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ORIGINAL ARTICLE

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An Australian experience using Tc-PSMA SPECT/CT in the primary diagnosis of prostate cancer and for staging at biochemical recurrence after local therapy

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Abstract

Background: Technetium 99 prostate-specific membrane antigen (Tc-PSMA) single-photon emission computed tomography/computed tomography (SPECT/CT) has the potential to provide greater accessibility globally than gallium 68 (Ga)-PSMA positron emission tomography (PET)/CT but has not been studied as extensively in primary diagnosis, staging, or relapse of prostate cancer (PC). We instituted a novel SPECT/CT reconstruction algorithm using Tc-PSMA and established a database to prospectively accumulate data on all patients referred with PC. This study extracts data on all patients referred over a 3.5-year period with the primary aim of comparing the diagnostic accuracy of Tc-PSMA and multiparametric magnetic resonance imaging (mpMRI) in the primary diagnosis of PC. The secondary aim was to assess the sensitivity of Tc-PSMA in detecting disease with relapse after either radical prostatectomy or primary radiotherapy.

Methods: A total of 425 men referred for primary staging (PS) of PC and 172 men referred with biochemical relapse (BCR) were evaluated. We evaluated diagnostic accuracy and correlations between Tc-PSMA SPECT/CT, magnetic resonance imaging (MRI), prostate biopsy, prostate-specific antigen (PSA), and age in the PS group and positivity rates at different PSA levels in the BCR group.

Results: Taking the biopsy's grade according to the International Society of Urological Pathology protocol as a reference, the sensitivity (true positive rate), specificity (true negative rate), accuracy (positive and negative predictive value), and precision (positive predictive value) for Tc-PSMA in the PS group were 99.7%, 83.3%, 99.4%, and 99.7%, respectively. Comparison rates for MRI in this group were 96.4%, 71.4%, 95.7%, and 99.1%. We found moderate correlations between Tc-PSMA uptake in the prostate and biopsy grade, the presence of metastases, and PSA. In BCR, the Tc-PSMA positive rates were 38.9%, 53.2%, 62.5%, and 84.6% at PSA levels of <0.2, 0.2 to <0.5, 0.5 to <1.0, and > 1.0 ng/mL respectively.

Conclusions: We have shown that Tc-PSMA SPECT/CT using an enhanced reconstruction algorithm has a diagnostic performance similar to Ga-PSMA PET/CT

and mpMRI in an everyday clinical setting. It may have some advantages in cost, sensitivity for primary lesion detection, and the ability for intraoperative localization of lymph nodes.

KEYWORDS
^{99m}Tc-PSMA, biochemical recurrence, prostate cancer, PSMA, SPECT/CT

1 | INTRODUCTION

The overexpression of prostate-specific membrane antigen (PSMA) occurs in prostate carcinoma (PC) and is targeted using a variety of radiolabels. Most commonly PSMA is labeled with gallium 68 (Ga-PSMA) and this technique has been widely studied and validated. PSMA scans now have an established role in the staging of primary and recurrent diseases. While Ga-PSMA has been widely studied for staging and detection of recurrent disease, a more nuanced role in primary diagnosis and choice of management has yet to be established. More recently intraprostatic tumor localization, therapy choices, and assessment of therapy have become increasingly important in the evolving field of personalized medicine. PSMA scanning may have an important clinical role in this process.

Prostate biopsy is the accepted gold standard for diagnosis of prostate cancer (PC) but can cause side effects with high morbidity such as bleeding and infection. Technetium 99 labeled PSMA (Tc-PSMA) in combination with other clinical indicators may contribute to improving the diagnostic accuracy for PC. Tc-PSMA single-photon emission computed tomography/computed tomography (SPECT/CT) has the potential to provide greater accessibility globally than Ga-PSMA positron emission tomography (PET)/CT,[1] has a lower cost and can be used for both radioguided surgeries,[2] and delayed imaging. Low cost-accessibility to such technologies is particularly important for low-to-middle-income countries.[3] However, there are relatively few Tc-PSMA clinical studies compared to hundreds of studies using Ga-PSMA, and almost all in the setting of biochemical relapse (BCR).[4–15]

Based on our own experience with xSPECT/CT bone imaging we developed and optimized a direct quantitative 256 matrix ordered subset conjugate gradient minimization (OSCGM) SPECT/CT soft tissue and bone reconstruction technique for Tc-PSMA. Based on our early emergent data this technique had an effective resolution closer to a Ga-PSMA PET scan compared to a conventional SPECT/CT scan.[16]

To establish the clinical value and accuracy of this approach, we instituted a database for all clinical and scan data on men referred for a Tc-PSMA scan. To prospectively establish the clinical value and accuracy of using Tc-PSMA scans in the PC diagnostic pathway an electronic database captured all clinical data and scan outcome data on men referred for a Tc-PSMA scan at a state-wide center in Australia from February 2017.

The primary aim of this study was to compare the diagnostic accuracy of Tc-PSMA to multiparametric magnetic resonance imaging (mpMRI) in the primary diagnosis of PC. The secondary aims were to assess the sensitivity of Tc-PSMA in detecting recurrent disease postprostatectomy and/or radiotherapy and to compare our results with the existing Ga-PSMA PET/CT literature.

2 | MATERIALS AND METHODS

2.1 | Study cohort

This study was approved by the Human Research Ethics Committee of the University of Canberra. All participants provided their written informed consent to use their deidentified clinical data and scan outcome data for research. Men with suspected or confirmed PC were referred by members of the multidisciplinary team based in an Australian metropolitan state and surrounding region (population 550,000) for a Tc-PSMA scan between February 2017 and August 2021. All men were eligible for inclusion (no participant refused informed consent) and clinical information was prospectively captured in an electronic database. The record linkage brought together documented written consent, the reason for referral, CT chest, abdominal and pelvis scan, age, prostate-specific antigen (PSA), Gleason score, biopsy outcome data, results of mpMRI scan, previous molecular scans (bone, fluorodeoxyglucose, or Ga-PSMA), surgical histopathology, previous treatments, and current management care plan.

