An Update on the Role of mpMRI and ^{68}Ga-PSMA PET Imaging in Primary and Recurrent Prostate Cancer

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Abstract

The objective of this work was to review comparisons of the efficacy of ^{68}Ga-PSMA-11 (prostate-specific membrane antigen) PET/CT and multiparametric magnetic resonance imaging (mpMRI) in the detection of prostate cancer among patients undergoing initial staging prior to radical prostatectomy or experiencing recurrent prostate cancer, based on histopathological data. A comprehensive search was conducted in PubMed and Web of Science, and relevant articles were analyzed with various parameters, including year of publication, study design, patient count, age, PSA (prostate-specific antigen) value, Gleason score, standardized uptake value (SUV_{max}), detection rate, treatment history, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and PI-RADS (prostate imaging reporting and data system) scores. Only studies directly comparing PSMA-PET and mpMRI were considered, while those examining combined accuracy or focusing on either modality alone were excluded. In total, 24 studies comprising 1717 patients were analyzed, with the most common indication for screening being staging, followed by relapse. The findings indicated that ^{68}Ga-PSMA-PET/CT effectively diagnosed prostate cancer in patients with suspected or confirmed disease, and both methods exhibited comparable efficacy in identifying lesion-specific information. However, notable heterogeneity was observed, highlighting the necessity for standardization of imaging and histopathology systems to mitigate inter-study variability. Future research should prioritize evaluating the combined diagnostic performance of both modalities to enhance sensitivity and reduce unnecessary biopsies. Overall, the utilization of PSMA-PET and mpMRI in combination holds substantial potential for significantly advancing the diagnosis and management of prostate cancer.

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Introduction

Prostate cancer (PCa) is the most prevalent form of cancer in men, categorized as non-clinically significant (Gleason score (GS) = 6) or clinically significant (GS = 7-10).[1] Diagnostic approaches for PCa include digital rectal examination (DRE), prostate-specific antigen (PSA) levels, and transrectal ultrasound biopsy (TRUS), which aid in determining the optimal treatment approach for favorable clinical outcomes.[2-5] Despite salvage radiation therapy (SRT) being recommended for low PSA levels (< 0.5 ng/mL), accurate localization of recurrence sites remains challenging for PCa patients.[6] Traditional imaging methods, such as CT and bone scans may be inadequate when PSA levels are below 10 ng/mL. Therefore, abdominal and pelvic imaging is suggested for moderate to high-risk patients to avoid unnecessary biopsies caused by false positives.[7-12] To address this challenge, multiparametric magnetic resonance imaging (mpMRI) has emerged as the gold standard for early diagnosis and relapse evaluation due to its higher diagnostic accuracy and lower false negatives.[13-26] The European Urological Association guidelines endorse systematic lesion biopsy using the

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PI-RADS reporting system and mpMRI data system for patients with a PI-RADS score of 3 or above. While mpMRI exhibits a high negative predictive value, it still yields false-positive rates of up to 60%-80%, including lesions with a PI-RADS > 4, resulting in 13% negative predictive value.[27-29] mpMRI has shown high sensitivity (PI-RADS ≥ 3: 0.96, PI-RADS ≥ 4: 0.90) and specificity (PI-RADS ≥ 3: 0.29, PI-RADS ≥ 4: 0.62) for detecting clinically significant prostate cancer (csPCa).[30] Although mpMRI is valuable for localizing tumors and regional staging of T-stage prostate cancer, it does not aid in detecting nodular (N-stage), bone, or visceral metastases (M-stage).[31,32] However, ^{68}Ga-PSMA-11/617 PET imaging has emerged as a promising tool for accurate PCa diagnosis and treatment planning.[14,33,34]

^{68}Ga-PSMA is favored over ^{18}F-PSMA for several reasons. Its shorter half-life of approximately 68 minutes facilitates quicker imaging procedures and reduces patient radiation exposure compared to the longer half-life of ^{18}F-PSMA (around 110 minutes). Furthermore, the production of ^{68}Ga-PSMA is more straightforward and accessible, as it can be generated on-site in hospitals and imaging centers using a generator system. In contrast, ^{18}F-PSMA requires a cyclotron for production, limiting its availability. Notably, studies have demonstrated that ^{68}Ga-PSMA offers imaging quality comparable to or even superior to ^{18}F-PSMA in detecting prostate cancer and metastases in both bone and soft tissue. While ^{18}F-PSMA is not disregarded in clinical practice, the advantages of ^{68}Ga-PSMA, including its shorter half-life, easier production, and imaging quality, contribute to its increased utilization.[35,36] In this light, the focus of this study was on only ^{68}Ga-PSMA radiotracer.

Histopathological evaluation revealed that mpMRI exhibited a mean sensitivity of 61.5% and a mean specificity of 85.5%, while PSMA-PET demonstrated similar specificity but higher sensitivity values (76%).[17,23,29,37-42] It remains unclear whether PSMA-PET improves the diagnosis of primary prostate cancer compared to mpMRI or if it accurately localizes tumors. Therefore, this study aims to compare the diagnostic accuracy of both modalities to address these questions. The primary markers under consideration include PSA value, Gleason score, semiquantitative analysis (SUV_{max}), sensitivity, specificity, and positive/negative predictive values (PPV/NPV).

Literature Search Strategy, Study Selection and Data Extraction

The key reporting elements of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for systematic review and meta-analysis were utilized in this study.[43] An independent and systematic search was conducted in PubMed and Web of Science to identify articles published up to August 2, 2023. The search keywords used were as follows: (PSMA or prostate-specific membrane antigen positron emission tomography) and (MR or magnetic resonance imaging or mp-MRI or multiparametric MRI or multi-parametric magnetic resonance imaging) combined with (prostate and [cancer OR adenocarcinoma]) and (PSMA or prostate-specific membrane antigen positron emission tomography) and (PET or positron emission tomography) and biopsy. Initially, screening was performed based on the titles and abstracts of the articles, and eligible studies were selected for full-text evaluation. This review included studies on biopsy-naïve patients as well as cases prior to negative biopsy results. Studies involving radiotracers other than ^{68}Ga-PSMA and those solely analyzing the accuracy of PET/MRI were excluded. The exclusion criteria comprised non-English articles, studies conducted on animal models, and case reports, poster presentations/conference abstracts, and letters to the editor. Data extraction followed standardized criteria and was individually checked by experts. The extracted data included author, year of publication, study design, number of patients included, median age, median PSA value, Gleason score, SUV_{max}, detection rate, setting of disease, treatments before PET radiopharmaceutical agent, study content, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and PI-RADS scores. Furthermore, studies not written in English were excluded. Only studies directly comparing PSMA-PET and mpMRI were included, while those focusing on the combined accuracy of both modalities or solely on the diagnostic accuracy of PSMA-PET or mpMRI alone were excluded. A total of 24 studies were eligible for qualitative analysis (Figure 1) and are presented in Tables 1 and 2 . Among them, five studies were prospective, while twenty were retrospective. In total, the analysis encompassed 1717 patients who underwent both mpMRI and PSMA-PET. The primary indication for screening was staging, which was the focus of 18 studies involving 1205 patients, followed by studies on relapse comprising seven studies involving 512 patients.

PSMA-PET Vs. mpMRI

Noninvasive mpMRI is commonly used prior to biopsy, particularly in individuals suspected of having PCa.[44-46] This study aimed to compare the diagnostic accuracy of PSMA-PET with mpMRI, the latter known for predicting response to radiation therapy, and to evaluate the higher accuracy of PSMA-PET/MRI in early-stage PCa.[47,48] Assessing these findings provides a clearer understanding of the diagnostic value differences between PSMA-PET and mpMRI. Furthermore, this method could assist in clinical decision-making for prostate cancer diagnosis and suggest potential areas for future exploration. For instance, Eiber et al. (2015)[49] and Giesel et al. (2016)[50] individually analyzed the detection rate of PSMA-PET and mpMRI in patients with early-stage PCa. Eiber et al. found that mpMRI, PSMA-PET, and PET/MRI detected cancer in 66% (35/53), 92% (49/53), and 98% (53/53) of patients, respectively. Additionally, PET/MRI exhibited a higher area under the curve (AUC: 0.88) compared to PET imaging (AUC: 0.83) and mpMRI (AUC: 0.73). PET also demonstrated a high absorption ratio between malignant and non-malignant tissues (0.89-29.8), but there was no correlation between PET parameters and Gleason score or PSA values. Giesel et al.[50] studied 10 patients and observed agreement between tumor attributes detected by both PSMA-PET/CT and mpMRI, particularly in cases with a high pre-test rate of large tumors. However, they suggested that further studies are needed to evaluate the advantages of PSMA-PET/CT in challenging situations such as prostatitis or benign prostatic hyperplasia, after multiple negative biopsy results, or to determine if patients would truly benefit from positive PSMA results (Figures 2 and 3).

