Prostate-Specific Membrane Antigen (PSMA) PET for assessment of primary and recurrent prostate cancer with histopathology as reference standard – a systematic review and meta-analysis

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The authors declare that they have no conflicts of interest that relates to the subject matter of the present review.

Keywords:

Prostate cancer, PSMA PET, histopathology, primary tumor location, lymph node metastases, personalized medicine

Key points:

- A total of 34 studies of PSMA PET in prostate cancer had systematic-sector based histopathology and data for diagnostic accuracy measures.
- PSMA PET showed overall high specificity, but variable sensitivity, to localize known prostate cancer and detect pelvic lymph node metastases.
- Sensitivity for detection of pelvic lymph node metastases is better in the recurrent than in the primary setting

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SYNOPSIS

Prostate-specific membrane antigen (PSMA) PET is a promising diagnostic tool in prostate cancer. The gold standard for detection of prostate tumor and lymph node metastases is histopathology, but variable reference standards are used in the vast literature of PSMA PET. Aim of the present review was to investigate accuracy measures of $^{68}Ga/^{18}F$ labeled PSMA PET tracers in primary and recurrent prostate cancer with systematic sector-based histopathology as reference standard. A systematic literature search was performed and 34 studies were included. Overall, PSMA PET showed high specificity, but variable sensitivity to localize known prostate cancer and detect pelvic lymph node metastases.

BACKGROUND

Prostate cancer is a major health problem. It is one of the most common cancers in males, and world-wide a substantial number of men die from prostate cancer each year.[1,2] Radical prostatectomy and external radiotherapy and/or brachytherapy are standard curative treatment options. However, more than 30% experience disease recurrence with a rising prostate-specific antigen (PSA).[3,4]

A key factor for treatment planning is knowledge of extent of spread and location of disease, thus selecting patients for local treatment options and/or combination with systemic therapy. Conventional imaging with computed tomography (CT) and bone scans is of limited value, particularly in primary and early biochemically recurrent prostate cancer. Multiparametric MRI is increasingly used, yet another promising option of molecular imaging is PET with PSMA-based tracers. The diagnostic principle has been further developed by theranostic medicine into PSMA-based targeted radiotherapy.[5-7]

PSMA is a transmembrane glycoprotein with catalytic properties, named glutamate carboxypeptidase II. It is not specific for prostate cancer but has proven useful as it is highly overexpressed in prostate cancer cells in about 95% of the patients.[8-11] When the ligand binds to the extracellular domain, it is internalized. Hence, the PET tracer accumulates in the cancer cells providing a high tumor-to-background ratio (Fig. 1).[12]

In biochemical recurrence, PSMA PET is included in the European guidelines, [13] and ^{68}Ga-PSMA-11 is currently under review by the Food and Drug Administration (FDA).[14]

The present review aims to investigate accuracy measures of ^{68}Ga- and ^{18}F-labeled PSMA PET tracers for assessment of primary and recurrent prostate cancer with systematic sector-based histopathology as reference standard.

EVIDENCE ACQUISITION

Search strategy

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[15] An information specialist (HS) planned and performed the systematic literature search in MEDLINE (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials – including references from ClinicalTrials.gov, The WHO International Clinical Trials Registry Platform (Wiley), and Scopus (Elsevier). Search terms were discussed in detail with two reviewers (EH, TS) and we searched for a combination of subject headings, where applicable, and text words, including synonyms for PSMA and PSMA PET tracers. In addition, we did a search for various terms for prostate cancer combined with PSMA. The following strategy was used in MEDLINE (Ovid) and adapted to the other databases: ((("glutamate carboxypeptidase II" or "PSMA antigen" or "PSM antigen" or (("folate hydrolase 1" or "FOLH1 protein") adj1 human) or "prostate specific membrane antigen" or "68Ga-PSMA-11" or "68Ga-HBED-CC" or "68Ga-PSMA-HBED-CC" or "Glu-NH-CO-NH-Lys-(Ahx)-((68)Ga(HBED-CC))" or "68Ga-PSMA-617" or "PSMA-617" or "68 Ga-PSMA-I-T" or "68 Ga-PSMA-I and T" or "68 Ga-PSMA-I &T" or "18F-PSMA-1007" or "PSMA-1007" or "18F-DCFPyL" or "2-(3-(1-carboxy-5-((6-fluoropyridine-3-carbonyl)amino)pentyl)ureido)pentanedioic acid" or "18F-DCFBC" or "N-(N-((S)-1,3-Dicarboxypropyl)carbamoyl)-4-(18F)fluorobenzyl-L-cysteine" or "18F-JK-PSMA-7" or "18F-PSMA-11" or CTT1057 or BAY1075553 or 68Ga-THP-PSMA or CTT-54 or "(2RS,4S)-2-[(18)F]Fluoro-4-phosphonomethyl-pentanedioic acid" or "18F-rhPSMA-7").mp.) OR (exp Prostatic Neoplasms/ or (prostat* adj3 (neoplasm* or cancer* or tumo?r* or carcinom*)).mp.) and (FOLH1 protein, human.rn. or Glutamate Carboxypeptidase II/ or PSMA.mp.)) Filters to exclude animal studies were applied in MEDLINE and Embase.