Men referred for Tc-PSMA SPECT/CT were divided according to the reason for referral for Tc-PSMA imaging (Figure 1).

- Group 1: Men referred for primary staging (PS) with either a confirmed diagnosis of PC on biopsy or had a high clinical suspicion of PC (two of abnormal mpMRI, abnormally high PSA, or abnormal digital rectal examination).
- Group 2: Men referred for the staging of BCR, defined as a rising PSA (from nadir) after definitive primary treatment (radical prostatectomy with limited lymphadenectomy, and/or radiotherapy, and/or brachytherapy).
- Group 3: Men referred for secondary staging, surveillance of cancer, and to evaluate therapy response, this group was excluded from the current study.

All men in groups 1 and 2 were included in the study. There were no exclusion criteria but as per Figure 1, the data set did not have

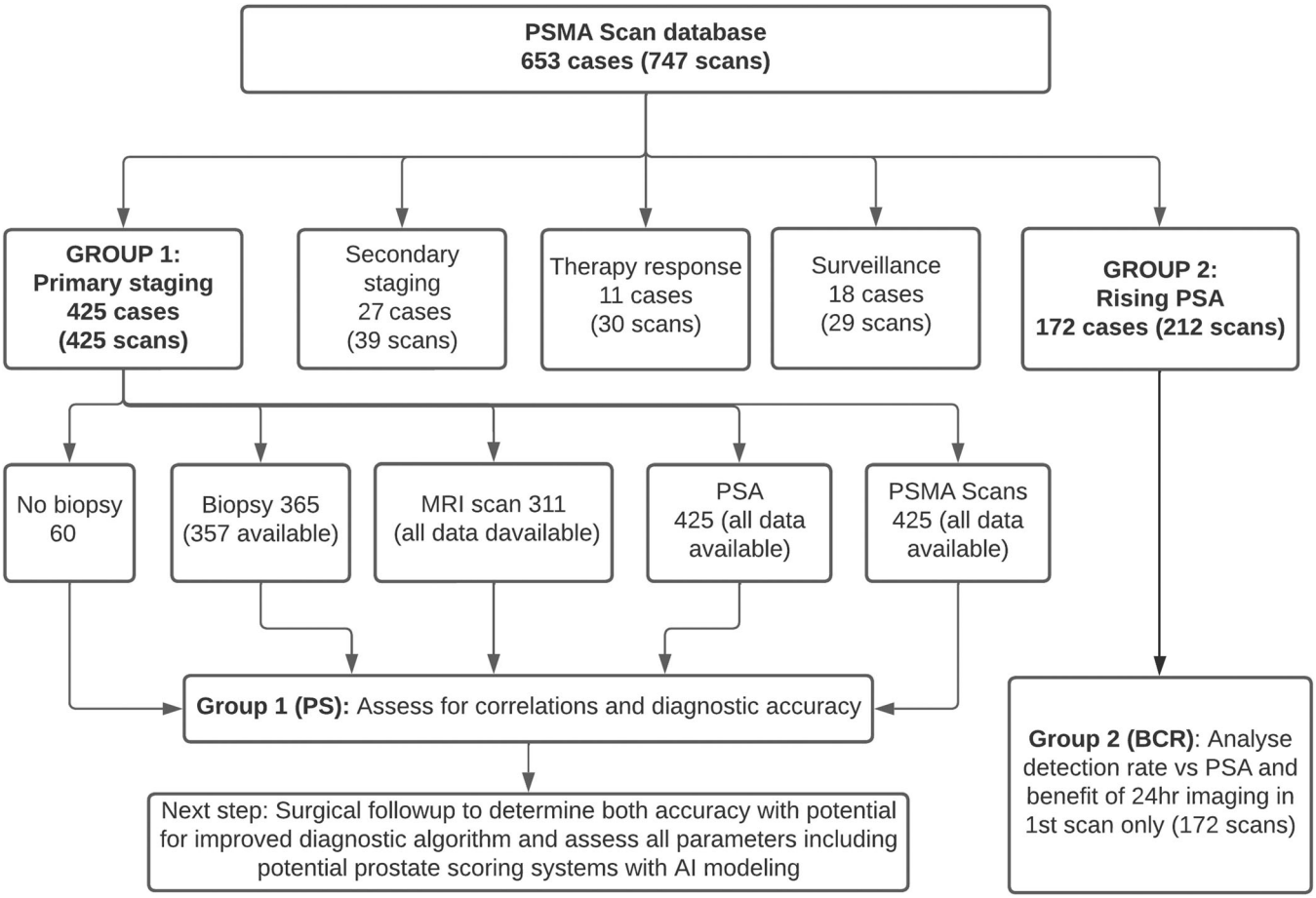

FIGURE 1 Study database showing a breakdown of referral and analysis groups and numbers available for analysis in each subgroup. BCR, biochemical relapse; MRI, magnetic resonance imaging; PS, primary staging; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

complete data for all participants. Only participants with biopsy results were considered for the estimation of Tc-PSMA accuracy in group 1. Only participants with mpMRI results were considered to compare the diagnostic accuracy of Tc-PSMA to mpMRI in the primary diagnosis of PC. Between February 2017 and August 2021, a total of 653 consecutive men enrolled in this study and underwent Tc-PSMA scanning. There was a total of 425 men (425 scans) in group 1, 172 men (212 scans) in group 2, and 56 men (98 scans) in group 3 who were excluded from the analysis, see Figure 1.

