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Not All Prostate-Specific Membrane Antigen Imaging Agents Are Created Equal: Diagnostic Accuracy of Ga-68 PSMA-11 PET/CT for Initial and Recurrent Prostate Cancer

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Abstract

Positron emission tomography (PET) radiotracers that target prostate-specific membrane antigen (PSMA), a transmembrane protein overexpressed in prostate cancer (PCa) cells, are highly sensitive and specific for the detection of metastatic PCa. The radioactive PET imaging agent Ga-68 PSMA-11 has demonstrated higher PCa detection rates compared with conventional imaging techniques, leading to its increased use in the diagnosis of PCa. In this review of literature published between February 2015 and December 2022, of 76 studies in >5000 men with PCa, we examined the accuracy and clinical use of Ga-68 PSMA-11 PET for the initial staging of PCa, assessment of biochemical recurrence (BCR), and how this technique may affect the clinical management of PCa. The majority of studies evaluating Ga-68 PSMA-11 PET for primary staging and for BCR demonstrated a sensitivity ≥80% and a specificity ≥90%. Ga-68 PSMA-11 PET led to a change in clinical management in 19% to 52% and 16% to 75% of patients with primary PCa and BCR, respectively. Variations in diagnostic accuracy parameters were observed among studies but were anticipated given differences in patient characteristics (eg, PSA, lesion sizes) and study designs. No serious adverse events were noted with Ga-68 PSMA-11 PET. Overall, Ga-68 PSMA-11 offers high sensitivity, is well tolerated, and can result in clinical management changes for patients with primary PCa and BCR.

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Keywords: Prostate-specific membrane antigen, Prostate cancer, Imaging, Positron emission tomography

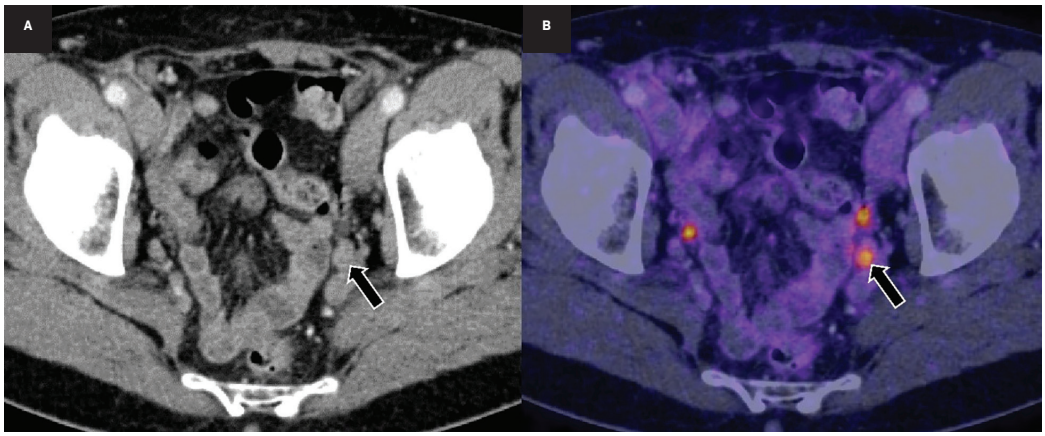

Figure 1. An adult with a history of grade group 2 prostate cancer presented with biochemical recurrence (prostate-specific antigen [PSA] 0.75 ng/mL) 18 months after radical prostatectomy. Contrast-enhanced computed tomography (CT) image (A) and Ga-68 prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT image (B) show a 0.8 x 0.7 cm left internal iliac node (arrow) with increased tracer uptake (SUVmax 7.2). *(Image provided by Dr. Andrei Purysko, Imaging Institute, Cleveland Clinic, Cleveland, Ohio.)*

Introduction

Prostate cancer (PCa) is diagnosed in approximately 1.3 million men each year and represents the second most common cancer in men worldwide.[1] The American Cancer Society estimated 288,300 new cases and 34,700 deaths from PCa in the United States in 2023.[2] The 5-year survival rate is 99% for patients with localized/regional PCa, but only 32% for patients with distant metastasis.[3]

PCa recurrence, defined as an increase in prostate-specific antigen (PSA) levels after treatment, occurs in up to 90% of cases, depending on initial risk categorization and definitive therapy. Biochemical recurrence (BCR) is defined as a PSA level of 0.2 ng/mL followed by a confirmatory PSA level of ≥0.2 ng/mL after radical prostatectomy (RP) and nadir PSA level + 2.0 ng/mL after radiotherapy.[4] Patients with preoperative PSA levels of <2.6 ng/mL, 2.6 to 10 ng/mL, and >10 ng/mL are expected to have recurrence rates of 10%, 20%, and 50%, respectively.[5] Approximately 40% to 90% of patients with high-risk features develop BCR following prostatectomy[3,6] and 30% to 50% experience BCR following radiation therapy.[7] However, multinomial nomograms based on other clinical factors, such as Gleason grade group and clinical stage, provide more accurate estimates of BCR.[8]

Figure 2. Results of literature searches to identify studies evaluating Ga-68 prostate-specific membrane antigen 11 (PSMA-11) for staging primary prostate cancer (PCa) and detecting biochemical recurrence (BCR). *Irrelevant articles included studies of radiotracers that were not Ga-68 PSMA-11, review articles, opinion articles, studies of laboratory results, studies of drug manufacturing process, studies regarding the use of Ga-68 PSMA-11 in other cancers, studies with no comparator or standard of truth, case reports, and nonclinical evaluations. †One study identified from second PubMed search from November 2021 to December 2022. ††Three studies identified from second PubMed search from November 2021 to December 2022.