Publication types such as editorials, conference abstracts, reviews, surveys, and letters were excluded. All searches were performed on July 13th 2020. The complete search strategies for all databases can be obtained from the corresponding author. The results from all searches were imported into EndNote and duplicates were removed.

Eligibility criteria

The PICO framework (patient, intervention, comparator, outcome) was used to define the eligibility criteria: The study must consist of prostate cancer patients (P), the patients must have had ^{68}Ga- or ^{18}F-labeled PSMA PET (I), the reference standard (comparator) must be systematic sector-based histopathology (C) and the outcome must be diagnostic performance given as sensitivity and specificity (O). Furthermore, the study must report the sector-based data either as individual 2x2 data or as summary diagnostic accuracy measurements for more than fifteen patients fulfilling all the above-mentioned criteria. In case of studies with mixed clinical settings (primary/recurrence) and anatomical location (prostate tumor location/lymph nodes), each subgroup must fulfill all criteria. Only original articles in English were eligible, accepting Brief Communications with substantial data material provided. Editorials, letters, review articles, comments, conference proceedings and case reports were excluded.

Screening and study selection

Two reviewers independently screened the titles and abstracts (EH, TS) using the Rayyan software,[16] and conflicts were resolved by consensus. The remaining articles assessed for inclusion eligibility were read in full-text and excluded with reasons when appropriate.

Quality assessment

Two reviewers (EH, TS) in consensus used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool to assess the risk of bias in four domains: patient selection, index test, reference standard and reference test timing.[17] For the first three domains applicability concerns were also assessed.

Data extraction

For each selected study the following information was collected:

- Basic study characteristics: authors, year of publication, country, PSMA-tracer, study design (prospective/retrospective), clinical setting (primary/recurrence), and anatomy (prostate/lymph nodes).
- Clinicopathological data: number of patients, age, PSA at time of PSMA PET, Gleason score of primary prostate cancer and pathological T-category (pT).
- Diagnostic accuracy data: number of true-positives (TP), true-negatives (TN), false-positives (FP), and false-negatives (FN) were recorded when available in order to obtain 2x2 contingency tables. Authors of studies that only reported summary diagnostics were contacted by email and asked for additional data.

Data synthesis and analysis

Sensitivity and specificity with 95% confidence intervals (CIs) were calculated from the 2x2 contingency tables for each study using the MedCalc Diagnostic test evaluator calculator,[18] or extracted from studies where 2x2 data were not available. Forest plots were drawn to show the variation and explore heterogeneity for sensitivity and specificity. Studies were assessed for inclusion in the quantitative analyses, performed separately for different

subgroups with respect to clinical setting (primary/recurrent disease) and disease location (prostate gland/lymph nodes). Summarized receiver operating characteristic (SROC) curves were estimated using the Python software (www.python.org), and area under the curve (AUC) was calculated.[19,20]

EVIDENCE SYNTHESIS

Literature search and study selection

A total of 9053 records were retrieved, reduced to 3843 after duplicate removal (Fig. 2).[15] After screening of titles and abstracts 3762 records were excluded. The remaining 81 studies were read in full-text, and 47 studies were excluded. Reasons for exclusion were most often a reference standard inappropriate for the review question or patient-based data only.[21-43] Other reasons for exclusion were insufficient data to extract required accuracy measures,[44-47] too few patients,[48-54] or study objective and design outside scope of the review.[55-67] Finally, a total of 34 studies were included.[68-101]