2.2 | Tc-PSMA SPECT/CT technique

2.2.1 | Isotope

A 550–800 MBq of Tc-PSMA. Before mid-2019 Tc-PSMA I&S (Technical University Munich) was administered but subsequently, ^{99m}Tc-PSMA (Izotop) was used. Every participant in the study received approval to receive the isotope, granted by the Australian Therapeutics Goods Administration.

2.2.2 | Scan protocols

Four to six hours after the administration of the radiotracer men underwent whole-body planar scans and SPECT/CT scans of the chest, abdomen, and pelvis on a Symbia Intevo system (Siemens Healthcare). Whole body scans (anterior and posterior views) were performed using a low-energy high-resolution collimation matrix size of 256 × 1024 and a scan speed of 15 cm/min. SPECT/CT images were then acquired using low energy high-resolution collimation, a 256 × 256 matrix. A total of 120 projections (60 for each field of view over 360° rotation) with a time of 24 s per projection continuous acquisition. SPECT scans were followed by low-dose CT (110–130 kV, 50–70 mA) using adaptive dose modulation (CAREDose4D; Siemens Healthineers).

SPECT data set reconstruction was performed using Siemens' implementation of an OSCGM algorithm known as xSPECT. We adapted this bone scan reconstruction and applied it to soft tissues which are the primary target for Tc-PSMA. Two reconstruction types were performed —xSPECT and xSPECT Advanced. Each used 60 iterations,1 subset, 10 mm Gaussian filtering and CT-based attenuation correction, and dual-energy window scatter correction. The xSPECT Advanced reconstruction

TABLE 1 Median values for each biopsy grade.

ISUP	pSUV	MTV_{tot}	PSA
No biopsy	4.8	21.1	7.9
1	5.1	36.4	6.3
2	6.4	38.4	7.7
3	8.3	47.4	7.8
4	8.1	63.2	6.9
5	13.6	293	12.0

Abbreviations: ISUP, International Society of Urological Pathology; MTV_{tot}, total molecular tumor volume; PSA, prostate-specific antigen; pSUV, SUV_{max} of the primary prostate lesion; SUV_{max}, maximum standard uptake value.

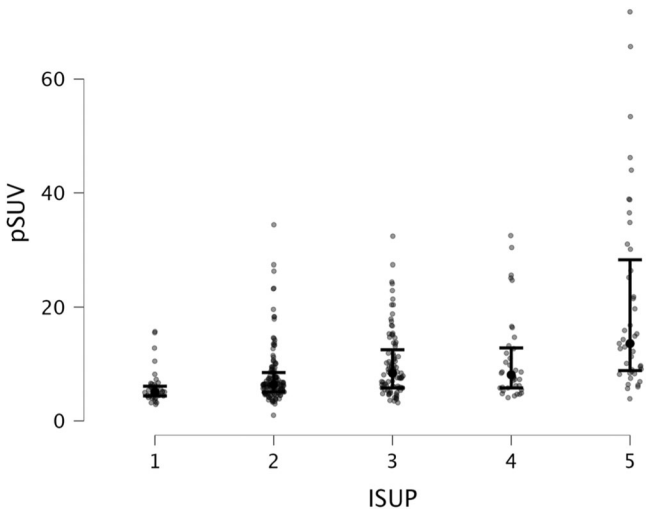

FIGURE 2 Scatterplot of biopsy grade (ISUP) on the *x*-axis versus SUV_{max} of the most avid primary prostate lesion (pSUV) on *y*-axis. Bars show a 25%–75% interquartile range in each group. ISUP, International Society of Urological Pathology; SUV_{max}, maximum standard uptake value.

was used for evaluating soft tissue uptake by using a CT-based zone map of different tissue segments to aid in the delineation of isotope uptake boundaries. A separate xSPECT without a zone map was used for evaluating uptake in bone. CT data were reconstructed with 3 mm slice thicknesses using B30s (soft tissue window) and B50s (bone window) kernels for image display and analysis and B31s kernel used for CT attenuation correction.

In a subset of men, additional SPECT/CT images of the pelvis were obtained at 24 h after administration of the radiotracer. Intravenous Lasix 20 mg was given 20–30 min before acquiring these images. SPECT/CT images were acquired of a single field of view, low energy high-resolution collimation, and a 256 × 256 matrix. A total of 60 projections over 360° with a projection time of 32 s. SPECT data set reconstruction parameters as well as CT acquisition and reconstruction parameters were the same as for the 4–6 h images.

TABLE 2 Pearson correlations.

		R value	Significance	95% lower CI	95% upper CI
MTV	PSA	0.663	***	0.588	0.728
MTV_{tot}	Mets	0.628	***	0.547	0.698
MTV	Mets	0.621	***	0.538	0.692
MTV_{tot}	PSA	0.571	***	0.482	0.649
PSA	Mets	0.476	***	0.399	0.546
ISUP	pSUV	0.445	***	0.357	0.526
ISUP	PIRADS	0.406	***	0.292	0.509
pSUV	Mets	0.392	***	0.307	0.47
ISUP	MTV_{tot}	0.36	***	0.235	0.472
ISUP	MTV	0.333	***	0.206	0.448
pSUV	PSA	0.324	***	0.235	0.407
ISUP	Mets	0.311	***	0.214	0.402
pSUV	PIRADS	0.244	***	0.125	0.357
Age	MTV_{tot}	0.238	***	0.118	0.352
Age	PIRADS	0.21	***	0.091	0.323
ISUP	PSA	0.177	***	0.074	0.275
PIRADS	Mets	0.15	*	0.028	0.266
Age	MTV	0.147	*	0.023	0.266
MTV	plesions	0.143	*	0.02	0.263
MTV_{tot}	PIRADS	0.135		−0.007	0.271
MTV	PIRADS	0.129		−0.013	0.266
ISUP	plesions	0.096		−0.008	0.198
ISUP	Age	0.083		−0.021	0.185
PSA	PIRADS	0.077		−0.045	0.197
MTV_{tot}	plesions	0.057		−0.067	0.18
pSUV	Age	0.055		−0.041	0.15
Age	plesions	0.049		−0.046	0.143
PIRADS	plesions	0.037		−0.085	0.158
Age	Mets	0.015		−0.08	0.11
PSA	plesions	−0.027		−0.122	0.068
Mets	plesions	−0.087		−0.181	0.008
Age	PSA	−0.141	**	−0.233	−0.047
pSUV	plesions	−0.17	***	−0.262	−0.075