Table 1 Summary of Research Studies Included in this Review

No.	Authors	Year of Pub	Study Design	Age (Median or Mean ± SD) in Years	No. of Pts	Mean-Median PSA ng/ml (SD-IQR)	GS (Range)	SUV_{max}	Detection Rate (PSMA PET vs. mpMRI) %	PPV (PSMA PET vs. mpMRI) %	NPV (PSMA PET vs. mpMRI)	PI-RADS (%)
1	Giesel et al.[1]	2016	Retrospective	70 years (range 61-74)	10	15 (9.92-36.2)	7-9	21.1 (range: 8.2-33.4)	96.8 vs. 89.4	NA	NA	NA
2	Berger et al.[2]	2018	Retrospective	64.9 years (±5.6)	50	10.6 (±8.1)	6-9	2.9 to 39.6 (M = 9.27 ± 6.41)	100 vs. 94	93.0 vs.14.3	28.6 vs. 6.9	NA
3	Sonni et al.[3]	2022	Prospective	65 (range 60-69)	74	11.1 (7.5-21.5)	6-9	7.8 to 33.4 (22.56 ± 5.1)	93 vs. 91	97 vs. 100	NA	NA
4	Li et al.[4]	2020	Retrospective	68 (42-85)	115	10.48 (3.15-19.76)	6-10	4.30 (2.10-41.30)	NA	87.88 (70.86- 96.04) vs. 63.64 (47.74-77.17)	88.24 (71.61- 96.16) vs. 78.26 (55.79-91.71)	PI (1-2): 23 (34.33)- PI (3):13 (19.40)- PI (4):23 (34.33)- PI (5):8 (11.94)
5	Hicks et al.[5]	2018	Retrospective	68 (range: 62-71)	32	13.4 (8.4-19.7)	7-10	3.8 to 23.9	NA	NA	NA	mpMRI depicted 287 regions graded as PI-RADS 3, 4, or 5 (three, 22, and 278 regions, respectively)
6	Glemser et al.[6]	2022	Prospective	65 (53-81)	53	1.60 (0.07-25.9)	7-9	15.8 (median = 10.9)	64.2 vs. 43.4	NA	NA	NA
7	Spohn et al.[7]	2020	Retrospective	70 (68-72)	101	10.9 (9.39-13.03)	6-9					
8	Lopci et al.[8]	2021	Retrospective	64.52	45	10.80 (2.25-30.41)	7-9	5.34 (2.25-30.41)	44%	NA	NA	NA
9	Martinez et al.[9]	2022	Retrospective	69 +/- 9.1 (41- 87)	165	5.56 +/- 11.1 (0.06-70.35)	NA	NA	83 vs. 57	NA	NA	NA
10	Barbosa et al.[10]	2020	Retrospective	66.0 (59.0-71.0)	91	6.0 (4.5-10.0)	NA	NA	NA	NA	NA	NA
11	Çelen et al.[11]	2020	prospective	65.07 ± 8.01 (46-82)	30	9.49 ± 6.97 (1.3-27	6-10	11.25 ± 11.03 (2.2-52.66)	NA	60 vs. 72.22	46.67 vs. 66.67	NA
12	Donato et al.[12]	2018	Retrospective	65.5 (60-68)	58	7.35 (5.6-12)	6-10	9.53 (6.3-14.32)	NA	NA	NA	NA

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Table 1 (*continued*)

No.	Authors	Year of Pub	Study Design	Age (Median or Mean ± SD) in Years	No. of Pts	Mean-Median PSA ng/ml (SD-IQR)	GS (Range)	SUV_{max}	Detection Rate (PSMA PET vs. mpMRI) %	PPV (PSMA PET vs. mpMRI) %	NPV (PSMA PET vs. mpMRI)	PI-RADS (%)
13	Skawran et al.[13]	2022	Retrospective	66 (61-72)	49	18.3 (7.1-18.8)	7-10	NA	NA	NA	NA	PI (1):0 (0 %)- PI (2):0 (0 %)- PI (3):4 (8.2 %)- PI (4):19 (38.8 %)- PI (5):26 (53 %)
14	Chen et al.[14]	2020	Retrospective	69 (55-84)	54	13.30 (4.04-110.00)	6-10	NA	NA	97 (83-100) vs. 95 (76-100)	67 (45-84) vs. 48 (31-66)	NA
15	Eiber et al.[15]	2015	Retrospective	66 (62-72)	53	12.0 (6.9-18.8)	6-10	4.48 (1.97-6.02)	66 vs. 92	NA	NA	PI (1-2): 4% (2 of 53) - PI (3): 30% (16 of 53)
16	Ferraro et al.[16]	2022	Retrospective	65 (59-68)	39	7.1 (6.3-10.4)	7-9	6.8 (4.7-10.5)	NA	84.4 vs. 83.3	82.9 vs. 80.7	PI (3): 5 (13%)- PI (4):24 (61%)- PI (5):10 (26%)
17	Zhou et al.[17]	2022	Retrospective	68.1 (50-89)	101	38.1 (3.5-100.0)	6-10	5.6 (3.7-7.8)	97 vs. 87.9	NA	NA	PI (1-2): 0 (0 %)- PI (3):8 (12.1%)- PI (4):14 (21.2%)- PI (5):44 (66.7%)
18	Coşar et al.[18]	2021	retrospective	63.1 ± 6.3	64	7.6 (1.0-32.9)	6-10	7.1 (2.7-78)	NA	86.8 vs. 80.6	79.8 vs. 77.2	PI (2): 3 (5.4%)- PI (3):6 (10.7%)- PI (4):22 (39.3%)- PI (5):25 (44.6%)
19	Radzina et al.[19]	2020	Retrospective	63 (49-81)	32	0.2-10.0	6-10	NA	NA	80 vs. 83.3	100 vs. 70.8	NA
20	Afshar-Oromieh et al.[20]	2019	Retrospective	69.8 (59-86)	43	4.1 (0.2-20)	6-9	NA	NA	NA	NA	NA
21	Moradi et al.[21]	2022	prospective	64.0 ± 6.3	73	1.48 (0.56-3.96)	7-9	4.93 (1.87-13.04)	NA	NA	NA	NA
22	Geboers et al.[22]	2023	Retrospective	63 (range: 49-80)	138	< 15	NA	NA	NA	90 vs. 86	77 vs. 70	NA
23	Cheng et al.[23]	2023	Prospective	64.0 (59.0, 70.0)	112	0.2 (0.1, 0.4)	≥ 3 + 4	6.0 (0.0, 9.4)	NA	NA	NA	PI-RADS (3): 0-PI-RADS (4):1.6696 -PI-RADS (5): 2.1270
24	Khanna et al.[24]	2023	Retrospective	Mean range (71.97)	135	≥ 0.2	4 + 5	NA	NA	NA	NA	NA

Table 2 Comparative Analysis of Findings From Various Study Contexts on PSMA PET and mpMRI

No.	Treatments Before PET	Radiopharmaceutical	Scope of the Study	Brief Outcomes	Sensitivity (PSMA PET Vs. mpMRI) %	Specificity (PSMA PET Vs. mpMRI) %
1[1]	NA	^{68}Ga-PSMA-11/mpMRI	Initial staging	PSMA-PET/CT and MRI correlated well in tumor isolation in patients with a high probability of pre-examination of large tumors.	NA	NA
2[2]	Median time between PSMA PET/CT and surgery was 5 weeks (IQR 3-12 weeks), and the median time between mpMRI and surgery was 18 weeks (IQR 13-25 weeks). The median time between mpMRI and PSMA PET/CT was 12 weeks (IQR 7-15 weeks)	^{68}Ga-PSMA-11/mpMRI	Staging	PSMA-PET/CT better detects prostate cancer lesions with higher sensitivity than mpMRI. PSMA-PET/CT can be used to improve local mpMRI to improve detection and characterization of lesions.	81.1 vs. 64.8	84.6 vs. 82.7
3[3]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	PSMA PET/CT and mpMRI are equally accurate in detecting and intraprostatic localization of prostate cancer lesions. For the evaluation of moderate-to-high-risk T-stage prostate cancer, mpMRI should continue to be considered the standard imaging modality.	84 vs. 86	55 vs. 59
4[4]	NA	^{68}Ga-PSMA-617/mpMRI	Staging	68Ga-PSMA-617 PET/CT has better diagnostic performance in terms of specificity than mpMRI in patients with suspected PCa and a PSA level of 4-20 ng/mL.	87.88 (80.86- 96.04) vs. 84.85 (67.33-	
94.28)	88.24 (71.61- 96.16) vs. 52.94 (35.40-					
69.84)						
5[5]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	The sensitivities of PET/MRI and multivariate MRI were 74% (95% confidence interval [CI]: 70%, 77%) and 50% (95% CI: 45%, 0.54%), respectively. Site-specific specificity of PET/MRI was comparable to multiparametric MRI (88% [95% CI: 85%, 91%] vs. 90% [95% CI: 87%, 92%], $P = .99$).	95 vs. 50	88 vs. 90
6[6]	RPx ± RT ± ADT	^{68}Ga-PSMA-11/mpMRI	Recurrence	Although there was no significant difference in lesion detection rates between PET/CT and PET/MRI, PET/MRI was particularly effective in detecting local recurrence.	NA	NA

