)
PSMA PET/CT	116	51 (44)	65 (56)	151	56 (37)	95 (63)
MRI + PSMA PET/CT	116	70 (60)	46 (40)	151	78 (52)	73 (48)

SVI = seminal vesicle invasion; MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography; PSMA = prostate-specific membrane antigen.

decreased by 10% (67% vs 77%) on addition of PSMA PET/CT. The risk of overstaging for SVI was lower, with specificity decreasing by only 3% (from 96% to 93%) and sensitivity increasing by 24% (from 36% to 60%).

Previous studies on this subject have reported conflicting results. Exterkate et al [12] did not observe significant differences between mpMRI and PSMA PET/CT for detection of EPE and SVI. Prive et al [15] reported that mpMRI was more accurate in detecting EPE than ^{18}F-PSMA-1007 PET/CT, whereas SVI detection was superior with PSMA PET/CT. Bahler et al [17] reported that PSMA PET/CT was more sensitive than MRI for detection of EPE along the neurovascular bundle. In a cohort of 74 patients, Sonni et al [14] observed that mpMRI outperformed PSMA PET/CT in detecting EPE and SVI, and there was a significant increase in AUC when the two modalities were combined. The largest prospective paired study (134 men) revealed that EPE diagnostic accuracy favored [^{18}F]PSMA-1007 PET/CT; the authors reported EPE sensitivity of 58%, in comparison to 33% with MRI (p = 0.01 obtained via personal communication) and higher SVI sensitivity (57% vs 33%), although the difference was not statistically significant (p = 0.6) [18].

The diagnostic accuracy of PSMA PET/CT and MRI for local staging varies between hospitals, and the variation in conclusions drawn from previous comparative trials may be attributable to sample variation inherent to the relatively small patient populations. This is supported by the wide sensitivity (from 29% to 83%) and specificity (from 42% to 95%) ranges for EPE detection with PSMA PET/CT among the hospitals in our study (Supplementary Table 8). Similar variability in EPE diagnostic accuracy with MRI has been reported. For instance, the Next Generation Trial reported MRI sensitivity of 33%, which is substantially lower than the 60% observed in our study and the 57% previously reported in a meta-analysis [18,30]. These discrepancies underscore the need for our large multicenter comparative study, as this study setting increases the generalizability of the findings and reduces the impact of site-specific biases. Future research should aim to further standardize PSMA PET/CT interpretation in this context. Initiatives such as the PRIMARY score are essential for reducing real-world variation in the performance characteristics of local staging modalities [31].

A potential advantage of [^{18}F]PSMA-1007 over [^{68}Ga]Ga-PSMA-11 is that there is no significant physiological excretion of [^{18}F]PSMA-1007 in the urinary bladder, so it may not impair sensitivity for detection of EPE lesions located in regions adjacent to the prostate. However, radioligand subgroup results for our cohort did not support this hypothesis: [^{68}Ga]Ga-PSMA-11 versus [^{18}F]PSMA-1007 had sensitivity of 48% versus 33% and specificity of 80% versus 88% for EPE detection (Supplementary Table 9). Although this analysis should be interpreted with caution, as it is a nonpaired comparison susceptible to selection bias, the results do not show a clear advantage for [^{18}F]PSMA-1007. Thus, there is still a need to identify the most effective radioligand for accurate EPE detection, highlighting the necessity of rigorous comparative studies in this context.

MRI remains the modality most widely used to assist in local staging and in selecting candidates for nerve-sparing surgery [2]. Given the widespread adoption of the prebiopsy MRI diagnostic pathway for PC detection, MRI information will be available for the majority of patients with newly diagnosed PC. According to our results, PSMA PET/CT is characterized by suboptimal sensitivity for EPE detection and should therefore not be preferred over MRI to assist in local staging. However, perhaps the most clinically relevant question is not which of the modalities is superior, but how the two modalities perform when combined. Our study results support the use of PSMA PET/CT in addition to MRI, especially for detection of SVI. Accurate detection of SVI at diagnosis is particularly important, as SVI diagnosed via PSMA PET/CT is associated with overall survival [32].