Abbreviations: age, patient age; CI, confidence interval; ISUP, International Society of Urological Pathology biopsy score; Mets, presence of metastatic disease; MTV, molecular tumor volume; MTV_{tot}, MTV × SUV_{mean} (all lesions); PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antibody; pSUV, SUV_{max} of the primary prostate lesion; plesions, number (per patient) of prostate lesions; SUV_{max}, maximum standard uptake value.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Almost all men also had a separate diagnostic CT Chest, abdomen, and pelvis. This was undertaken using a 160 slice 0.5 mm detector (Canon Aquilion PRIME), 1 mm and 5 mm axial and 5 mm coronal images were acquired in the arterial phase chest and liver and portal venous phase abdomen and pelvis.

2.2.3 | Image analysis

All scans were analyzed with commercially available software (Syngo.via VB30; Siemens Healthcare), allowing review of SPECT, CT, and fused imaging data. A review of the fused data was done separately for bones and soft tissues. xSPECT advanced reconstruction was fused with the B30 CT subset for review of the soft tissues and the xSPECT with the B50 CT subset for review of the skeletal structures. The visual evaluation was performed by an experienced nuclear medicine physician (Iain Duncan) and radiologists (Kevin Osborn and Jatinder Shekhawat) who were aware of the clinical status but not the magnetic resonance imaging (MRI) or biopsy findings of the men. Direct quantification was used to assess lesions and background uptake. Lesions within the prostate with a weight-adjusted maximum standard uptake value (SUV_{max}) of greater than 3.2 were considered positive, as this has been found to have a 97% sensitivity and 90% specificity for the diagnosis of PC versus benign prostate lesions in an immunohistochemical study using Ga-PSMA.[17] Any uptake in lymph nodes or soft tissues above the background (gluteal muscle or adjacent vessel) was considered abnormal, except in tissues of known physiological uptake. Any uptake in bones above the background (vertebral body) was considered abnormal when no other physiological or pathological explanation was apparent.

TABLE 3 Positivity rate for recurrent disease in biochemical relapse group.

PSA, ng/mL	Negative	Positive	Total	%
<0.2	28	15	43	38.9
0.2 to <0.5	20	20	40	53.2
0.5 to <1.0	9	17	26	62.5
>1.0	10	53	63	84.6
Total	67	105	172	61

Abbreviation: PSA, prostate biopsy.

2.2.4 | Lesion classification

For suspected pathological lesions the SUV_{max} and volume of interest were determined with isocontours set at 40% of the maximum uptake. The SUV_{max} in the prostate was designated SUVp. Additionally, we determined the molecular tumor volume (MTV) for each lesion, a total MTV for each scan (sum of all lesions), and a total activity burden for each man (MTV_{tot}), where MTV_{tot} is calculated as the SUVmean (mean of uptake in all lesions) multiplied by the sum of individual lesion MTV. For the purposes of spatial comparison between biopsy, mpMRI, and Tc-PSMA the prostate was divided into a total of six zones: apex, mid, and base for each lobe. The exact location of the primary lesion within the prostate was stored as a single transverse image within the database. This image capture allows us to retrospectively apply a prostate scoring system such as the one developed by Emmett et al.[18] (not reported in this study).

All men who underwent a mpMRI had scans reported according to the modified Prostate Imaging-Reporting and Data System (PIRADS) by radiologists experienced in prostate MRI[19] and all scans were done on 3-T systems. A mpMRI was considered positive with a PIRADS score of 3 or above. Comparison between Tc-PSMA and both biopsy or MRI scans was undertaken using the sextant model. The comparison was classified as equivalent when the same number and sextant location of lesions and discordant when locations were different. It was noted if more or less lesions were seen on mpMRI, biopsy, or Tc-PSMA but no extended location analysis was undertaken pending surgical outcome data.