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Table 2 (*continued*)

No.	Treatments Before PET	Radiopharmaceutical	Scope of the Study	Brief Outcomes	Sensitivity (PSMA PET Vs. mpMRI) %	Specificity (PSMA PET Vs. mpMRI) %
7[7]	NA	NA	Staging	PSMA-PET detected lesions in both lobes whereas MRI did not detect them in 26 patients (26%), conversely MRI detected lesions in both lobes but PET did not detect them in 12 patients (12%).	NA	NA
8[8]	NA	NA	Staging	Mean and median 68Ga-PSMA PET/CT absorbance (i.e., SUVmax or SUVratio) was significantly higher in GS 7 lesions than in GS 6 or benign lesions ($P < .001$).	100 vs. 100	76 vs. 88
9[9]	RPx ± RT ± ADT	^{68}Ga-PSMA-11/mpMRI	Recurrence	PSMA PET/MRI was more sensitive than mpMRI.	NA	NA
10[10]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	When considering both 68Ga-PSMA PET-CT and PET-MRI, the accuracy was 85.7% (95% CI: 0.76-0.92; $P = .015$), the sensitivity was 50%, and the specificity was 97%.	58.3 vs. 40	95 vs. 100
11[11]	NA	^{68}Ga-PSMA-I/T-mpMRI	Staging	Both mpMRI and 68Ga-PSMA-I/T PET-CT were not statistically significant in preoperative SVI, BNI, and ECE assessments, but were statistically significant in LNM assessments.	53.94 vs. 76.47	53.85 vs. 61.54
12[12]	RPx	^{68}Ga-PSMA-11/mpMRI	Recurrence	68Ga-PSMA PET/CT correctly identified more lesions (78%, AUC 0.817) than mpMRI (69%, AUC 0.729).	71.4 vs. 72.6	90.5 vs. 81
13[13]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	The diagnostic accuracy of the mpMRI versus 68Ga-PSMA-PET/MRI reader at T3 or higher was AUC: 0.72, 0.62 versus 0.71, 0.72 ($P > .38$) and for N1, AUC: 0.39, 0.55 versus 0.72, 0.78 ($P < .01$). Reader agreement for ≥ T3 was similar for mpMRI and 68Ga-PSMA-PET/MRI, but higher for 68Ga-PSMA-PET/MRI for N1.	69 vs. 54	81 vs. 87
14[14]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	Both PET/CT and comMRI/PET were more sensitive than mpMRI for ECE diagnosis (78% vs. 54%, $P < .05$ and 83% vs. 54%, $P < .05$). No differences were observed between PET/CT and comMRI/PET (78% vs. 78%). 83%, $P = .17$).	78 (62-90) vs. 54 (37-71)	94 (71-100) vs. 94 (71-100)

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Table 2 (*continued*)

No.	Treatments Before PET	Radiopharmaceutical	Scope of the Study	Brief Outcomes	Sensitivity (PSMA PET Vs. mpMRI) %	Specificity (PSMA PET Vs. mpMRI) %
15[15]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	mpMRI, PET, and PET/MRI detected cancer in 66% (35 of 53), 92% (49 of 53), and 98% (52 of 53), respectively.	64 (56-72) vs. 43 (33-53)	94 (86-98) vs. 98 (94-100)
16[16]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	The specificity of the two imaging modalities increased to 98% and 99% in mpMRI and PSMA PET/MRI, respectively, and the sensitivity improved to 63.9% and 72.1%, respectively.	66.7 vs. 61.4	92.9 vs. 92.9
17[17]	Biopsy and/or RPx	^{68}Ga-PSMA-11/mpMRI	Recurrence	In the high-risk cohort, 68Ga-PSMA PET/CT was positive in 64/66 (97.0%) patients, with a higher detection rate than mpMRI patients (58/66, 87.9%; $P < .05$). However, mpMRI provided higher diagnostic certainty for detecting low- and intermediate-risk PCa (30/35, 85.7% versus 21/35, 60.0%; $P < .05$).	NA	NA
18[18]	RPx	^{68}Ga-PSMA-11/mpMRI	Recurrence	68Ga-PSMA PET/MRI has higher sensitivity and specificity than mpMRI. Combined imaging showed significantly higher diagnostic accuracy compared to mpMRI and PET/MRI using 68Ga-PSMA (change in AUC: 0.084 and 0.046, $P < .001$ and $P = .028$, respectively), and there was no significant statistical difference between mpMRI and 68Ga-PSMA.	60.8 vs. 55.7	94.3 vs. 91.8
19[19]	RPx ± RT ± ADT ± B	^{68}Ga-PSMA-11/mpMRI	Recurrence	Compared to the reference standard, the sensitivity, specificity and accuracy of PET/CT local recurrence was 63.6%. 73.7%; 77.8% each. MRI reached 90.9%. 94.7%; 92.3% each. In conclusion, mpMRI provides better diagnostic accuracy for detecting local recurrence, whereas PSMA PET/CT better detects distant and lymph node metastases.	83.3 (75.3-100) vs. 41.7 (29.3-58.1)	80.0 (60.4-96.6) vs. 94.4 (56.4-96.6)
20[20]	RPx ± RT	^{68}Ga-PSMA-11/mpMRI	Recurrence	30/43 patients (69.8%) had abnormal MRI and 38/43 (88.4%) had abnormal PSMA-PET/CT of the pelvis. MRI revealed 53 pelvic PCa lesions (13 classified as "indeterminate") and PSMA-PET/CT revealed 75 pelvic lesions (3 classified as "indeterminate"). The superiority of PSMA-PET/CT was statistically significant only when indeterminate lesions were classified as false positive.	NA	NA

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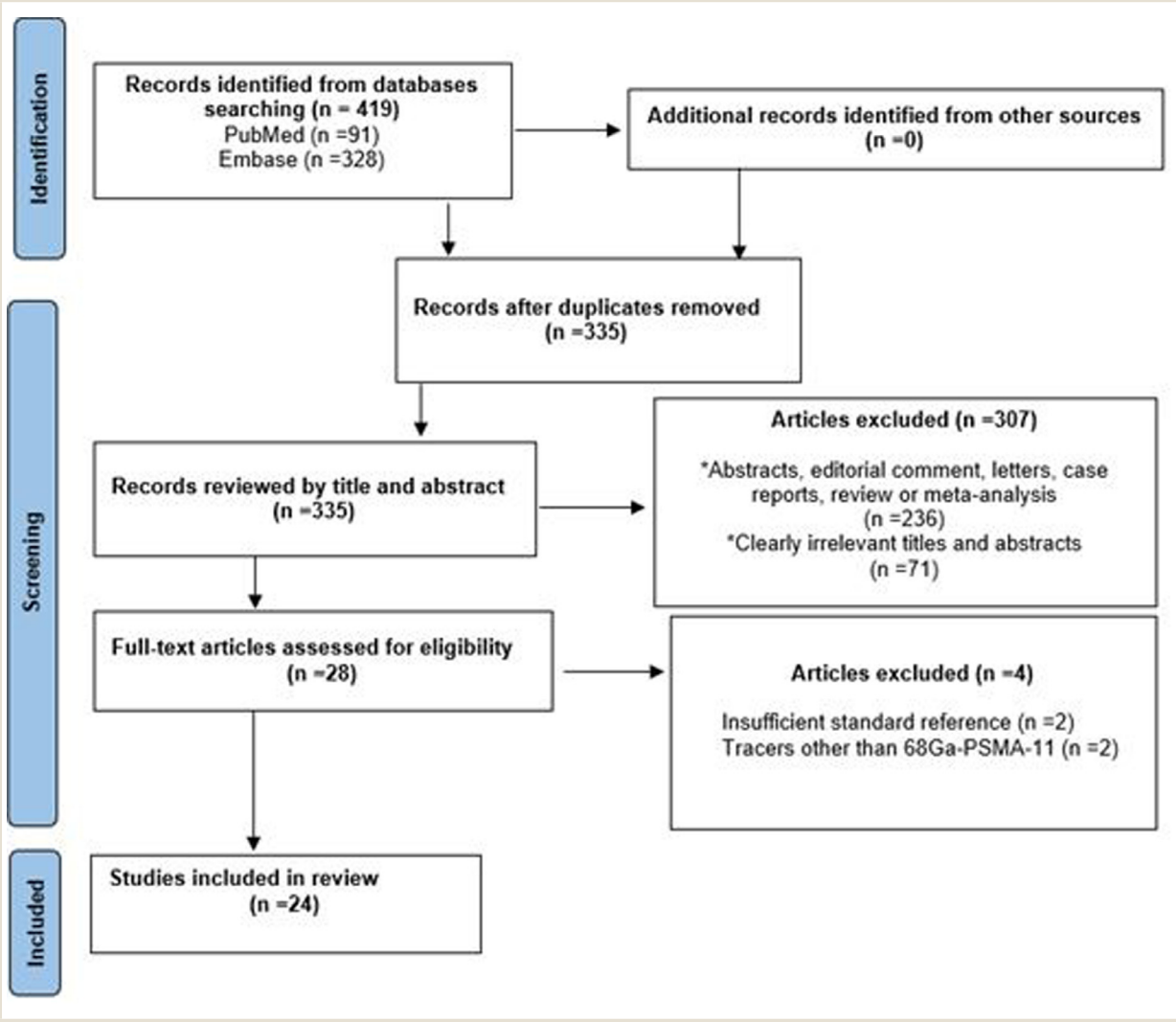
Table 2 (*continued*)