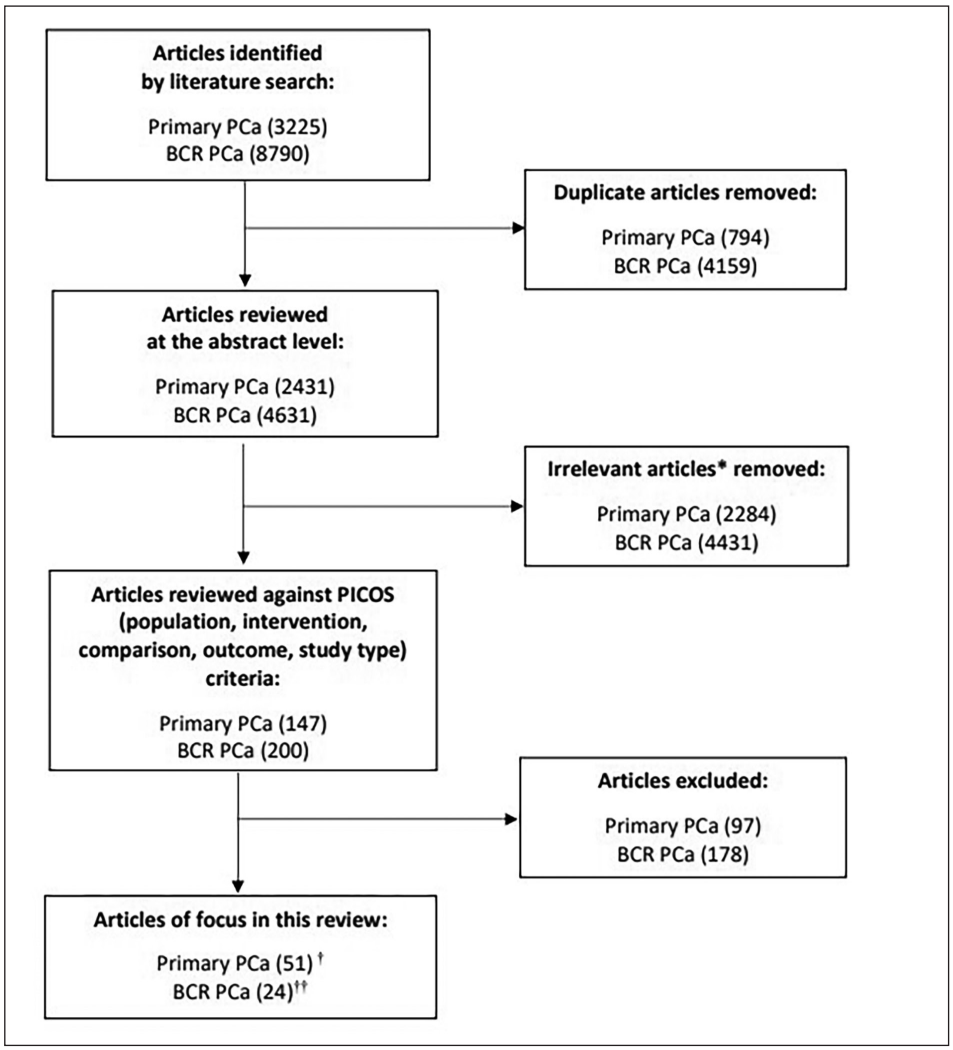

Table 1. Efficacy of Ga-68 PSMA-11 imaging in detecting primary PCa.

STUDY*	N	MODALITY	REGION	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	CHANGE IN CLINICAL MANAGEMENT (%)
Al-Bayati et al, 2018[17]	22	PET, PET/MRI	Prostate	M-1 PET: 81, PET/MRI: 88 M-2 PET: 91, PET/MRI: 94				
Basha et al, 2019[18]	173	PET/CT	Prostate	96				
Berger et al, 2018[19]	48	PET/CT	Prostate	81 (p) 100 (lesion-based)	85 (p)	89 (p)	74 (p)	
Budaus et al, 2016[20]	30	PET/CT	ln	33 (ln)	100	100	69	
Chen et al, 2019[21]	51	PET/CT	Prostate	90	94			
Chen et al, 2020[22]	54	PET/CT/MRI	Prostate	78 (ece) 75 (svi)	94 (ece) 95 (svi)	97 (ece) 82 (svi)	67 (ece) 93 (svi)	19
Demirci et al, 2019[23]	141	PET/CT	Prostate	78	81			
Donato et al, 2019[25]	58	PET/CT	Prostate	93				
Donato et al, 2020[24]	144	PET/CT	Prostate	90	94			
El Hajj et al, 2019[26]	23	PET/CT	Prostate	42	89	74	67	
Fendler et al, 2016[27]	21	PET/CT	Prostate	67 73 (svi)	92 100 (svi)	97 100 (svi)	42 77 (svi)	
Fendler et al, 2017[28]	10	PET/CT	Prostate, ln	93[a]	85[a]			
Ferraro et al, 2020[29]	60	PET/CT	ln	58	98	88	90	
Gao et al, 2019[30]	49	PET/CT	Prostate	76 (pp) 77 (pl)	86 (pp) 88 (pl)			
Gupta et al, 2017[31]	12	PET/CT	ln	67	99	86	96	
Gupta et al, 2018[32]	23	PET/CT	Prostate, ln	63 (epe) 55 (svi) 66 (lnm)	100 (epe) 100 (svi) 99 (lnm)	100 (epe) 100 (svi) 88 (lnm)	36 (epe) 25 (svi) 98 (lnm)	
Herlemann et al, 2016[33]	20	PET/CT	ln	84	82	84	82	
Hicks et al, 2018[12]	32	PET/MRI	Prostate, ln	73[b]	88[b]			
Hinsenveld et al, 2020[34]	53	PET/CT	ln	100	86			
Hirmas et al, 2019[35]	21	PET/CT	Prostate, ln, bone	86 (pro) 92 (pln) 100 (eln) 100 (bm)	100 (pln) 100 (eln) 92 (bm)	100 (pro) 100 (pln) 100 (eln 90 (bm))	89 (pln) 100 (eln) 100 (bm)	52
Hoffman et al, 2017[36]	25	PET/CT	Prostate, ln, bone, lung	84[c]	100[c]	67[c]	100[c]	
Hofman et al, 2020[37]	150	PET/CT	Prostate, ln	85	98			28
Hope et al, 2021[63]	277	PET/CT, PET/MRI	ln	40	95	75	81	
Jena et al, 2018[38]	82	PET/MRI	Prostate, ln	78	86			
Kalapara et al, 2020[39]	205	PET/CT	Prostate	94				
Kopp et al, 2020[40]	90	PET/CT	ln	44	96	70	89	
Liu et al, 2020[41]	31	PET/CT	Prostate	100 (csPCa) 93 (PCa)	68 (csPCa) 75 (PCa)	67 (csPCa)	100 (csPCa)	
Lopci et al, 2018[43]	45	PET	Prostate	82	72			
Lopci et al, 2021[42]	97	PET/CT	Prostate	60	97	92	81	24
Maurer et al, 2016[44]	130	PET/CT, PET/MRI	ln	74	99	95	95	

Table 1 (cont). Efficacy of Ga-68 PSMA-11 imaging in detecting primary PCa.