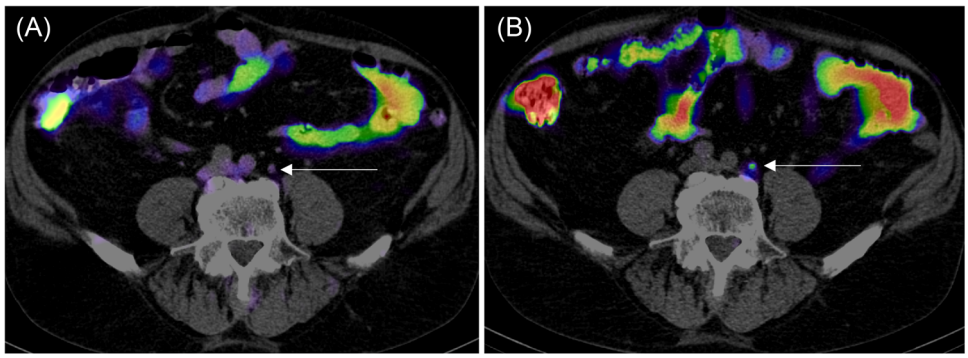

FIGURE 3 Seventy year postradical prostatectomy and radiotherapy for PC ISUP grade 3 with BCR (PSA = 4.1) Tc-PSMA SPECT/CT images. (A) A 5 mm para-aortic lymph node with equivocal PSMA uptake on the 5 h image—degree of uptake no greater than blood pool activity, however (B) shows the 24 h image with an increase in uptake compared to the earlier scan and uptake significantly higher than the background, consistent with a metastatic node. This patient also had larger metastatic nodes in the paraaortic chain that were both positive on 4 and 24 h images. BCR, biochemical relapse; ISUP, International Society of Urological Pathology; PC, prostate cancer; PSA, prostate-specific antigen; SPECT/CT, single-photon emission computed tomography; Tc-PSMA, technetium 99 prostate-specific membrane antigen. [Color figure can be viewed at wileyonlinelibrary.com]

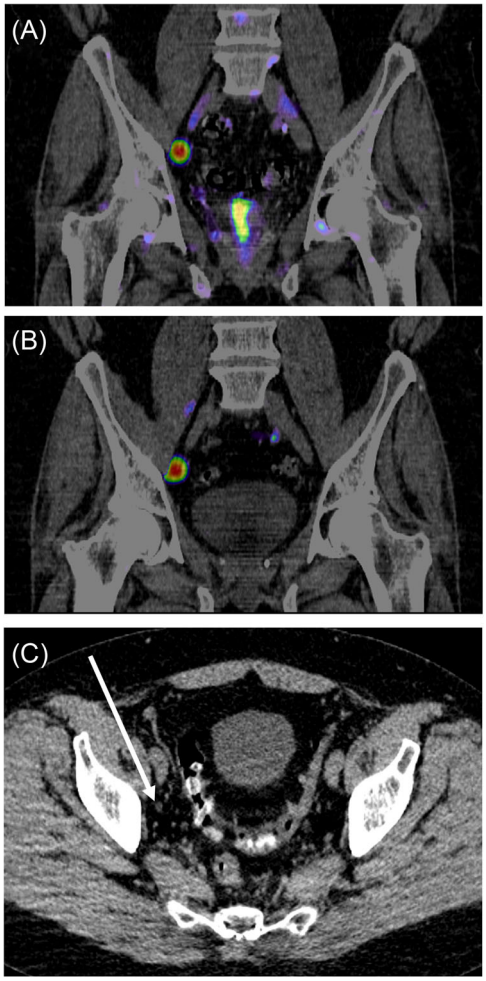

FIGURE 4 Tc-PSMA SPECT/CT in 67-year male with previous radical prostatectomy and postradiotherapy for ISUP grade 4 PC. Biochemical recurrence 3 years posttherapy with PSA = 0.37. (A) Four hours image and (B) 24 h image show a 3 mm right external iliac metastatic lymph node (SUV_{max} = 8). (C) The node (arrow) on the axial CT scan. ISUP, International Society of Urological Pathology; PC, prostate cancer; PSA, prostate-specific antigen; SPECT/CT, single-photon emission computed tomography; SUV_{max}, maximum standard uptake value; Tc-PSMA, technetium 99 prostate-specific membrane antigen. [Color figure can be viewed at wileyonlinelibrary.com]

2.2.5 | Biopsy classification

All men who underwent transperineal or transrectal prostate biopsy under ultrasound guidance were graded according to the International Society of Urological Pathology (ISUP) protocol.[20] Location was according to the sextant model of the prostate.

2.3 | Statistical analysis

Data was prospectively captured in an electronic database, exported into Microsoft Excel, and imported to JASP open-source statistical software (©University of Amsterdam).[21] Data were examined for accuracy of data entry, missing values, and univariate outlines. Traditional exploratory data analysis was initially conducted, and conventional statistical significance was considered at $p < 0.05$. Biopsy's grade was used as a reference to calculate the diagnostic accuracy of Tc-PSMA and mpMRI in the primary staging of PC. A biopsy was considered positive for clinical PC when the ISUP score was 2 or above. A mpMRI was considered positive with a PIRADS score of 3 or above, and Tc-PSMA was considered positive for SUV_{max} greater than 3.2. The diagnostic performance of mpMRI and Tc-PSMA in the PS group was measured in terms of sensitivity (true positive rate), specificity (true negative rate), accuracy (positive and negative predictive value), and precision (positive predictive value). The detection rate in the BCR group was the number of scans with positive findings divided by the total number of scans. Pearson correlation coefficients were used to compare ISUP grade, PSA, pSUV, and MTV_{tot}. The number of complete entries and data available for each group is shown in Figure 1.

3 | RESULTS

A total of 653 men (747 scans) consented to this study and 597 (637 scans) were included (see Figure 1). There were 425 men in group 1 and 172 men in Group 2, of which 151 had a prior prostatectomy. In group 1, 60 had no biopsy before their scan (referred on the basis of clinical PC and/or positive mpMRI), 365 had biopsies, 311 had MRI, and all 425 had PSA data available for analysis.