Although beyond the scope of our study, it has been suggested that PSMA PET/MRI may potentially outperform PSMA PET/CT with regard to local staging owing to its specific advantage in predicting EPE in patients with MRI-occult PC [33]. In a retrospective comparative analysis of 40 patients, Muehlematter et al [34] reported that [^{68}Ga]Ga-PSMA-11 PET/MRI resulted in higher patient-based sensitivity for EPE detection in comparison to mpMRI (69% vs 46%; p = 0.04) at the cost of a slight reduction in region-specific specificity (90% vs 94%; p = 0.007). Future comparative studies comparing PSMA PET/CT to PET/MRI are imperative to determine which modality provides superior accuracy in local staging.

Our study has a number of limitations. First, the study cohort included selected patients with PC (2% low-risk, 43% intermediate-risk [including 51% ISUP grade group 3] and 55% high-risk PC) for whom PSMA PET/CT was indicated for primary staging, and the generalizability of our results to patients with low-risk or favorable intermediate-risk PC is therefore limited. Second, there was no central review of

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MRI, PSMA PET/CT, or histopathology. Third, data regarding specific MRI protocols used at the patient level were unfortunately unavailable, limiting the ability to stratify between bpMRI and mpMRI. Nevertheless, these limitations are inherent to daily clinical care, and the variability for the PSMA PET/CT and MRI study procedures corresponds with the real-world clinical situation. Another limitation is the potential for workup bias, as both PSMA PET and MRI were used to guide surgical planning. This may have influenced the resection area, leading to a remote risk of missing EPE or SVI when obscured by positive margins. Conversely, resection may have been widened in areas with suspected EPE or SVI according to imaging findings. Finally, we were unable to analyze the association between our findings and patient-relevant outcomes, such as long-term oncological results, toxicity in patients with a false-positive imaging result, and treatment changes for patients with discordant MRI and PSMA PET/CT findings.

5. Conclusions

PSMA PET/CT alone is characterized by suboptimal sensitivity for detection of EPE in comparison to MRI, and should not be preferred over MRI as the primary modality for local staging of PC. However, it improves the sensitivity of MRI alone in detecting EPE and SVI, and local staging results from both modalities should be used to guide treatment selection.

Author contributions: Timo F.W. Soeterik 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.

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Acquisition of data: Soeterik, Heetman, Hermsen, Wever, Lavalaye, Vinken, Bahler, Yong, Kesch, Seifert, Telli, Chiu, Wu, Zattoni, Evangelista, Bettella, Barone.
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Appendix A. Supplementary data

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References

[1] D'Amico AV, Whittington R, Malkowiz B, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.
[2] Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer—2024 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2024;86:148–63.
[3] Rehman A, El-Zaatari ZM, Han SH, et al. Seminal vesicle invasion combined with extraprostatic extension is associated with higher frequency of biochemical recurrence and lymph node metastasis than seminal vesicle invasion alone: proposal for further pT3 prostate cancer subclassification. Ann Diagn Pathol 2020;49:151611.
[4] Merriman KM, Harmon SA, Belue MJ, et al. Comparison of MRI-based staging and pathologic staging for predicting biochemical recurrence of prostate cancer after radical prostatectomy. Am J Roentgenol 2023;221:773–87.
[5] Soeterik TFW, van Melick HHE, Dijksman LM, Stomps S, Witjes JA, van Basten JPA. Nerve sparing during robot-assisted radical prostatectomy increases the risk of ipsilateral positive surgical margins. J Urol 2020;204:91–5.
[6] Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JA. Multiparametric magnetic resonance imaging should be preferred over digital rectal examination for prostate cancer local staging and disease risk classification. Urology 2021;147:205–12.
[7] Baboudjian M, Gondran-Tellier B, Touzani A, et al. Magnetic resonance imaging-based T-staging to predict biochemical recurrence after radical prostatectomy: a step towards the iTNM classification. Eur Urol Oncol 2023;6:406–13.
[8] Mazzone E, Gandaglia G, Ploussard G, et al. Risk stratification of patients candidate to radical prostatectomy based on clinical and multiparametric magnetic resonance imaging parameters: development and external validation of novel risk groups. Eur Urol 2022;81:193–203.
[9] Jochumsen MR, Bouchelouche K. PSMA PET/CT for primary staging of prostate cancer – an updated overview. Semin Nucl Med 2024;54:39–45.
[10] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208–16.
[11] Donato P, Roberts MJ, Morton A, et al. Improved specificity with ^{68}Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. Eur J Nucl Med Mol Imaging 2019;46:20–30.
[12] Exterkate L, Hermsen R, Kusters-Vandevelde HVN, et al. Head-to-head comparison of ^{18}F-PSMA-1007 positron emission tomography/computed tomography and multiparametric

magnetic resonance imaging with whole-mount histopathology as reference in localisation and staging of primary prostate cancer. Eur Urol Oncol 2023;6:574–81.