STUDY*	N	MODALITY	REGION	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	CHANGE IN CLINICAL MANAGEMENT (%)
Muehlematter et al, 2019[45]	40	PET/MRI	Prostate	69 (ece) 55 (svi)	67 (ece) 94 (svi)			
Nandurkar et al, 2019[46]	101	PET/CT	Prostate, ln	47 (svi)	87 (svi)			
Obek et al, 2017[47]	51	PET/CT	Prostate	53	86	62	81	
Pallavi et al, 2020[48]	29	PET/CT	Prostate, ln	86 71 (lnm) 75 (ppe) 60 (svi) 50 (bni)	95			
Park et al, 2018[49]	33	PET/MRI	Prostate	100 (pp) 86 (pl) 50 (pn)	88 (pl) 98 (pn)			
Petersen et al, 2020[50]	20	PET/CT	ln	39	100	100	47	
Rahbar et al, 2016[51]	6	PET/CT	Prostate	92	92	96	85	
Rahman et al, 2019[52]	28	PET/CT	Lymph node				100	
Sahlmann et al, 2016[53]	12	PET/CT	Prostate, lymph node	99a	89a	100a		
Thalgott et al, 2018[54]	73	PET/MRI	Prostate, ln	60 (lnm) 94 (ece) 82 (svi)	100 (lnm) 45 (ece) 80 (svi)	100 (lnm) 82 (ece) 77 (svi)	83 (lnm) 75 (ece) 84 (svi)	
Tulsyan et al, 2017[55]	36	PET/CT	Prostate, ln	49	95	85	88	
van Leeuwen et al, 2017[56]	30	PET/CT	ln	54	99	92	94	
van Leeuwen et al, 2019[57]	140	PET/CT	ln, SVI	53 (lnm) 46 (svi)	88 (lnm) 93 (svi)	71 (lnm) 74 (svi)	76 (lnm) 80 (svi)	
von Klot et al, 2017[58]	21	PET/CT	Prostate	95	75	97	60	
Wong et al, 2018[68]	131	PET/CT	Prostate, ln	66	99			28
Yaxley et al, 2019[64]	208	PET/CT	ln	38 (pb) 24 (ln)	94 (pb) 100 (ln)	68 (pb) 75 (ln)	81 (pb) 96 (ln)	
Yilmaz et al, 2019[59]	24	PET/CT	Prostate, ln	30 (epe) 75 (svi) 33 (bni) 100 (lnm)	93 (epe) 90 (svi) 100 (bni) 100 (lnm)	75 (epe) 60 (svi) 100 (bni) 100 (lnm)	65 (epe) 95 (svi) 82 (bni) 100 (lnm)	
Zang et al, 2017[60]	22	PET/CT	ln	97	100			43
Zhang et al, 2017[61]	42	PET/CT	ln	93	96	93	96	
Zhang et al, 2019[62]	58	PET/CT	Prostate	92	82	89	86	

*Klingenberg et al 2022 is not included in this table, as endpoints recorded in this table were not reported in the study.
Abbreviations: bm, bone metastases; bni, bladder neck invasion; csPCa, clinically significant prostate cancer; CT, computed tomography; ece, extracapsular extension; eln, extrapelvic lymph nodes; epe, extraprostatic extension; ln, lymph node; lnm, lymph node metastasis; M-1, method-1; M-2, method-2; MRI, magnetic resonance imaging; NPV, negative predictive value; p, primary/index localization; pb, patient based; PCa, prostate cancer; pl, per lobe; pln, pelvic lymph node; pn, per node; pp, per patient; ppe, periprostatic lesions; pro, prostate, PET, positron emission tomography; PPV, positive predictive value; PSMA, prostate-specific membrane antigen; svi, seminal vesicle invasion.
[a]N staging results pooled data over patients with primary PCa and biochemical recurrence of PCa.
[b]Median.
[c]Comparison between Gleason scores based on a receiver operating characteristic curve analysis cutoff score.
Collation of publicly available data. Cross-trial comparisons not based on head-to-head studies should be interpreted with caution.

PCa is diagnosed via biopsy of the prostate, with imaging playing an important role in its diagnosis and management. However, staging for higher-risk disease is often performed using conventional imaging with computed tomography (CT) and bone scintigraphy, which have suboptimal sensitivities for detecting metastases for initial staging.[9] CT and Tc-99m methyl diphosphonate bone scintigraphy are routinely used to stage disease in patients with confirmed PCa and to assess suspected PCa recurrence. These methods, however, have limited sensitivity in detecting metastatic disease, particularly when patients have smaller lesions and lower PSA levels.[10]

Recent advances in diagnostic imaging have overcome these limitations. Positron emission

Table 2. Efficacy of Ga-68 PSMA-11 imaging in detecting BCR of PCa.

STUDY	N	POST-RADIATION OR POST-RP	BCR DEFINITION	MODALITY	REGION	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	CHANGE IN CLINICAL MANAGEMENT (%)	MEAN SUV_{MAX}
Abghari-Gerst et al, 2022 [122]	2005	Both	Not defined	PET/CT	Full body			82 (lb) 83 (pb) 72 (ln)			
Abufaraj et al, 2019[69]	65	Post-RP	2 consecutive increases in PSA above 0.2 ng/mL	PET/CT, PET/MRI	Lymph node	72–100	96–100	95–100	93–100		
Afshar-Oromieh et al, 2015[83]	42	Both	Not defined	PET/CT	Prostate, lymph node	77	100	100	91		13.3 ± 14.6
Calais et al, 2019[70]	15	Post-RP	Not defined	PET/CT	Prostate, lymph node	67		100			8.21 ± 4.1
Cerci et al[88]	1004	Either	PSA >0.2 ng/mL after RP, or absolute increase in PSA of 2 ng/mL above nadir after RT	PET/CT	Full body or prostate					57	
Deandreis et al, 2020[89]	17	Both	Not defined	PET/CT	Prostate					35	
Emmett et al, 2019[71]	11	Post-RP	Not defined	PET/CT	Prostate, lymph node	67	100	50	100	46	
Farolfi et al, 2019[90]	119	Post-RP	Not defined	PET/CT	Prostate, lymph node					30	
Fendler et al, 2017[28]	25	Both	Not defined	PET/CT	Prostate, lymph node	93 (ln)	85 (ln)				
Fendler et al, 2019[72]	87	Both	PSA ≥0.2 ng/mL more than 6 weeks after prostatectomy or PSA rise of ≥0.2 above nadir after RT	PET/CT	Prostate, lymph node	92 (pb) 90 (lb)		84 (pb) 84 (lb)			5.1
Fourquet et al, 2021[73]	294	Both	2 consecutive rising PSA values >0.2 ng/mL or PSA rise of ≥0.2 above nadir after RT	PET/CT	Prostate, lymph node	70	70			68	5.3 (p) 5.9 (ln)