3.1 | Clinical value and accuracy of Tc-PSMA SPECT/CT (group 1 PS)

Group 1 (PS) had an average age of 69 years with a standard deviation of 13.9 years, and in the biopsy subgroup, there were 12%, 38%, 26%, 10%, and 12% with ISUP grades 1–5, respectively. Two percent had negative biopsies. Fifty-four men (13%) in group 1 had metastatic disease (42 [10%] lymph nodes, 26 [6%] bone, and 7 [2%] visceral or bladder). Of the 365 men who received a biopsy, 357 were available for analysis. One man had a Tc-PSMA scan designated false positive as both biopsy and MRI were negative, one man was false negative (positive biopsy), and five men had true negative (biopsy and MRI also negative). The sensitivity, specificity, accuracy, and precision for Tc-PSMA in the PS group were 99.7%,8 3.3%, 99.4%, and 99.7%, respectively. Comparison rates for MRI in this group were 96.4%, 71.4%, 95.7%, and 99.1% (positive mpMRI considered PIRADS score 3 or above). There were 60 men who did not have a biopsy with an average age of 72.9. Fifty-nine had positive Tc-PSMA and clinical PC, of which 18 had metastatic disease. The single man with a negative Tc-PSMA scan had a PSA of 2.7 ng/mL, negative MRI, and was considered unlikely to have PC.

In the 311 cases comparing Tc-PSMA and MRI scans in the prostate (using the six-zone model), 51% showed highly correlated findings, 41% showed more abnormalities on the Tc-PSMA scan

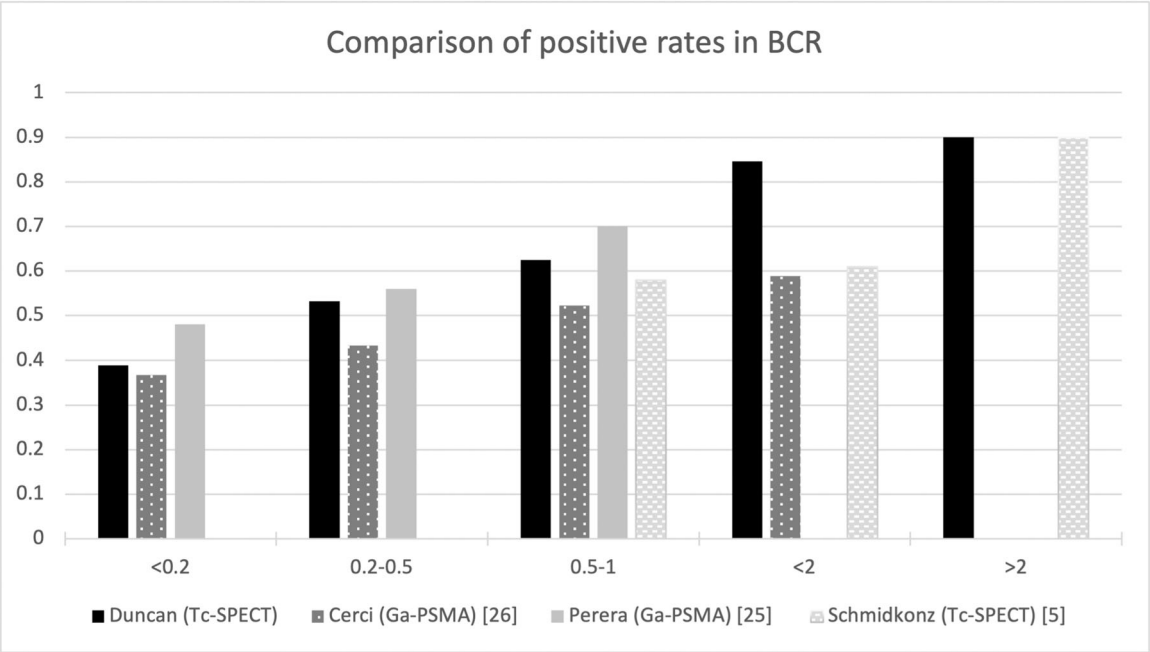

FIGURE 5 Positivity rate versus PSA in biochemical recurrence: Our results compared with three other studies: Cerci et al.[30]; Perera et al.,[31] and Schmidkonz et al.[8] BCR, biochemical relapse; Ga-PSMA, gallium 68 prostate-specific membrane antigen; Tc-SPECT, technetium 99 single-photon emission computed tomography.

compared with MRI, 3% had less abnormalities, and 5% showed discordance of disease location. Of the 357 with biopsy data, 84 (23%) had insufficient anatomic information in the biopsy for comparison with Tc-PSMA scan data using the six-sector model. Of the remaining 273, 200 (73%) showed the same extent of disease, 39 (14%) showed more disease on biopsy, 37 (14%) more disease on Tc-PSMA scan, and in 5 (2%) there was discordance.

Table 1 shows the median values for pSUV, MTV_{tot}, and PSA for each biopsy grade, and Figure 2 shows a scatterplot of pSUV at different ISUP scores. Table 2 shows correlation coefficients between measured variables. The strongest correlation is between both the MTV and MT_{Vtot} and both metastases and PSA. Of note, all Tc-PSMA scan variables (pSUV, MTV, and MTV_{tot}) correlate moderately with biopsy grade (ISUP). There is a weak correlation between PIRADS score on MRI and pSUV on Tc-PSMA and a moderate correlation between PIRADS and ISUP biopsy scores. Correlations between age and other variables were either weak or not statistically significant.

3.2 | Clinical value and accuracy of Tc-PSMA (group 2 BCR)

Group 2 (BCR) included 172 men with an average age of 69 years (SD 15.0). In group 2, 95 had an additional 24-h pelvic scan. Overall, detection rates at different PSA levels are shown in Table 3. The overall positive rate was 61%: 57 (33%) local recurrences, 39 (23%) lymph node spread, and 21 (12%) bone metastases. In the 95 men with 24 h scans, 10 (11%) had scans showing recurrent disease only on the 24 h images (see example in Figure 3). In a further 17 men (18%), the 24 h images aided clinical confirmation of any equivocal lesions or lesions both in a negative and positive manner. Figure 3 shows an example of a small lymph node that became positive at 24 h and both Figures 3 and 4 demonstrate the improved target to background contrast and reduced or absent bladder tracer on the 24-h images.