No.	Treatments Before PET	Radiopharmaceutical	Scope of the Study	Brief Outcomes	Sensitivity (PSMA PET Vs. mpMRI) %	Specificity (PSMA PET Vs. mpMRI) %
21[21]	NA	^{68}Ga-PSMA-11/mpMRI	Staging	High uptake in primary (SUVmax > 12.5, $P = .008$) and presence of PSMA metastases ($P = .013$) were associated with biochemical deficits and corresponding risk ratios for relapse at 2 years (4.93 and 3.95, respectively) was similar or higher than other clinicopathological prognostic factors.	NA	NA
22[22]	NA	NA	Staging	In contrast to using only SUVmax, the model exhibited remarkable diagnostic accuracy, with enhanced specificity (0.910, 95% CI: 0.824-0.963) and positive predictive values (0.811, 95% CI: 0.648-0.920). The calibration curve and decision curve analysis provided additional validation that the model displayed a substantial clinical advantage and a minimal error rate.	NA	NA
23[23]	NA	NA	Staging	The AUC, sensitivity, specificity, PPV, and NPV for csPCa were 0.79, 75%, 83%, 81%, and 77% for combined mpMRI and systematic biopsies, and improved after addition of PSMA-PET to 0.84, 87%, 80%, 81%, and 86% respectively ($P < .001$). On final histopathology 46/138 (33%) patients were not suitable for hemi-ablative FT. Addition of PSMA-PET correctly identified 26/46 (57%) non-suitable patients and resulted in 4/138 (3%) false positive exclusions.	72 vs. 59	92 vs. 91
24[24]	Before biopsy	NA	Staging	The constructed model in this study was capable of accurately predicting csPCa prior to biopsy with excellent discriminative ability. As such, this model has the potential to be an effective noninvasive approach for the diagnosis of csPCa.	NA	NA

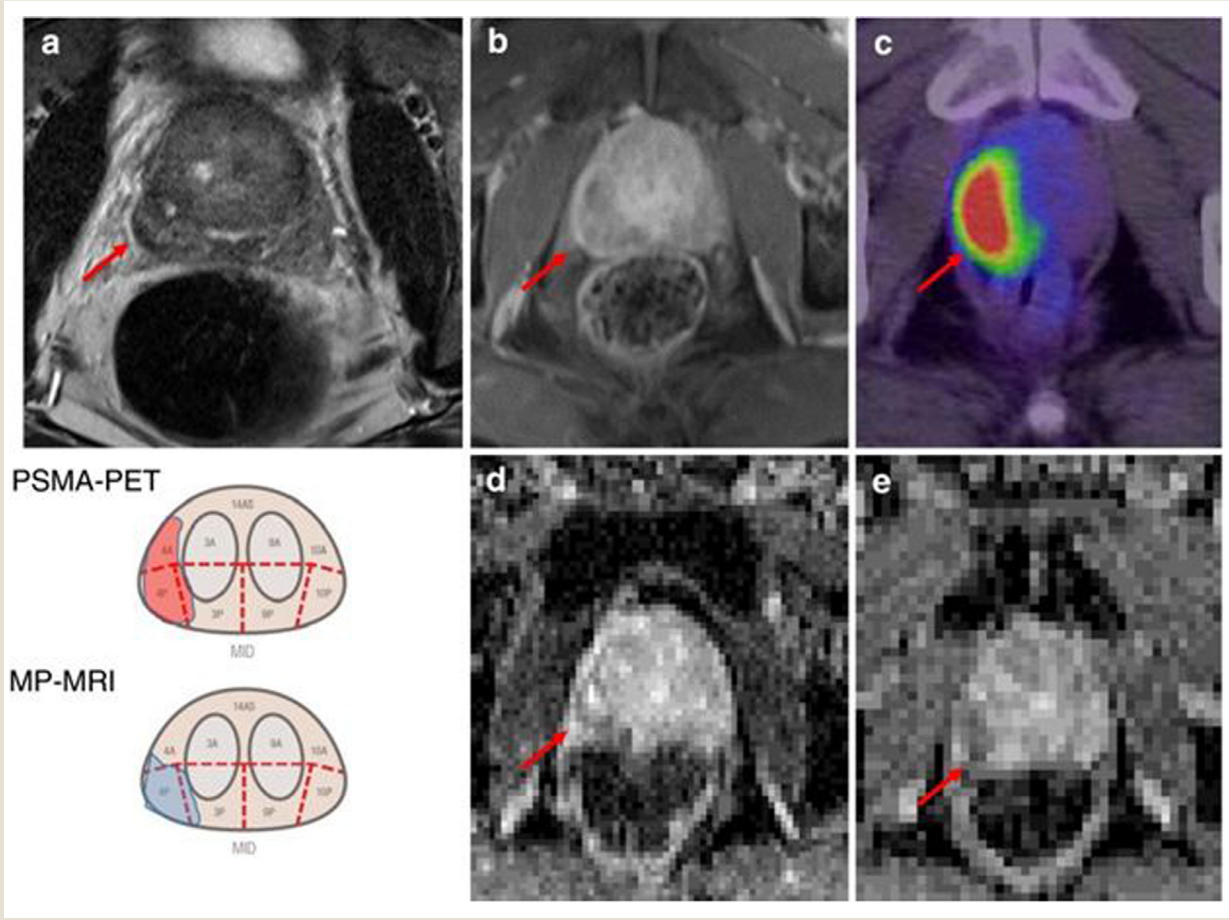
Figure 1 The PRISMA method adopted for this study.



In a retrospective study by Berger et al., which analyzed 50 PCa patients using both mpMRI and PSMA-PET imaging, the sensitivity and specificity for diagnostic accuracy were 64.8% vs. 81.1% and 82.7% vs. 84.6%, respectively.[39] Histopathology confirmed 50 lesions, all of which were detected by PSMA-PET/CT (100% detection), while mpMRI detected 47 lesions (94% detection). Among the 31 secondary lesions found, PSMA-PET/CT identified 29 (93.5%) compared to mpMRI, which detected only 16 (51.6%). Hence, it was evident that PSMA-PET/CT is more sensitive than mpMRI in detecting prostate cancer. This imaging modality could also enhance the accuracy of local mpMRI for lesion detection and characterization. In 2018, Hicks et al. and Donato et al. conducted separate studies on PSMA-PET/CT, but no recommendations for accurate diagnosis and reporting of results were made.[23,27] However, the limited sample sizes of 32 and 58 patients in each study make it difficult to generalize their results. Hicks et al. found that site-specific PET/MRI had a sensitivity rate of 74% (95% CI: 70%, 77%), while mpMRI had a sensitivity rate of 50% (95% CI: 45%, 0.54%), both exhibiting similar specificity when using external methods or population mean estimations (88% [95% CI: 85%, 91%] vs. 90% [95% CI: 87%, 92%], $P = .99$; 70% [95% CI: 64%, 76%] vs. 70% [95% CI: 64%, 75%], $P = .99$). SUV_{max} was found to be associated with a Gleason score of 7 or higher (odds ratio: 1.71 [95% CI: 1.27, 2.31], $P = .001$). Overall, the sensitivities for lesion index, bilateral, and multifocal lesions were 90%, 21%, 19% for mpMRI and 93%, 42%, 34% for ^{68}Ga-PSMA PET/CT, respectively. Among the 88 histologically confirmed cancerous lesions with Gleason grades of 3 + 3 (4%), 3 + 4 (64%), 4 + 3 (19%), 4 + 4 (3%), and 4 + 5 (10%) or higher, ^{68}Ga-PSMA PET/CT correctly identified 78% of them.