tomography (PET) radiotracers that target prostate-specific membrane antigen (PSMA), a transmembrane protein overexpressed in PCa cells, are highly sensitive and specific, with a high detection rate for metastatic PCa lesions. Thus, PSMA radiotracers are recommended for PET imaging of PCa without the prerequisite use of conventional imaging.[11] Ga-68 PSMA-11 is one such radioactive PET imaging agent that has demonstrated higher PCa detection rates compared with conventional imaging techniques, leading to its increased use along with other PET imaging agents.[12] Figure 1 shows an example of a pelvic node in the setting of BCR that was positive on Ga-68 PSMA-11 PET/CT, but negative on CT.

Ga-68, a β+ emitting radionuclide, is one of the most common radioisotopes used in PET scans worldwide.[13] PET imaging using Ga-68 PSMA-11[14] was approved by the US Food and Drug Administration (FDA) as the first PSMA-targeted imaging agent on December 1, 2020, followed by approval of a kit for the preparation of Ga-68 PSMA-11 (TLX591-CDx) on December 17, 2021 for widespread commercial use.[15]

Ga-68 PSMA-11 is approved for the detection of suspected metastasis in the initial staging of patients with PCa and the identification of suspected PCa BCR after treatment.[14] Ga-68 PSMA-11 is also approved in the US to identify and select patients who are candidates for FDA-approved PSMA-directed radioligand therapy. A recent study also reported a significant effect of Ga-68 PSMA-11 on the staging and management of PCa across all relevant clinical scenarios,

Table 2 (cont). Efficacy of Ga-68 PSMA-11 imaging in detecting BCR of PCa.

STUDY	N	POST-RADIATION OR POST-RP	BCR DEFINITION	MODALITY	REGION	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	CHANGE IN CLINICAL MANAGEMENT (%)	MEAN SUV_{MAX}
Grubmuller et al, 2018[82]	117	Post-RP	Not defined	PET/CT, PET/MRI	Prostate, lymph node					75	
Hamed et al, 2019[74]	151	Both	Rising PSA >0.2 ng/mL	PET/CT	Prostate, lymph node	99	100	100	91		
Herlemann et al, 2016[33]	14	Post-RP	Not defined	PET/CT	Lymph node	83	63	86	56		
Jilg et al, 2017[75]	28	Both	Not defined	PET/CT	Lymph node	93 (mr) 81 (sr)	100 (mr) 100 (sr)	100 (mr) 99 (sr)	89 (mr) 93 (sr)		
Kunikowska et al, 2022[91]	108	Either	PSA ≥2 ng/mL after RT	PET/CT	Prostate, torso					16	
Lawhn-Heath et al, 2019[76]	72	Both	Not defined	PET/CT, PET/MRI	Prostate, lymph node	89	31	91	21		
Mandel et al, 2020[77]	23	Post-RP	Not defined	PET/CT, PET/MRI	Lymph node	90 (sb) 76 (fb)	74 (sb) 88 (fb)	71 (sb) 69 (fb)	91 (sb) 91 (fb)		
Morigi et al, 2015[92]	9	Both	Not defined	PET/CT, PET/MRI	Prostate, lymph node					54	
Pfister et al, 2016[78]	28	Both	Not defined	PET/CT	Prostate, lymph node	87	93	76	97		
Radzina et al, 2020[79]	8	Both	Not defined	PET/CT	Prostate, lymph node, bone	64 (lr) 83 (ln) 83 (bm)	74 (lr) 80 (ln) 92 (bm)	58 (lr) 80 (ln) 71 (bm)	78 (lr) 100 (ln) 96 (bm)		
Rauscher et al, 2016[80]	48	Both	PSA >0.2 ng/mL	PET/CT, PET/MRI	Lymph node	78 (lb) 100 (pb)	97 (lb) 50 (pb)	95 (lb) 93 (pb)	88 (lb) 100 (pb)		12.7±10.8
Rousseau et al, 2019[93]	8	Post-RP	Not defined	PET/CT	Prostate					73	
Sahlmann et al, 2016[53]	23	Both	Not defined	PET/CT	Prostate, lymph node	94[a]	99[a]	89[a]	100a		
Zacho et al, 2018[81]	10	Both	Not defined	PET/CT	Prostate	80[b]	98[b]	89[b]	97[b]	44	

Abbreviations: BCR, biochemical recurrence; bm, bone metastasis; CT, computed tomography; fb, field based; lb, lesion based; ln, lymph node; lr, local recurrence; M1, bone metastasis present; mr, main region; MRI, magnetic resonance imaging; NPV, negative predictive value; p, prostate; pb, patient based; PCa, prostate cancer; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; sb, side based; sr, subregion.
[a]Results pooled data over patients with primary PCa and BCR of PCa.
[b]Pessimistic analysis considered equivocal as M1.
Collation of publicly available data. Cross-trial comparisons not based on head-to-head studies should be interpreted with caution.

including patients with PSA below the threshold for BCR, those with known metastatic or advanced castration-resistant disease, and those who have undergone primary treatments other than surgery or radiotherapy.[16]

Herein we review the available literature to assess the sensitivity and specificity of Ga-68 PSMA-11 PET for PCa imaging along with its safety and clinical use for PCa management. Literature searches were conducted using PubMed to identify published studies relevant to the use of Ga-68 PSMA-11 PET for the detection and staging of primary PCa and to detect and localize BCR. Search terms included "primary prostate cancer," "prostate cancer," "PSMA," "PET," "staging," and "biochemically recurrent." The initial search was limited to studies published in English from February 2015 to November 2021. A second search was conducted to identify articles from November 2021 to December 2022 using the same search terms. Overall, 75 studies in >5000 men with PCa were identified that examined the accuracy and clinical use of Ga-68 PSMA-11 PET for the initial staging of PCa and assessing BCR (Figure 2).