4 | DISCUSSION

This study set out to determine the clinical value and accuracy of Tc-PSMA in both the primary diagnostic staging and the biochemical recurrence setting. To the best of our knowledge, this is the largest prospective series of patients available which has evaluated the clinical role of Tc-PSMA SPECT/CT in the clinical assessment of PC. A strength of this study was the quality of data captured in the prospective electronic database, which is an important consideration for the reliability of testing diagnostic accuracy.

The role of PSMA scans for the diagnosis of PC is less studied than its role in assessing extraprostatic spread and posttherapy recurrence. This study found that 99% of biopsy-proven PC had a pSUV ≥3.2 in the prostate which is similar to the 97% in the Tc-PSMA study of Schmidkonz et al.[6] and higher than the 94% in the Tc-PSMA study of Goffin et al.[11] The latter study used a conventional SPECT reconstruction and a lesion evaluation using the target to background ratio for evaluation, rather than our preferred OSCGM reconstruction and direct quantification. Like this study, Goffin et al. also found a

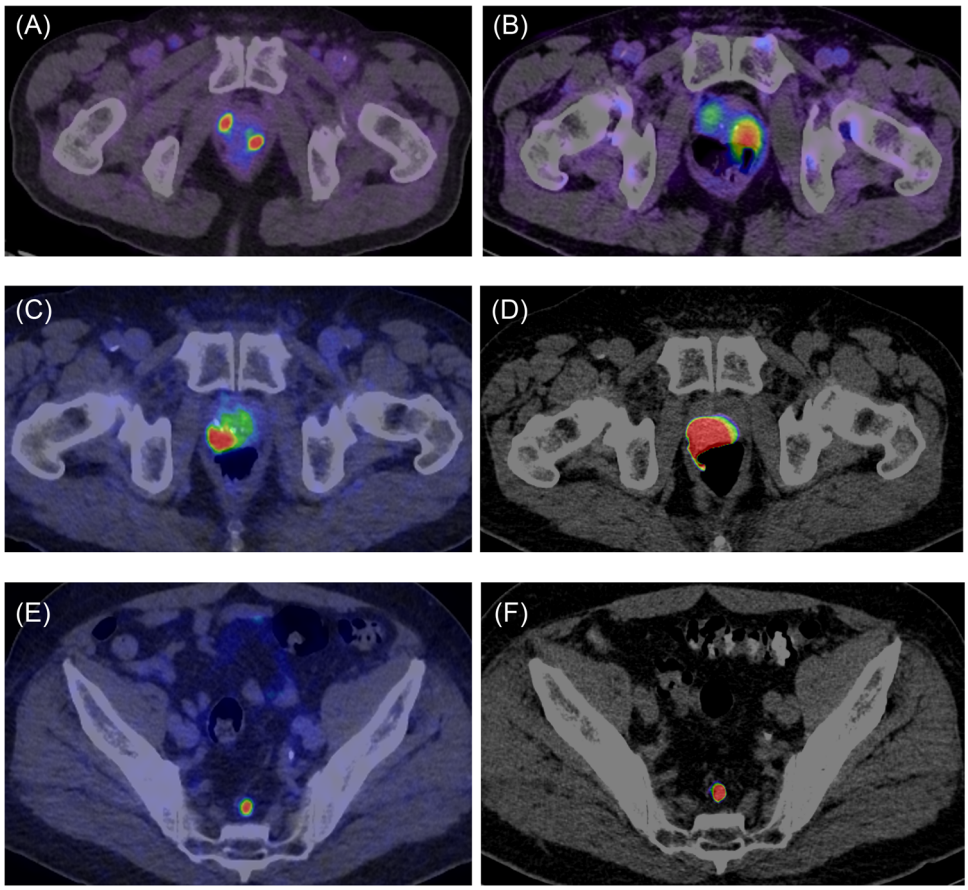

FIGURE 6 Tc-PSMA and Ga-PSMA in the two patients with carcinoma of the prostate. Scans a few weeks apart in each case. Patient 1 had bilateral PC, ISUP 4, and PSA = 13: (A) Ga-PSMA PET/CT and (B) Tc-PSMA SPECT/CT. Patient 2 had a PSA = 23.7 and a PIRADS 5 lesion in the right PZ: (C) Ga-PSMA PET/CT and (D) Tc-PSMA SPECT/CT. The SUV_{max} was significantly higher on the Tc scan (D). This patient also had a solitary metastatic presacral lymph node shown in (E) Ga-PSMA PET/CT and (F) Tc-PSMA SPECT/CT. Ga-PSMA, gallium 68 prostate-specific membrane antigen; ISUP, International Society of Urological Pathology; PET, positron emission tomography; PIRADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen; SPECT/CT, single-photon emission computed tomography/computed tomography; SUV_{max}, maximum standard uptake value; Tc-PSMA, technetium 99-PSMA. [Color figure can be viewed at wileyonlinelibrary.com]

relationship between prostate uptake and biopsy grade.[11] By comparison Roberts et al. found a lower detection rate with Ga-PSMA: 92% of 848 men with biopsy-proven PC had primary lesions with $SUV_{max} \geq 3$.[22] In a meta-analysis of Ga-PSMA, Perera et al. found that for men with Gleason score of ≤7 had a positivity of 72% compared with 80% in men with a Gleason sum of ≥8.[23] In a lesion-based rather than patient-based analysis, Sonni et al. found a PC detection rate of 85% for PSMA PET/CT, 83% for mpMRI and 87% for combined evaluation.[24] A patient-based analysis was not undertaken in that study. We found Tc-PSMA SPECT/CT has a higher sensitivity for the primary tumor when compared with MRI confirming several earlier studies with both Tc-PSMA[11] and Ga-PSMA.[18,24,25]

These findings suggest Tc-PSMA SPECT/CT is more sensitive than Ga-PSMA PET/CT and mpMRI in the detection of a primary lesion in PC. However, a Tc-PSMA study from Albalooshi et al.[5] in comparing Tc-PSMA with Ga-PSMA found 5 of 28 cases of PC negative on Tc-PSMA but positive in Ga-PSMA, which is contrary to our own experience where only 2 of 365 biopsy positive men had negative Tc-PSMA scans, but might be explained by their use of a lower resolution scan (128 × 128 matrix), different reconstruction (not specified in their paper), and lack of direct quantification.