Study and patient characteristics

The included studies were published during the years 2016-2020 (Table 1). Patient populations originated world-wide, the majority from Germany. All but two studies used ^{68}Ga-labeled PSMA PET tracers. The imaging modality was PET/CT in all but five studies, which used either PET/MRI[75,82,91] or mixed PET/CT and PET/MRI.[86,89] There were 26 studies in primary prostate cancer (1083 patients), and 8 studies (256 patients) in biochemically recurrent prostate cancer. Patient and tumor characteristics are outlined in Tables 2A - C. Median PSA was 6.1 - 55.9 ng/mL in the primary setting, and median 0.8 - 2.4 ng/mL in biochemically recurrent prostate cancer (mean PSA 3.9 ng/mL in one study).

Quality assessment

Table 3 outlines the results of assessment according to the QUADAS-2 tool. Most studies had low risk of bias and low applicability concerns with regard to patient selection, index test and

reference standard. A substantial number of studies did not report time from PET to surgery, thus the flow and timing remained unclear.

Prostate tumor location

A total of 12 included studies assessed tumor location within the prostate gland. The 2x2 contingency data are outlined in Table 4A. Most studies used multiple sectors of whole-mount prostatectomy specimens, whereas three studies used lobe-based data.[73,91,99] One study was pre-diagnostic, in men with suspected prostate cancer and previous negative biopsies.[87] Sensitivity ranged from 42 to 98%, and specificity from 71 to 99% (Fig. 3A).

The presence of extra-prostatic extension (EPE) was reported in one study using merged data from four different PET readers.[90] Sensitivity was limited (47%), and specificity was high (90%). Four studies reported data on seminal vesicle infiltration (SVI). The sensitivity for SVI detection was variable (47-75%), and the specificity was high (81-100%).[79, 90, 99,100]

Primary lymph node metastases

A total of 13 included studies assessed regional lymph node metastases in primary prostate cancer. The 2x2 contingency data are outlined in Table 4B. Data were reported either per-side,[78,79,81,91] for multiple-sectors,[72,85,86,89,92,97] or per-node (many).[71,98,99] Sensitivity ranged from 15 to 96%, and specificity from 88 to 100% (Fig. 3B). Studies reported size of true PET positive lymph node metastases to be larger (median 4.0 - 13.6 mm) than false PET negative lymph node metastases (median 2.5 -5.0 mm).[71,72,86,92,97,98]

Recurrent lymph nodes metastases

A total of 8 included studies assessed regional lymph node metastases in biochemically recurrent prostate cancer after curative intended therapy. The 2x2 contingency data are outlined in Table 4B. Sensitivity ranged from 32 - 95%, specificity from 88 - 100% (Fig. 3C). Studies reported size of true PET positive lymph node metastases to be larger (median 5.8 - 10.0 mm) than false PET negative lymph node metastases (median 3.8 - 4.0 mm).[68, 74,83]

Meta-analysis

A total of 32 studies were included in the quantitative synthesis (meta-analysis). Two studies with EPE and/or SVI data only were excluded.[90,100] In one study the mean value for sensitivity/specificity of sub-regions was used.[68] The SROC curves and AUC for localization of primary tumor within the prostate,[69,70,73,75,76,77,87,91,95,96,99] primary lymph node metastases,[71,72,78,79,81,85,86,89,91,92,97,98,101] and recurrent lymph node metastases[68,74,80,83,84,88,93,94] are shown in Fig. 4.

DISCUSSION

This systematic review of PSMA PET in prostate cancer identified 34 studies with systematic sector-based histopathology as reference standard. Fourteen of the studies were in primary prostate, 13 in primary lymph nodes and 8 in recurrent lymph nodes.
Overall, sensitivity was variable whereas specificity was high.

This review revealed two main trends. Firstly, the specificity was consistently higher than the sensitivity. Secondly, the sensitivity for detection of lymph node metastases was better in the recurrent than in the primary setting. The overall high specificity probably reflects high tumor-to-background ratio from high accumulation of tracer in prostate tumors and pelvic lymph node metastases compared to surrounding normal tissue. The PSMA protein is not specific for prostate cancer cells, but the combination of high overexpression in tumor cells and internalization after ligand binding yields high tumor specificity. This is supported by the findings by Calais *et al.* that reported better inter-reader agreement for PSMA than for fluciclovine PET.[102] The uptake value threshold for positive versus negative PET findings is still a challenge for all tracers.