Primary staging of PCa using Ga-68 PSMA-11

Table 1 summarizes the results of studies that assessed Ga-68 PSMA-11 for the primary staging of PCa. The majority of studies demonstrated a sensitivity ≥80% and a specificity ≥90%. Sensitivity of Ga-68 PSMA-11 ranged from 30% to 100% for detecting PCa, 24% to 100% for detecting cancer in the lymph nodes, and 84% to 100% for detecting bone metastases; its specificity ranged from 45% to 100% for the prostate, 82% to 100% for the lymph nodes, and 92% to 100% for bone metastases. The positive

predictive value (PPV) ranged from 60% to 100%, and the negative predictive value (NPV) ranged from 25% to 100% in both localized and metastatic PCa, with the majority of these studies reporting values in the upper range.[12, 17-64] Additionally, a prospective study highlighted the prognostic value of 68-Ga PSMA-11 PET/CT versus conventional imaging with 99mTc bone scintigraphy and CT for primary staging in 247 high-risk patients with PCa treated with RP. Primary staging with 68-Ga PSMA-11 PET/CT resulted in a significantly lower biochemical recurrence risk after RP vs conventional imaging, likely due to improved selection of patients for RP.[65]

Initial PCa detection and T staging

In a study evaluating 144 patients (median PSA 8.6 ng/mL), Ga-68 PSMA-11 PET/CT was compared with multiparametric MRI (mpMRI) for the detection of localized PCa, with biopsy histopathology used as a reference standard for the full cohort and RP specimen used as the reference standard in a subset of patients.[24] Ga-68 PSMA-11 showed a higher sensitivity for detecting index lesions (90.1%) compared with mpMRI (83.1%), although this difference was not significant ($p = 0.267$). The median size of index tumor foci missed by mpMRI (1.66 cm^3; interquartile range [IQR], 0.79–2.53 cm^3) was significantly larger than that of tumor foci missed by Ga-68 PSMA-11 PET/CT (0.72 cm^3; IQR, 0.36–1.0 cm^3; $p = 0.034$). Among the 136 patients who had clinically significant PCa detected on biopsy (defined as Gleason score of ≥7), Ga-68 PSMA-11 was significantly more sensitive than mpMRI in detecting cancer within the prostate (95% vs. 86%, respectively; $p = 0.017$), but both imaging methods had high specificities (93% vs. 94%, respectively). Overall, Ga-68 PSMA-11 PET/CT detected significantly more cancer than mpMRI for the entire cohort based on both biopsy ($p = 0.004$) and RP histopathology ($p = 0.020$).

In another study evaluating 54 patients with PCa with a median PSA level of 13.30 ng/mL, Ga-68 PSMA-11 PET/CT and PET/MRI were more sensitive in detecting extracapsular extension (PET/CT, 78%; PET/MRI, 83%) compared with mpMRI (mpMRI, 54%; $p < 0.05$).[22] Ga-68 PSMA-11 PET/CT and PET/MRI also tended to have higher sensitivity for detecting seminal vesicle invasion (75%) compared with mpMRI (67%), but the difference was not statistically significant. The specificity, PPV, and NPV were also not significantly different among these modalities. The timing of biopsy (before vs after Ga-68 PSMA-617 PET/CT) did not seem to affect the outcomes of Ga-68 PSMA PET/CT imaging in high-risk patients with PCa.[66]

Initial PCa N and M staging

In the multicenter proPSMA study, 302 patients were randomly assigned to undergo Ga-68 PSMA-11 PET/CT or conventional imaging (combination of CT and bone scan) for the evaluation of pelvic nodal and distant metastatic disease.[37] Patients were included in the study if they had untreated, biopsy-proven PCa; were being considered for curative-intent treatment; and had ≥1 high-risk criterion (PSA ≥20 ng/mL, International Society of Uropathology grade group 3–5, or clinical stage ≥T3). In these patients, Ga-68 PSMA-11 PET/CT demonstrated a 27% (95% confidence interval [CI], 23%–31%; $p < 0.0001$) absolute greater area under the curve (AUC) for accuracy than conventional imaging (92% vs. 65%, respectively). Conventional imaging, when compared with Ga-68 PSMA-11 PET/CT, had lower sensitivity (38% vs. 85%) and specificity (91% vs. 98%).

In another multicenter trial evaluating 764 patients, Ga-68 PSMA-11 PET/CT or PET/MRI was assessed for its accuracy in detecting pelvic nodal metastases compared with histopathology at the time of RP and pelvic lymph node dissection.[63] Patients were included if they had histopathology-proven PCa, were planning to undergo RP, and had intermediate- to high-risk disease (PSA level >10 ng/mL, T-state ≥T2b, Gleason score >6, or other risk factors). The sensitivity and specificity of Ga-68 PSMA-11 PET for pelvic nodal metastases were 40% and 95%, respectively. The sensitivities from this study were lower than the 59% weighted sensitivity reported in a systematic review, although the sensitivities in the systematic review did range from 23% to 100%.[67] This large variance in sensitivity and specificity for Ga-68 PSMA-11 across studies is likely explained by differences in study design such as the reference standard used, whether data were collected prospectively or retrospectively, and whether patients were recruited consecutively or nonconsecutively.

Effect of Ga-68 PSMA-11 PET On the initial management of PCa

Six studies ($n = 493$) reported a change in clinical management with Ga-68 PSMA-11 PET in 19% to 52% of patients with primary PCa.[22,35,37,42,60,68] Hofman and colleagues[37] reported a significant change in treatment plan in 28% of patients undergoing Ga-68 PSMA-11 PET/CT compared with 15% of patients undergoing conventional imaging ($p = 0.0076$). Similarly, Wong and colleagues[68] evaluated the effect of Ga-68 PSMA-11 PET on disease staging in 131 patients with biopsy-proven PCa. Ga-68 PSMA-11 PET led to a change in PCa stage in 28% of patients, with disease being upstaged in 13% of patients and downstaged in 15% of patients ($p < 0.001$) when compared with the stage assigned using conventional imaging. These findings suggest that Ga-68 PSMA-11 has the potential to provide more accurate staging for metastatic disease, thereby allowing for more risk-appropriate management through the selection of local vs systemic management. Patients may, therefore, receive more appropriate treatment, although the effects of these changes on cancer-specific and overall survival are yet to be determined.