We found a moderately strong relationship between all Tc-PSMA uptake measures in the primary tumor and pSUV and ISUP grade, the likelihood of metastatic disease, and PSA. The relationship between pSUV and biopsy has been noted in both a previous Tc-PSMA study and several Ga-PSMA studies.[6,26] Other studies have shown a relationship between pSUV and histopathology at the surgery for Ga-PSMA.[27] For Ga-PSMA, pSUV has also been (negatively) linked to other outcome measures such as biochemical recurrence-free survival.[22,28] The pSUV has also been found to predict loss of phosphatase and tensin homolog expression status which is a marker for more aggressive disease.[29]

These findings suggest that Tc-PSMA may, like Ga-PSMA, be a valuable and sensitive tool for both the diagnosis and prognosis of prostate carcinoma. We had inadequate data for comparison with participants' cancer of the prostate risk assessment (CAPRA) scores but plan to evaluate this with a series of group 1 patients who have proceeded to prostatectomy.

PSMA scan detection rates in BCR have been widely studied for PET PSMA scans, mostly Ga-PSMA. This study had an overall detection rate of 61% at all PSA levels which compare with 67% and 59% in two meta-analyses of Ga-PSMA PET/CT.[30,31] Our study shows detections rates of 39%, 53%, 63%, and 85% for PSA less than 0.2 ng/mL, between 0.2 and 0.5 ng/mL, between 0.5 and 1.0 ng/mL and PSA > 1 ng/mL, respectively. This compares with the meta-analysis of PSMA PET/CT by Perera et al. which showed rates of 48%, 56%, and 70% at levels of <0.2, 0.2–0.5, and between 0.5 and 1.0 ng/mL, respectively.[31] Comparable Tc-PSMA SPECT/CT studies showed lower detections rates of 58% for PSA < 1 ng/mL, 62% <3 ng/mL, and 90% above that level.[8] Figure 5 shows the sensitivity of our study compared with these two studies and a further meta-analysis of Ga-PSMA PET/CT.[30] Our results lie between the two Ga-PSMA meta-analyses and our sensitivity is slightly higher than Schmidkonz (Tc-PSMA) which might be related to the use of 24 h imaging, a difference in the patient cohort, and or our different reconstruction technique. Our addition of 24 h imaging was based on the previous demonstration of efficient tracer uptake in PCa lesions over time that led to steadily increasing lesion-to-background ratios up to 21 h after injection.[13] While this study was not designed to detect a significant change in the overall detection rate with 24 h imaging our findings showed it had an influence in up to 29% of group 2 scans. The 24 h images improved the target-to-background ratio (Figures 3B and 4B) and make the resultant images closer to a Ga-PSMA PET image (Figure 6) and may have resulted in our improved detection rates in BCR compared with earlier Tc-PSMA-based studies. Of note, delayed imaging of Ga-PSMA PET/CT from 1 to 1.5 h may also have the potential to increase the detection of recurrent PC.[32,33]

Despite SPECT/CT being considered a modality with poorer spatial resolution than PET/CT, this study has shown equivalent detection rates in BCR and possibly higher sensitivity for primary diagnosis than PET/CT. Figure 6 shows examples from men who have had both Ga-PSMA PET/CT and Tc-PSMA SPECT/CT within a few weeks of each other. Factors that might account for a similar clinical performance between these different techniques include improved SPECT/CT reconstruction techniques, a high avidity of technetium tracer for prostate carcinoma cells, the longer half-life allowing improved cellular uptake of technetium radiotracer compared to gallium,[13] and possibly local practice factors such as scan interpretation, referral patterns, local technical skill, and experience, and so forth.

The high sensitivity of Tc-PSMA SPECT/CT for PC suggests a possibility of developing a diagnostic algorithm that might help identify clinically significant prostate carcinoma (CSPC) and/or predict ISUP biopsy grade using pSUV, MTV, mpMRI, and PSA before biopsy. This has been suggested by others, most notably Chikatamarla et al.[26] Preliminary work by Emmett et al.[18] using Ga-PSMA looked at scores based on localization in the prostate and intensity of uptake and found a high diagnostic accuracy for CSPC. We are currently evaluating the diagnostic value of Tc-PSMA in the primary diagnosis of CSPC using artificial intelligence with inputs including location, number of lesions of PC in the prostate, pSUV, MTV, MTV_{tot}, MRI, clinical risk strata (i.e., CAPRA score) and PSA. The primary outcome measure will be surgical histopathology in group 1 patients who undergo radical prostatectomy.

5 | CONCLUSION

We have shown that Tc-PSMA SPECT/CT using an enhanced reconstruction algorithm has a diagnostic performance similar to Ga-PSMA PET/CT and mpMRI in an everyday clinical setting. It may have some advantages in cost, sensitivity for primary lesion detection, and the ability for delayed imaging including intraoperative localization of lymph nodes, that will compensate for the lower native resolution of SPECT.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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