The diagnostic accuracy of PSMA-PET vs. mpMRI in the detection of PCa and their differences in specificity and sensitivity have been discussed to shed light on the comparative diagnostic value of these imaging modalities (Figure 4).[51] Afshar-Oromieh et al.[52]

Figure 2 An instance of near-total agreement is demonstrated in this case. Biopsy-confirmed prostate cancer is observed in the right peripheral zone. The multiparametric MRI (MP-MRI) findings include a signal decrease in T2-weighted imaging (A), rapid contrast washout in the T1-weighted sequence (B), focal diffusion restrictions in diffusion-weighted imaging (D), and corresponding apparent diffusion coefficient (ADC) mapping (E), all indicating tumor infiltration of segment 4P. Notably, the PSMA-PET scan (C) visually reveals a remarkably similar tumor extent; however, it was interpreted as tumor involvement in segments 4A and 4P, showing a slight discrepancy in the scoring. Reprinted under the terms of the Creative Commons Attribution 4.0 International License from.[50]



observed that PSMA-PET/CT detected a higher number of pelvic lesions compared to mpMRI, with statistically significant differences noted when unidentified lesions were classified as false positives. Differences in the pathological types of PCa, such as csPCa and ncsPCa, as well as variations in imaging modalities with different sensitivities and specificities, may contribute to these disparities.[53,54] Lopchi et al.[55] reported higher sensitivity compared to other studies, where clinically significant disease was defined as GS = 7-9. SUV_{max} of 5.4 and SUV_{ratio} of 2 were able to differentiate clinically significant PCa with a sensitivity rating of 100% and specificity ratings of 76% and 88%, respectively.[56] It should also be noted that ^{68}Ga-PSMA PET/CT can detect PCa in cases where mpMRI yields negative results, suggesting its potential to provide improved imaging in selected patients.[57] Two main points were discussed: firstly, a strong correlation was observed between ^{68}Ga-PSMA uptake intensity and PSA/GS levels in detected lesions; and secondly, SUV_{max} of the primary tumor could be used to predict csPCa.[58-61] Li et al.[59], recently investigated the role of ^{68}Ga-PSMA PET/CT in the initial diagnosis of PCa in patients with clinical or biochemical suspicion. The study demonstrated a sensitivity and specificity of 87.88% (80.86-96.04) and 88.24% (71.61-96.16), respectively, with positive and negative likelihood ratios of 87.88 (70.86-96.04) and 78.26 (55.79-91.71). Generally, mpMRI utilizes PI-RADS > 3 as potential evidence for csPCa detection.[62]

However, variations in reader perception and image quality can affect its diagnostic performance.[63-67] Li et al.'s study presented the following PI-RADS scores: PI (1-2): 23 (34.33%), PI (3): 13 (19.40%), PI (4): 23 (34.33%), and PI (5): 8 (11.94%). In contrast, Skawran et al.'s retrospective study showed different results, with PI (1): 0 (0%), PI (2): 0 (0%), PI (3): 4 (8.2%), PI (4): 19 (38.8%), and PI (5): 26 (53%).[68] These discrepancies may be attributed to the smaller sample size of Skawran et al. compared to Li et al.'s study, which included 115 cases. To further investigate these variations, Zhou et al. conducted a retrospective analysis on 101 patients,

Figure 3 A 68-year-old patient exhibited a substantial tumor mass extension at the base of the prostate gland, with involvement of seminal vesicles. This presentation was evident in the multiparametric MRI (MP-MRI), characterized by a signal reduction in the T2-weighted sequence (A in sagittal view, and B in axial view), contrast enhancement in the T1-weighted sequence (F), and the manifestation of diffusion restriction, as depicted in the apparent diffusion coefficient (ADC) map (C). The PSMA-PET scans (D in sagittal view, and E in axial view) revealed a concordant extension of the tumor, corroborating the findings from the MP-MRI. Reprinted under the terms of the Creative Commons Attribution 4.0 International License from.[50]

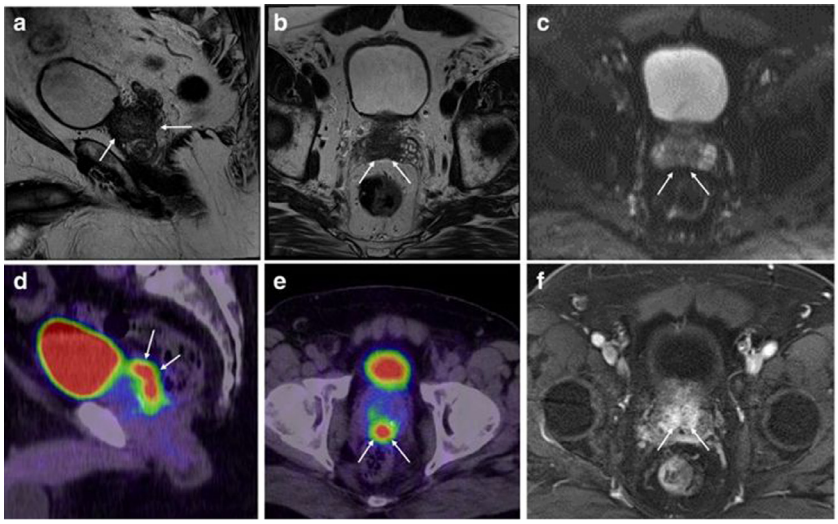
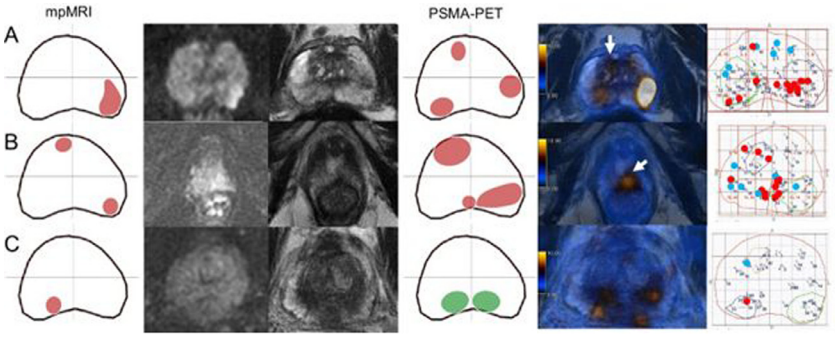


Figure 4 Illustration of the imaging and histopathological findings in cases exhibiting discordance between PSMA PET/MRI and mpMRI results. Each row represents an individual patient. The images from left to right include the mpMRI readout, DWI, T2-weighted sequence, PSMA PET/MRI readout, the fused PSMA PET/MRI image, and the template biopsy map. In the readouts, suspicious lesions are highlighted in red, while non-suspicious ones are denoted in green. On the template biopsy maps, red dots correspond to biopsy cores with a Gleason Score (GS) of 3 + 4 or higher, while blue dots signify GS 3 + 3. (A) The left posterior quadrant lesion was visualized on both mpMRI and PSMA PET, aligning with clinically significant prostate cancer (csPCa) on template biopsy. However, the two lesions in the right quadrants were exclusively detected on PSMA PET (indicated by the arrow, anterior lesion). (B) PSMA PET and mpMRI concurred in identifying lesions in the anterior right and posterior left quadrants, while the apex lesion extending into the posterior right quadrant was solely visible on PSMA PET (arrow). (C) In this case, the lesion in the right posterior quadrant was identified on mpMRI but not on PSMA PET due to the interference of physiological uptake in the central zones, which impeded visual analysis. Reprinted under the terms of the Creative Commons Attribution 4.0 International License from.[51]



resulting in PI (1-2): 0 (0%), PI (3): 8 (12.1%), PI (4): 14 (21.2%), and PI (5): 44 (66.7%). The PSMA PET vs. mpMRI detection rate was 97% vs. 87%.[69] Coşar et al.[70] reported PI (2): 3 (5.4%), PI (3): 6 (10.7%), PI (4): 22 (39.3%), and PI (5): 25 (44.6%) in 64 patients with a mean PSA ng/mL of 7.6 (1.0-32.9) and a GS range of 6-10. It is worth noting that different diagnostic criteria for clinically suspected csPCa were more evident in PSMA-PET/CT scans. Although SUV_{max} is often used as a semi-quantitative predictor, determining an appropriate threshold remains challenging.[71]