[13] Emmett L, Buteau J, Papa N, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682–9.

[14] Sonni I, Felker ER, Lenis AT, et al. Head-to-head comparison of ^{68}Ga-PSMA-11 PET/CT and mpMRI with a histopathology gold standard in the detection, intraprostatic localization, and determination of local extension of primary prostate cancer: results from a prospective single-center imaging trial. J Nucl Med 2022;63:847–54.

[15] Prive BM, Israel B, Schilham MGM, et al. Evaluating F-18-PSMA-1007-PET in primary prostate cancer and comparing it to multiparametric MRI and histopathology. Prostate Cancer Prostat Dis 2021;24:423–30.

[16] Ucar T, Gunduz N, Demirci E, et al. Comparison of ^{68}Ga-PSMA PET/CT and mp-MRI in regard to local staging for prostate cancer with histopathological results: a retrospective study. Prostate 2022;82:1462–8.

[17] Bahler CD, Tachibana I, Tann M, et al. Comparing magnetic resonance imaging and prostate-specific membrane antigen-positron emission tomography for prediction of extraprostatic extension of prostate cancer and surgical guidance: a prospective nonrandomized clinical trial. J Urol 2024;212:290–8.

[18] Mookerji N, Pfanner T, Hui A, et al. Fluorine-18 prostate-specific membrane antigen-1007 PET/CT vs multiparametric MRI for locoregional staging of prostate cancer. JAMA Oncol 2024;10:1097–103.

[19] Turkbey B, Rosenkrantz AB, Haider MA. Prostate Imaging Reporting and Data System version 2.1: 2019 update of Prostate Imaging Reporting and Data System version 2. Eur Urol 2019;76:340–51.

[20] Soeterik TFW, Heetman JG, Hermsen R, et al. The association of quantitative PSMA PET parameters with pathologic ISUP grade: an international multicenter analysis. Eur J Nucl Med Mol Imaging. 2024 Aug 1. https://doi.org/10.1007/s00259-024-06847-y (Online ahead of print).

[21] Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-ligand PET/CT. J Nucl Med 2018;59:469–78.

[22] Fendler WP, Eiber M, Beheshti M, et al. ^{68}Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging 2017;44:1014–24.

[23] Ceci F, Oprea-Lager DE, Emmett L, et al. E-PSMA: the EANM standardized reporting guidelines v1.0 for PSMA-PET. Eur J Nucl Med Mol Imaging 2021;48:1626–38.

[24] Donswijk ML, Ettema RH, Meijer D, et al. The accuracy and intra- and interobserver variability of PSMA PET/CT for the local staging of primary prostate cancer. Eur J Nucl Med Mol Imaging 2024;51:1741–52.

[25] Epstein J, Egevad L, Mahul A, Delahunt B, Srigley J, Humphrey P. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244–52.

[26] Fine SW, Amin MB, Berney DM, et al. A contemporary update on pathology reporting for prostate cancer: biopsy and radical prostatectomy specimens. Eur Urol 2012;62:20–39.

[27] McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947;12:153–7.

[28] Moskowitz CS, Pepe MS. Comparing the predictive values of diagnostic tests: sample size and analysis for paired study designs. Clin Trials 2006;3:272–9.

[29] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.

[30] de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70:233–45.

[31] Emmett L, Papa N, Counter W, et al. Reproducibility and accuracy of the PRIMARY score on PSMA PET and of PI-RADS on multiparametric MRI for prostate cancer diagnosis within a real-world database. J Nucl Med 2024;65:94–9.

[32] Karpinski MJ, Hüsing J, Claassen K, et al. Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study. Lancet Oncol 2024;25:1188–201.

[33] Liu FY, Sheng TW, Tseng JR, et al. Prostate-specific membrane antigen (PSMA) fusion imaging in prostate cancer: PET-CT vs PET-MRI. Br J Radiol 2022;95:20210728.

[34] Muehlematter UJ, Burger IA, Becker AS, et al. Diagnostic accuracy of multiparametric MRI versus ^{68}Ga-PSMA-11 PET/MRI for extracapsular extension and seminal vesicle invasion in patients with prostate cancer. Radiology 2019;293:350–8.

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