Detection of BCR

Table 2 summarizes studies that evaluated Ga-68 PSMA-11 PET to assess BCR. The majority of studies demonstrate a sensitivity ≥80% and a specificity ≥90%. Sensitivity values ranged from 64% to 99% for the prostate, 72% to 100% for the lymph nodes, and one study reported a sensitivity of 83% for bone metastases. Specificity values ranged from 31% to 100% for the prostate, 50% to 100% for the lymph nodes, and one study reported a specificity of 92% for bone metastases.[28,33,53,69-83] The large variance in sensitivity and specificity can be explained by varying factors across studies, such as areas examined (prostate vs lymph nodes) and the reference standard used (Table 2).

In comparison with conventional imaging, Ga-68 PSMA-11 PET/CT has higher sensitivity, specificity, and accuracy for detecting local recurrence and lymph node metastases, as well as higher detection rates in patients with low PSA levels (≤0.5 ng/mL). In a study of patients who had BCR after definitive PCa treatment with RP (n = 24), radiotherapy (n = 117), or combined treatment (n = 47), patients underwent Ga-68 PSMA-11 PET/CT for the detection of PCa recurrence, with either histologic examination of biopsy sections or 12 months of clinical and imaging follow-up used as the reference standard.[74] Ga-68 PSMA-11 PET/CT was found to have a sensitivity of 99% and a specificity of 100% for detecting PCa recurrence. Receiver operating characteristic analysis yielded an ideal PSA cutoff value of >0.65 ng/mL (AUC = 0.964; 95% CI, 0.736–1.000; $p < 0.0001$), which was associated with a sensitivity of 93% and a specificity of 100% for detecting PCa recurrence with Ga-68 PSMA-11 PET/CT. In patients with lower PSA values (0 to <0.5 ng/mL), the detection rate was 54.2%.

In a study evaluating 66 patients (median PSA 0.23 ng/mL), Ga-68 PSMA-11 PET/MRI was 55% effective in detecting BCR after RP at low PSA levels (≤0.5 ng/mL), including in patients who had previously undergone or were currently undergoing androgen deprivation therapy (ADT).[84] Subgroup analysis of patients with a very low (0 to 0.2 ng/mL) and low PSA (0.2 to 0.5 ng/mL) demonstrated detection rates of 39% and 65%, respectively. Ga-68 PSMA-11 PET/MRI also detected PSMA-positive lesions outside a standard radiotherapy target volume in 39% of patients.

Another study evaluated the accuracy of Ga-68 PSMA-11 PET in detecting lymph node metastases in 65 patients with BCR after RP who were scheduled to undergo salvage lymph node dissection.[69] The salvage lymph node dissection templates included lymph nodes from the right and left pelvis, presacral region, and retroperitoneal region. The median diameter of lymph nodes detected on Ga-68 PSMA-11 PET was 7.2 mm (IQR, 5.3–9 mm), whereas the median diameter of false-negative lymph nodes was 3.4 mm (IQR, 2.1–5.4 mm; $p = 0.01$). Diagnostic accuracy was 99% in the left pelvic region and 95% in the right pelvic, presacral, and retroperitoneal regions. Specificity values were >96% in all regions; sensitivity values were >90% in all but the retroperitoneal region (73%), perhaps because of less dissection of the retroperitoneum during salvage lymph node dissection.

In a study comparing the accuracy of Ga-68 PSMA-11 PET/CT with that of 18F-fluciclovine (a PET radiotracer) PET/CT in detecting BCR after RP in 50 patients, Ga-68 PSMA-11 had a significantly higher detection rate than 18F-fluciclovine (56% vs. 26%, respectively; $p = 0.0026$).[70] Detection rates were significantly higher for Ga-68 PSMA-11 compared with 18F-fluciclovine in the pelvic lymph nodes (30% vs. 8%, respectively; $p = 0.0034$) and in extrapelvic lesions (16% vs. 0%, respectively; $p = 0.0078$). Among the 15 patients in whom lesions were verified by histopathology/biopsy, both 18F-fluciclovine and Ga-68 PSMA-11 had PPVs of 100%. Another retrospective analysis of 37 patients with relapsed PCa showed a significantly higher lesion detection rate with Ga-68 PSMA-11 PET/CT versus standard 18F-fluoromethylcholine PET/CT, especially in patients with low PSA levels.[85]

Finally, in a pilot study of 14 patients with BCR after RP, 43% of the patients had positive PET scans, including 36% with positive Ga-68 PSMA-11 scans and 29% with positive 18F-PSMA-1007 scans.[86] No additional lesions were identified in the prostate fossa by 18F-PSMA-1007 in comparison to Ga-68 PSMA-11. In a study of 102 patients with BCR, 18F-PSMA-1007 was found to have a significantly higher incidence of PSMA-expressing lesions of benign origin than Ga-68 PSMA-11 (245 vs. 52, respectively).[87] Furthermore, the maximum standardized uptake value of these benign lesions was significantly higher ($p < 0.0001$) for 18F-PSMA-1007, indicating a potentially higher source of false positives with this agent than with Ga-68 PSMA-11.

Effect of Ga-68 PSMA-11 PET On the Management of BCR

Ten studies (n = 1697) reported a change in clinical management with Ga-68 PSMA-11 imaging in 16% to 75% of patients with BCR.[71,73,81,82,88-93] In a study of 294 patients, a change in clinical management occurred in 68% of patients, and Ga-68 PSMA-11 PET/CT affected this change in 86% of these patients.[73] Treatment modifications guided by Ga-68 PSMA-11 PET/CT were considered effective in 89% of patients; modifications not guided by Ga-68 PSMA-11 PET/CT were considered effective in 61% of patients ($p < 0.001$). Among patients with BCR following primary curative PCa treatment, delayed imaging with Ga-68 PSMA-11 PET/CT generally led to significantly better uptake and improved contrast, ultimately leading to a change in clinical management for 16% of patients.[91] Moreover, in a study of high-risk patients with PCa, primary staging with Ga-68 PSMA-11 PET/CT reduced BCR versus conventional imaging

techniques (HR = 0.58; p=0.004).[91] Another multicenter prospective trial from 15 countries in 1004 patients with PCa with BCR demonstrated that Ga-68 PSMA-11 PET/CT positivity correlated with Gleason score and PSA level at time of PET scan, PSA doubling time, and radiotherapy as primary treatment. Moreover, treatment modification occurred in 57% of PCa patients with BCR based on the outcomes of Ga-68 PSMA-11 PET/CT imaging.[88]