Ferraro et al. (2022) studied 39 PCa patients with GS 7-9 and a mean PSA ng/mL of 7.1 (6.3-10.4). The PPV on PSMA-PET was 84.4% compared to 83.3% on mpMRI, and the NPV was 84.4% compared to 83.3%, respectively. PI-RADS scores for detecting csPCa were 5 (13%) for PI (3), 24 (61%) for PI (4), and 10 (26%) for PI (5).[72] These findings are consistent with Sonni et al.'s report of 97% vs. 100% PPV and 97% vs. 95% NPV from PSMA PET to mpMRI, as well as Li et al.'s 88% vs. 78% PPV and 82% vs. 80% NPV from PSMA PET to mpMRI, respectively.

^{68}Ga-PSMA-617 PET/CT has shown greater specificity than mpMRI in detecting PCa in individuals with PSA levels ranging from 4-20 ng/mL. The positive correlation between ^{68}Ga-PSMA-617 PET/CT uptake and Gleason Score suggests its potential as a non-invasive, objective predictor of PCa risk and grade. Lopci et al. demonstrated that compared to mpMRI, PSMA PET had a sensitivity of 7.88% and specificity of 88.24%. Additionally, the receiver operating characteristic (ROC) analysis revealed that SUV_{max} 5.4 and SUV_{ratio} 2 had 100% sensitivity and 76% and 88% specificity, respectively, in detecting clinically significant PCa.[61] Glemser et al. prospectively analyzed 53 cases of PCa and compared PET/CT, PET/MRI, and MRI. Recurrent PCa lesions were detected in 64.2%, 67.9%, and 43.4% of patients, respectively. No notable differences were found between the modalities; however, PET/MRI was more reliable in detecting local recurrences. Additionally, no statistically significant correlation was observed between Gleason scores and scan positivity rates across all modalities.[73] In terms of lesion localization, the findings of the study revealed that PSMA-PET detected a higher number of bilateral lesions compared to MRI. Among the patient cohort, 37.6% exhibited differences in lesion arrangement between PET and MRI, with PSMA-PET identifying bilateral lobe lesions in 26 individuals that were not recognized by MRI, while MRI showed bilateral lobe lesions in 12 patients that were not detected by PET.[74] In the evaluation of patients with biochemical relapse, the use of PSMA PET/MRI resulted in a higher detection rate compared to mpMRI.[75] Another study examined the accuracy of ^{68}Ga-PSMA PET-CT for lymph node staging in PCa. Barbosa et al.'s findings demonstrated accuracy, sensitivity, and specificity of 86.5% (95% CI: 0.74-0.94; $P = .06$), 58.3%, and 95%, respectively. The accuracy of ^{68}Ga-PSMA PET-MRI was 84.6% (95% CI: 0.69-0.94; $P = .09$), with a sensitivity and specificity of 40% and 100%, respectively. When both techniques were combined, the accuracy was 85.7% (95% CI: 0.76-0.92; $P = .015$), with a sensitivity and specificity of 50% and 97%, respectively.[74]

Çelen et al.[76] found that both mpMRI and ^{68}Ga-PSMA-I/T PET-CT were not significantly different in terms of preoperative assessment of seminal vesicle invasion (SVI), bladder neck invasion (BNI), and extracapsular extension (ECE). However, a statistically significant difference was observed in the assessment of lymph node metastasis (LNM), with mpMRI showing higher overall sensitivity for ECE, SVI, and BNI, as well as a higher positive predictive value for ECE, SVI, and BNI. Additionally, ^{68}Ga-PSMA-I/T PET-CT had higher overall sensitivity for BNI and negative predictive values for BNI and LNM. It is worth noting that PSMA ligand expression is related to the FOLH1 gene, and alternative imaging modalities may be required to detect tumors that cannot be visualized on mpMRI. The activation of PI3K, which promotes prostate cancer growth, is associated with PSMA expression;[77] however, the link between PSMA expression and cellularity remains unknown. A combination of PSMA-PET/CT and mpMRI could be an appropriate approach for tumors that are not visible on mpMRI alone, as previous studies have demonstrated high sensitivity and specificity when using this combination[78,79] (Figure 5).

The PRIMARY (the additive diagnostic value of PSMA-PET/CT to mpMR triage in the diagnosis of PC) study has also shown that combining PSMA-PET/CT with MRI improves the sensitivity and NPV for csPCa compared to MRI alone, thus avoiding unnecessary biopsies in PSMA + MRI-negative men[56] (Figure 6).

Considering the advantages of csPCa detection, a combination of both imaging approaches may be optimal, particularly for definitive findings such as PI-RADS 3 lesions.[80] However, it is important to note that most studies analyzing ^{68}Ga-PSMA-PET/CT and MRI have been retrospective and conducted on patients who have already been diagnosed with PCa.[27,28,39] Therefore, new prospective studies are needed to understand the role of PSMA-PET/CT in cancer detection. Additionally, biopsy results using single-point techniques tend to focus on lesions with strong PSMA expression, potentially overlooking tumors with negative or low PSMA expression during screening (5%).[81,82]

In order to enhance the accuracy of detecting csPCa, numerous recent studies have investigated the simultaneous use of both mpMRI and ^{68}Ga- PSMA PET-CT. The inclusion of prostate-specific antigen density (PSAd), the PI-RADS category, and SUV_{max} in the model resulted in outstanding predictive accuracy when applied to both the training and validation groups. Specifically, the AUC was 0.936 for the training group and 0.940 for the validation group. When compared to using only SUV_{max}, the model displayed remarkable diagnostic performance with improved specificity (0.910, 95% CI: 0.824-0.963) and positive predictive values (0.811, 95% CI: 0.648-0.920). Furthermore, the calibration curve and decision curve analysis provided additional confirmation that the model offers a significant clinical benefit and has a low error rate.[83]

Geboers and colleagues assessed the utility of PSMA-PET alongside traditional methods to identify candidates for hemi-ablative Focal Therapy (FT).[84] Their study involved a retrospective examination of 138 patients from various medical centers, who had undergone mpMRI, PSMA-PET, and systematic biopsies prior to Radical Prostatectomy (RP). Patients were considered eligible if they met the consensus criteria for FT, which included a PSA level of less than 15 ng/mL, a clinical/radiological T stage of $\leq$ T2b, and an international society of pathology (ISUP) grade of 2-3. csPCa was defined as an ISUP grade of ≥ 2, extra capsular extension > 0.5 mm, or seminal vesicle involvement in the final histopathology. They

Figure 5 A 73-year-old patient presenting with a PSA level of 4.29 ng/ml underwent a biopsy, which revealed chronic granulomatous inflammation in prostate tissue. Over a 3-month follow-up period, PSA levels exhibited fluctuations within the range of 3.52 to 5.39 ng/ml, indicating the likelihood of benign lesions. Evaluation via ^{68}Ga-PSMA-617 PET/CT (A) indicated no substantial change in ^{68}Ga-PSMA-617 uptake within the prostate, with an SUVmax of 3.0, consistent with benign prostatic lesions. Magnetic resonance imaging with multiparametric sequences (mpMRI) revealed no discernible abnormal signal on T2-weighted imaging (B). However, diffusion-weighted imaging (DWI) (C) detected a focal abnormal signal in the central region of the right side of the prostate (indicated by the arrow), suggesting the possibility of prostate cancer (PCa). Notably, this finding did not align with the pathological results obtained. Reprinted under the terms of the Creative Commons CC BY license from.[59]

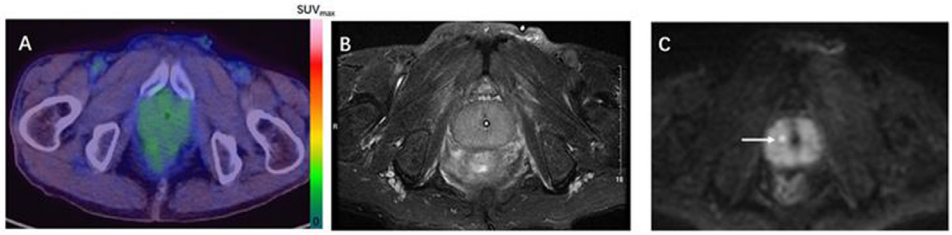
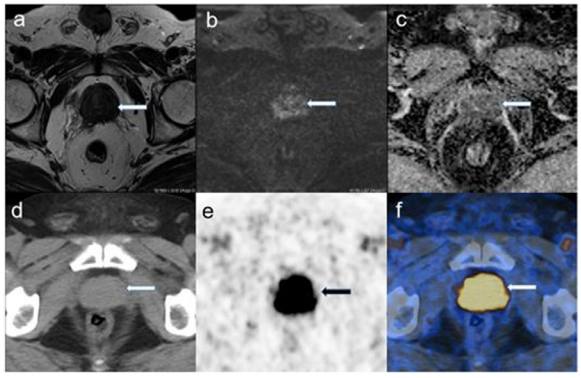


Figure 6 High-risk PCa with negative findings on multiparametric MRI (mpMRI) and positive results on ^{68}Ga-PSMA PET/CT. This case involves a 69-year-old patient with a serum PSA level of 15.4 ng/ml and a Gleason Score of 5 + 5. The pelvic MRI scans, including T2-weighted imaging (A) and b-value 1500 diffusion-weighted imaging (B), do not reveal any significant lesions within the prostate gland. However, the ^{68}Ga-PSMA PET/CT (D-F) exhibits intense tracer uptake, highly suggestive of a positive diagnosis, as indicated by the arrow in images (E and F). This disparity between mpMRI and ^{68}Ga-PSMA PET/CT findings underscores the value of the latter in detecting high-risk prostate cancer. Reprinted under the terms of a Creative Commons Attribution 4.0 International License from.[104]



evaluated the diagnostic accuracy of mpMRI, systematic biopsies, and PSMA-PET (both separately and in combination) for identifying csPCa using a 4-quadrant prostate model, employing receiver-operating characteristic analysis and 2 × 2 contingency analysis. Furthermore, they determined whether these diagnostic tools correctly identified patients suitable for hemi-ablative FT. In total, they analyzed 552 prostate quadrants, with 272 (49%) containing csPCa upon final histopathology. The AUC, sensitivity, specificity, PPV, and NPV for csPCa were 0.79, 75%, 83%, 81%, and 77% for combined mpMRI and systematic biopsies. These values improved when PSMA-PET was added, with an AUC of 0.84, and sensitivity, specificity, PPV, and NPV of 87%, 80%, 81%, and 86%, respectively ($P < .001$). Notably, in final histopathology, 46 out of 138 (33%) patients were deemed unsuitable for hemi-ablative FT. The inclusion of PSMA-PET accurately identified 26 out of 46 (57%) of these unsuitable patients, with only 4 out of 138 (3%) false-positive exclusions. Consequently, the addition of PSMA-PET to the standard diagnostic workup involving mpMRI and systematic biopsies could enhance the selection process for hemi-ablative FT and help in excluding patients for whom whole-gland treatments might be a more appropriate therapeutic choice (Figures 6–8).

Çelen et al. compared the diagnostic value of PSMA-PET to mpMRI alone and found similar sensitivities (53.94% vs. 76.47%). Interestingly, the specificity of PSMA-PET had higher PPV and

Figure 7 Example of inconsistent evaluations using mpMRI (+) and ^{68}Ga-PSMA PET/CT (-) in the context of low- and intermediate-risk prostate cancer (PCa). This case involves a 59-year-old patient with a serum PSA level of 8.0 ng/ml and a Gleason Score (GS) of 3 + 3. The pelvic MRI scan reveals a lesion in the left transition zone of the prostate gland, as indicated by the arrow in the T2-weighted sequence (A) and the contrast-enhanced T1-weighted sequence (B). The presence of a significant PCa is supported by diffusion restriction in the b 1500 DWI image (C) and the corresponding ADC map (D), both denoted by arrows. However, the ^{68}Ga-PSMA PET/CT scan does not exhibit strong tracer uptake, suggesting a less likely diagnosis of PCa, as shown by the arrow in images (E) and (F). For clarification, the imaging modalities are represented as follows: (A-D) correspond to MRI, while (E, F) represent ^{68}Ga-PSMA PET/CT. Within the MRI category, a displays T2-weighted images, b displays contrast-enhanced T1-weighted images, (C) shows b 1500 DWI, and d illustrates the ADC map. In the ^{68}Ga-PSMA PET/CT category, (E) shows the maximum intensity projection of the PET, and f depicts the fusion of ^{68}Ga-PSMA PET and low-dose CT. Reprinted under the terms of a Creative Commons Attribution 4.0 International License from.[104]

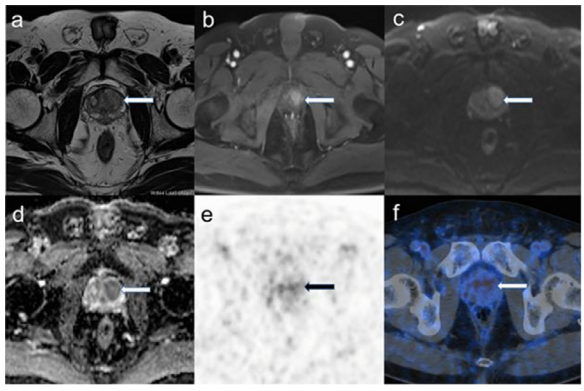
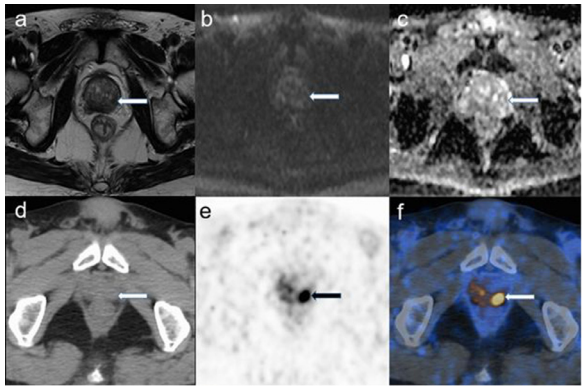


Figure 8 Low- and intermediate-risk prostate cancer (PCa) cases with a PSA level exceeding 9.4 ng/ml and an age surpassing 62.5 years, exhibiting a pattern of negative findings in multiparametric MRI (mpMRI) and positive results in ^{68}Ga-PSMA PET/CT scans. This case involves a 73-year-old patient with a serum PSA level of 17.9 ng/ml and a Gleason Score (GS) of 3 + 4. The pelvic MRI scan, encompassing T2-weighted images (A) and b 1500 DWI (B), does not reveal any notable lesions in the prostate gland. Conversely, in the ^{68}Ga-PSMA PET/CT scan, a robust tracer uptake is evident, indicating a highly likely diagnosis of PCa, as denoted by the arrow in images (E) and (F). To provide a detailed description of the imaging modalities utilized in this case: (A-C) pertain to MRI, with (A) representing T2-weighted images, (B) displaying b 1500 DWI, and (C) illustrating the ADC map. As for ^{68}Ga-PSMA PET/CT imaging, (D) corresponds to low-dose CT, (E) represents the maximum intensity projection of the PET, and (F) showcases the fusion of ^{68}Ga-PSMA PET and low-dose CT. Reprinted under the terms of a Creative Commons Attribution 4.0 International License from.[104]



NPV compared to MRI alone (53.85%, 60%, 46.67 vs. 61.54%, 72.22%, 66.67%, respectively).[76] The current recommendations, which rely on traditional imaging methods, suggest that patients with high-risk features should still undergo treatment even if their imaging results are negative.[85] They identified a group of 47% of patients who experienced biochemical recurrence (BCR), comprising 55 out of 117 cases, despite having negative results from both mpMRI and PSMA PET scans. Among these patients, 14.5% (8 out of 55) were found to have high-risk disease (with over 50% of patients having Gleason 9 scores and 87.5% displaying positive surgical margins) and subsequently received immediate salvage radiotherapy. Remarkably, 62.5% of these patients (5 out of 8) exhibited a positive response to the treatment. However, it is important to note that 85.5% of the patients (47 out of 55) experienced biochemical recurrence without detectable lesions on imaging. Slightly over 50% of this group eventually saw a rise in their PSA levels and required follow-up imaging (25 out of 47). Through the use of paired PSMA and MRI imaging, it was possible to determine the type of recurrence in these patients. As a result, they proceeded to salvage radiotherapy for proven local recurrence or received Stereotactic Ablative Radiotherapy (SABR) or systemic treatments for distant recurrences. The incorporation of PSMA PET/CT alongside MRI demonstrated an enhancement in both the overall sensitivity (97% as opposed to 83%, with a *P*-value below .001) and the NPV when compared to MRI alone (91% in comparison to 72%). This translates to a test ratio of 1.27 (with a confidence interval of 1.11 to 1.39), and a *P*-value below .001. Notably, this approach had the potential to spare unnecessary prostate biopsies in 19% of cases, particularly in 38% of those with PI-RADS 2/3.[86]