Safety Profile of Ga-68 PSMA-11

Ga-68 PSMA-11 is a well-tolerated imaging agent. Five studies (n = 880) reported on the safety of Ga-68 PSMA-11 and found no patients experienced serious adverse events, 18 patients reported experiencing mild adverse events (dizziness, nausea, constipation, diarrhea, headache), and one patient reported a fall after imaging that he attributed to furosemide injection, although there were no associated vital sign changes.[12,26,60,72,76] Hofman and colleagues[37] also reported a substantially lower radiation exposure with Ga-68 PSMA-11 PET/CT (8.4 mSv) compared with conventional imaging (combination of CT and bone scan) (19.2 mSv; $p < 0.001$).

Health Economics and Outcomes Research

The cost-effectiveness of Ga-68 PSMA-11 in comparison with conventional imaging has been examined by multiple groups showing that Ga-68 PSMA-11 reduced overall costs because of its increased accuracy in staging, which can obviate the need for unnecessary and costly therapies. In an exploratory analysis evaluating 30 patients over 10 years in Australia, a strategy using Ga-68 PSMA-11 PET/MRI had an average cost of $39,426 and produced an average of 7.48 years of survival, whereas a strategy involving conventional imaging (bone scan and MRI) had an average cost of $44,667 and produced an average of 7.41 years of survival.[94] When the duration of the model was reduced to 5 years, the use of Ga-68 PSMA-11 PET/MRI resulted in cost savings of $3,278 and 0.018 more life-years than conventional imaging. In a cost-effectiveness analysis of the proPSMA study, Ga-68 PSMA-11 PET/CT was found to have a lower estimated cost per scan than the combination of CT and bone scan ($886 vs $1040, respectively).[95] In an intention-to-treat analysis evaluating 83 patients with BCR after RP with or without previous radiotherapy, the percentage of patients receiving appropriate curative radiotherapy instead of palliative ADT was 100% with Ga-68 PSMA-11 PET/CT, 74% with C-11 choline PET/CT, and 33% with CT. A retrospective analysis of 244 patients undergoing PSMA PET/CT for recurrent PCa showed that imaging with Ga-68 PSMA-11 was cost-effective compared with 18F-PSMA-1007.[96] Outcomes research data are yet to be reported from studies in the United States.

18F-PSMA PET/CT

Although Ga-68 PSMA-11 is mainly used for PET imaging of PCa, other 18F ligands are increasingly becoming available. The US FDA recently approved another PSMA-targeted drug, piflufolastat F-18, for imaging of PCa.[97] Similar results were observed with the two agents in other studies in patients with recurrent PCa.[92,98,99] In a head-to-head comparison in 16 patients with intermediate/high-risk PCa, Ga-68 PSMA-11 and 18F-PSMA-1007 PET/CT showed similar performance in identifying dominant prostate lesions.[100] Another study comparing the 18F-PSMA-1007 PET/CT with Ga-68 PSMA-11 PET/CT in 40 treatment-naïve intermediate/high-risk PCa patients showed comparable detection of primary and metastatic lesions.[101]

However, defluorination of 18F radiotracers may influence the accuracy of lesion detection in bones due to unspecified bone uptake,[102] which can alter the choice of treatment and subsequently affect the quality of life of patients.[103] Several recent studies have highlighted that 18F radiotracers are likely to lead to misdiagnosis of bone lesions, with one study reporting nearly 6 times more unspecified bone uptake seen on 18F-PSMA-1007 than with Ga-68 PSMA-11 PET imaging.[87,96,104-109] A retrospective analysis of data from 10 patients with PCa who underwent PET-guided biopsy to confirm observations of indeterminate bone lesions on 18F-PSMA-1007 PET/CT imaging demonstrated that 91% (10/11) of the bone lesions were not metastatic and showed no signs of PSMA expression.[110]

Another study of 243 patients with high-risk or recurrent PCa reported 98 of 267 bone lesions (37%) in 48 (20%) patients with 18F-DCFPyL PET/CT imaging were indeterminate. Of these indeterminate bone lesions, 37 of 98 (38%) were confirmed benign, 42 of 98 (43%) were malignant, and 19 of 98 (19%) remained equivocal at the lesion level. At the patient level, 24 of 48 (50%) had a benign lesion, 11 of 48 (23%) had a malignant lesion, and 13 of 48 (27%) had equivocal findings.[103]

A retrospective matched-pair comparison of 18F-rhPSMA-7 with 68-Ga PSMA-11 PET/CT in patients with primary or recurrent PCa showed a higher incidence of benign tumors among PSMA-positive lesions reported with18F-rhPSMA-7 versus 68-Ga PSMA-11 (67% [379/566] vs 35% [100/289]).[111]

In addition, a study of 283 patients who had 68-Ga PSMA-11 PET and 409 patients who had 18F-PSMA-1007 PET due to BCR showed that 18F-PSMA-1007 PET resulted in a significantly higher rate of nonspecific bone uptake compared with 68-Ga PSMA-11 PET ($p < 0.001$); however, the rate of bone metastases was not significantly different.[109]

The updated joint European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging

Table 3. Key Ga-68 PSMA-11 imaging guidelines and recommendations*

GUIDELINE	RECOMMENDATION
NCCN Guidelines Version 1.2023[114]	Conventional imaging is no longer a necessary prerequisite to PSMA PET for primary staging or BCR. PSMA PET/CT or PSMA PET/MRI can serve as an equally effective, if not more effective, front-line imaging tool.
SNMMI, ACNM, ACP, ASCO, AUA, ANZSM, EANM Appropriate Use Criteria[115]	**Primary staging:** - Patients with suspected PCa (eg high/increasing PSA levels, abnormal digital rectal examination results): to evaluate for targeted biopsy and detection of intraprostatic tumor (Score 3: PSMA use is rarely appropriate) - Patients with very low, low, and favorable intermediate-risk PCa (Score 2: PSMA use is rarely appropriate) - Newly diagnosed unfavorable intermediate, high-risk, or very high-risk PCa (Score 8: PSMA use is appropriate) - Newly diagnosed unfavorable intermediate, high-risk, or very high-risk PCa with negative/equivocal or oligometastatic disease on conventional imaging (Score 8: PSMA use is appropriate) - Newly diagnosed PCa with widespread metastatic disease on conventional imaging (Score 4: PSMA use may be appropriate) **BCR:** - PSA level persistence or PSA increase from undetectable level after RP (Score 9: PSMA use is appropriate) - PSA increase above nadir after definitive radiotherapy (Score 9: PSMA use is appropriate) - PSA increase after focal therapy of the primary tumor (Score 5: PSMA use may be appropriate)
EANM Standardized Reporting Guidelines v1.0 for PSMA PET[116]	Primary staging: PSMA PET is a suitable replacement for conventional imaging in patients with high risk of nodal involvement; patients at lower risk should be spared by PSMA PET BCR: Perform PSMA PET in any case of proven BCR
Joint EANM and SNMMI Procedure Guideline for Prostate Cancer Imaging: version 1.0[123]	Primary staging: In patients with high-risk disease (Gleason score >7, PSA level >20 ng/mL, clinical stage T2c–3a), Ga-68 PSMA PET/CT can replace abdominopelvic CT for detection of lymph node metastases for local tumor delineation, pelvic MRI cannot be replaced BCR: Ga-68 PSMA PET/CT use is recommended for patients with low PSA level (0.2–10 ng/mL) to identify the site of recurrence and potentially guide salvage therapy
Joint EANM and SNMMI Procedure Guideline for Prostate Cancer Imaging: version 2.0[112]	PSMA-ligand PET should be combined with multiparametric MRI for biopsy guidance

*Note that this table is not comprehensive of all available guidelines.
Abbreviations: ACNM, American College of Nuclear Medicine; ACP, American College of Physicians; ASCO, American Society of Clinical Oncology; AUA, American Urological Association; ANZSM, Australia and New Zealand Society of Nuclear Medicine; BCR, biochemical recurrence; CT, computed tomography; EANM, European Association of Nuclear Medicine; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; SNMMI, Society of Nuclear Medicine and Molecular Imaging.

(SNMMI) procedure guidelines for PCa imaging also note non-specific bone uptake with 18F-rhPSMA-7.3.[112] 18F PET imaging may also lead to higher interobserver variability, as demonstrated by a retrospective study of 584 patients with newly diagnosed PCa. Significantly increased interobserver variability was observed with 18F-PSMA-1007 for bone metastases versus 18F-DCFPyL and Ga-68 PSMA-11 ($p = 0.001$ and $p = 0.03$, respectively), and for overall agreement and locoregional lymph node metastases versus 18F-DCFPyL ($p < 0.001$ and $p = 0.01$, respectively).[113]

Guidelines for PSMA imaging

The updated National Comprehensive Cancer Network guidelines now include guidance regarding the use of Ga-68 PSMA-11.[114] The guidelines state that, because of the increased sensitivity and specificity of PSMA PET tracers for detecting micrometastatic disease at initial staging and in cases of BCR, conventional imaging is no longer considered a necessary prerequisite to PSMA PET, and PSMA PET/CT or PSMA PET/MRI can serve as an equally effective or more effective first-line imaging tool for these patients.[114] The updated joint EANM and SNMMI procedure guidelines for PCa imaging also include the use of Ga-68 PSMA-11 PET/CT and recommend combining PSMA-PET/CT with multiparametric MRI for guiding biopsy for confirmation of PCa.[112] Recently,the Society of Nuclear Medicine and Molecular Imaging, American College of Nuclear Medicine, American Urological Association, Australia and New Zealand Society of Nuclear Medicine, American Society of Clinical Oncology, EANM, and the American College of Physicians worked collaboratively to develop appropriate use criteria for PSMA PET imaging (Table 3).[115] In addition, the EANM criteria, PROMISE criteria, and PSMA-RADS have also been published to streamline the interpretation of PSMA PET imaging.[116]

Discussion

Ga-68 PSMA-11 PET/CT is effective in the initial staging and detection of PCa BCR and has advantages over MRI in the initial local staging of PCa, mainly detection of extraprostatic disease in initial staging and BCR and at low PSA levels (≤0.5 ng/mL); potential for leading to a change in radiotherapy target planning[84]; and cost-effectiveness while reducing the amount of radiation exposure to the patient.[94] Bone lesions are easier to interpret on Ga-68 PSMA-11 compared to 18F-based radiotracer imaging.[87,104,111,112] Ga-68

PSMA-11 is well tolerated, further supporting its potential as the imaging agent of choice in PCa.

Ga-68 PSMA-11 has also been used for confirming primary or recurrent PCa in several studies, demonstrating its diagnostic value in clinical practice. Ga-68 PSMA-11 PET/CT was used in combination with MRI to triage patients for biopsy during initial diagnosis and improved NPV for ruling out clinically significant PCa, thereby reducing the number of unnecessary biopsies.[117] In addition, Ga-68 PSMA-11 PET/CT was useful for guiding metastasis-directed radiotherapy in patients with oligometastatic PCa recurrence, delaying the need for ADT and potentially prolonging BCR-free survival.[118]

In a study of patients with metastatic castration-resistant PCa, Ga-68 PSMA-11 PET provided reliable parameters that could be used to predict response to systemic therapies.[119] 68-Ga PSMA-11 was also used for confirmation of metastatic castration-resistant PCa and identification of appropriate patients for PSMA-based radioligand therapy in the phase 3 VISION trial,[120] and is approved in the US for patient selection for PSMA-directed radioligand therapy. Finally, Ga-68 PSMA-11 PET/CT may also be useful in determining appropriate candidates for RP, as the technique has high PPV and specificity for identifying lymph node metastases and local recurrence.[121]

The main limitation of this review is the heterogeneity of the included studies (varying sample sizes, patients being grouped by differing PSA ranges). Variations in reported diagnostic accuracy parameters were seen as anticipated given differences in patient characteristics (eg, PSA, lesion sizes) and study designs. Also, additional studies are needed to determine the effects of Ga-68 PSMA-11 on cost.

In summary, Ga-68 PSMA-11 PET has a favorable safety profile that affords high accuracy for PCa initial staging and the detection of PCa BCR. Although more studies are needed, its use frequently leads to changes in treatment that may positively affect patient outcomes. With increased access, the use of Ga-68 PSMA-11 is expected to expand and include additional applications.

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