While PET/MRI has its benefits, such as reduced patient radiation dose and high soft-tissue contrast, there are still limitations such as high cost and quantification of absorbance.[87] Additionally, there are few tools currently available for this technique, so further research is needed to fully assess its efficacy in relation to mpMRI and PSMA PET/CT alone. Before introducing PSMA-PET/CT into routine clinical practice, its cost and impact on outcomes should be examined. Benign diseases, such as prostatitis and prostatic atrophy, have been known to reduce signal on apparent diffusion coefficient (ADC) maps of mpMRI,[88-90] while benign tumors or inflammation can lead to false positives on non-prostatic cases for PSMA-PET/CT.[91,92] It has been suggested that smaller tumors may have a significant clinical impact on prognosis.[93] Accurate localization of PC lesions is crucial for proper biopsy and treatment planning.[94-96] The low sensitivity of both mpMRI and PSMA-PET/CT underscores the need for new techniques to improve localization. Different histologic criteria for csPCa may influence relevant case reporting, as well as the sensitivity and specificity of the two imaging modalities. GS = 7 (GS = 3 + 4/GS = 4 + 3) is the most commonly used criterion in clinical practice and is associated with a poor prognosis in terms of the risk of progression and survival.[97-101] However, employing more stringent csPC diagnostic criteria may result in higher rates of false positives on both mpMRI and PSMA PET/CT. In our systematic review, we aimed to assess the potential applications of ^{68}Ga-PSMA PET/CT and mpMRI, but the limited number of studies available and the variability in definitions of csPCa made it challenging to determine their true impacts[102] (brief data was shown in Table 2). Consequently, further investigations are warranted to determine whether there are significant differences in the specificity between mpMRI and PSMA PET/CT. Future studies should focus on exploring standardized image interpretation protocols for PSMA-PET/CT, incorporating histopathological scores, and establishing a standardized ring system to minimize methodological discrepancies and improve the overall diagnostic accuracy of these imaging modalities.

Discussion

PCa is a prevalent malignancy that often requires accurate localization for proper biopsy and treatment planning. Noninvasive imaging techniques, such as mpMRI and PSMA-PET, have gained prominence in the diagnosis and management of PCa. This literature review aims to compare the diagnostic accuracy of PSMA-PET with mpMRI and explore differences in specificity and sensitivity. In this study focusing on ^{68}Ga-PSMA PET imaging, we analyzed imaging extending from the base of the skull to the mid-thigh, adhering to guidelines that prioritize characterizing primary and recurrent cancer sites across various stages of the disease. PET/CT acquisition protocols commonly conform to standard imaging procedures defined in the EANM and SNMMI guidelines for ^{68}Ga-PSMA, ensuring consistency with the procedure followed in this study as comprehensively described by Fendler et al.[103]

The findings presented shed light on the potential applications of these imaging modalities and highlight the need for further investigations to improve localization and standardize interpretation protocols. Several studies have compared the detection rates and diagnostic accuracy of PSMA-PET and mpMRI in patients with early-stage PCa. Eiber et al.[49] found that PSMA-PET/MRI exhibited higher sensitivity and AUC compared to PET imaging and mpMRI. Similarly, Giesel et al.[50] observed agreement between tumor attributes detected by PSMA-PET/CT and mpMRI, particularly in cases with a high pre-test rate of large tumors. However, the advantages of PSMA-PET/CT in challenging situations, such as prostatitis or benign prostatic hyperplasia, require further investigation. A retrospective study by Berger et al.[39] demonstrated that PSMA-PET/CT was more sensitive than mpMRI in detecting prostate cancer, suggesting its potential to enhance the accuracy of local mpMRI for lesion detection and characterization.

Specificity and Sensitivity: Studies have reported variations in specificity and sensitivity between PSMA-PET and mpMRI. Afshar-Oromieh et al.[52] observed that PSMA-PET/CT detected a higher number of pelvic lesions compared to mpMRI, highlighting potential disparities in pathological types and imaging modalities. Li et al.[104] investigated the role of PSMA-PET/CT in the initial diagnosis of PCa and reported high sensitivity and specificity rates. However, variations in reader perception, image quality, and diagnostic criteria, such as the PI-RADS, can affect the performance of mpMRI. Further research is needed to evaluate these variations and establish standardized criteria for accurate diagnosis and reporting of results.

Combined Imaging Approaches and Clinical Relevance: Combining PSMA-PET/CT with MRI has shown promising results in improving the sensitivity and negative predictive value for clinically signifi-

cant prostate cancer compared to MRI alone. The PRIMARY study demonstrated the potential of this combined approach in avoiding unnecessary biopsies in PSMA + MRI-negative men. However, most studies have been retrospective and focused on patients already diagnosed with PCa, highlighting the need for prospective studies to understand the role of PSMA-PET/CT in cancer detection. Additionally, the limitations of both imaging modalities, including high cost and quantification challenges, should be considered before introducing PSMA-PET/CT into routine clinical practice.

Standardization and Future Directions: To address methodological discrepancies and improve the overall diagnostic accuracy, future studies should focus on standardized image interpretation protocols for PSMA-PET/CT, incorporating histopathological scores, and establishing a standardized ring system. Furthermore, exploring the role of other imaging modalities, such as PSMA-PET/MRI, in combination with mpMRI, could provide valuable insights into the diagnosis and management of PCa.

Overall, PSMA-PET has shown higher sensitivity in detecting prostate cancer lesions, particularly in challenging cases. However, further investigations are needed to determine the differences in specificity between the two modalities. Standardization of image interpretation protocols and histopathological scoring systems is crucial for improving the diagnostic accuracy of both imaging modalities. Future prospective studies are required to fully understand the role of PSMA-PET/CT and its potential integration with mpMRI in the diagnosis and management of prostate cancer.

In recent years, the emergence of ^{18}F-PSMA PET/CT has marked a significant advancement in routine clinical PET imaging practice. Notably, the superior image quality achievable with ^{18}F-PSMA compared to its ^{68}Ga-PSMA counterpart has garnered considerable attention. This enhancement in image quality is primarily attributed to the lower energy of ^{18}F, contrasting with the higher energy associated with ^{68}Ga-labeled compounds. The impact of such high-energy positron emitters on image quality is substantial, with ^{18}F-PSMA, demonstrating clear superiority in comparative studies.

Moreover, the longer half-life of ^{18}F (~2 hours) in contrast to the shorter half-life of ^{68}Ga (68 minutes) offers distinct advantages, including the feasibility of delayed imaging. This feature not only enhances the sensitivity of lesion detection but also broadens the clinical utility of ^{18}F-PSMA PET/CT. Comparative studies have consistently demonstrated the superior image quality of ^{18}F-PSMA PET/CT and its potential for wider availability due to commercial production .[105,106]

As part of our forthcoming investigations, we aim to explore the efficacy of ^{18}F-PSMA and ^{68}Ga-PSMA PET imaging modalities in detecting the involved lesions in prostate cancer. Recognizing the distinct advantages and pitfalls associated with each imaging modality, we anticipate that this comparative study will provide valuable insights into optimizing diagnostic approaches for prostate cancer management.

Conclusion

This survey demonstrated that ^{68}Ga-PSMA-PET/CT yields favorable outcomes in the initial diagnosis of PCa among patients with clinical and/or suspected PCa. Notably, both methods exhibited similar efficacy in detecting lesion-specific abnormalities. PSMA-PET/CT emerged as a valuable systemic approach surpassing pelvic mpMRI. However, it is crucial to acknowledge the significant heterogeneity observed within our study, necessitating the standardization of image interpretation and histopathology systems to minimize inter-study variations. Further analysis should prioritize assessing the combined diagnostic performance of mpMRI and PSMA-PET/CT imaging modalities. Additionally, the incorporation of MRI can enhance PCa sensitivity and reduce the need for unnecessary biopsies.

Disclosure

The authors declare that they have no competing interests.

CRediT authorship contribution statement

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