Small amount of tumor cells is challenging to detect by imaging and many of the included studies reported detection rate to be linked to size.[68,71,72,74,83,86,89,92,97,98]
Furthermore, Perera *et al.*[103] found in a large meta-analysis that likelihood of PSMA PET findings increased with PSA level, possibly reflecting larger tumor amounts.
Hanske *et al.*[80] that reported lowest sensitivity for detection of recurrent lymph node metastases also had lowest PSA level.

In a study of 4846 pelvic lymph nodes, Thoeny *et al.* found that the majority of metastases were 3 mm or less at histopathology.[104] With the limited spatial resolution of PET, false negatives are unavoidable. Another source of false negatives is tumors with low PSMA expression (5-10% of prostate cancer patients).[8,9] Clinical parameters that may contribute to the variable sensitivity of PSMA PET within the prostate gland are T-category that often reflects tumor size, and Gleason grade (aggressiveness). The two studies with lowest sensitivity, El Haij *et al.* and Rhee *et al.*, had the highest percentage of T2-stage tumors, ≥65%.[76,95] Rhee *et al.* also had high percentage of low-grade cancers. Information of EPE and SVI is important in personalized treatment planning. We found one study investigating SVI and EPE and three studies investigating SVI. These studies also showed limited sensitivity and high specificity. The potential of EPE and SVI detection by PSMA PET is probably limited by spatial resolution of PET and short extent of tumor growth beyond the prostate gland. In addition, tracer excretion in the urine may out-signal discrete uptake in the seminal vesicles.

The review revealed that there was consistently higher sensitivity for recurrent lymph node metastases than for primary lymph node metastases. We can only speculate why. Based on our findings as discussed above, the amount of tumor and the aggressiveness of the tumor seem to influence the sensitivity/specificity. In terms of tumor biology, it is possibly the more aggressive tumors that recur as lymph node metastases. This could contribute to higher PSMA PET tracer uptake and better sensitivity. Furthermore, it might be that recurrent lymph node metastases are larger than the primary lymph nodes. However, this is not supported by the studies in this review that revealed similar wide and largely overlapping range for both settings (see Results primary and recurrent lymph nodes).

Distant metastases (M+) and local relapse in biochemically recurrent prostate cancer are not assessed by the present review, because systematic sector-based histopathology is not feasible and targeted biopsies cannot provide false negatives. The clinical usefulness of PSMA PET in these clinical settings therefore cannot be assessed by sensitivity/specificity. Clinical outcome measured as time to progression, time to systemic treatment and/or survival is needed. There is a concern among clinicians to use new diagnostic tools when impact on patient outcome is unknown.[105] The arising use of PSMA-based radionuclide therapy must also be evaluated in controlled studies with clinical end-points, e.g. the ongoing VISION study.[14,106]

In many centers PSMA PET/CT has replaced choline PET/CT, as is reflected by the literature.[107] Also, ^{18}F-fluciclovine PET/CT has demonstrated superiority compared to choline PET/CT.[108] In comparison to PSMA PET there is limited evidence of ^{18}F-fluciclovine PET/CT.[109] All but two of the included studies used ^{68}Ga-PSMA. Due to its physical properties with longer half-life and shorter positron travelling distance, ^{18}F-labeled PSMA may improve detection of smaller lesions compared to ^{68}Ga-labeled PSMA. Within the criteria for our literature there were no studies comparing ^{68}Ga- and ^{18}F-PSMA. Future ^{18}F-PSMA studies are awaited.

In conclusion, PSMA PET in prostate cancer has overall high specificity, but variable sensitivity, to localize known prostate cancer and detect pelvic lymph node metastases. Sensitivity seems to depend on tumor size and aggressiveness.

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Legends for figures

Fig. 1 Maximum intensity projection (MIP) image of ^{18}F-PSMA-1007 PET and fused PET/CT images for three different patients. One patient with a large primary prostate cancer and pelvic lymph node metastases (A,D,G). Another patient with biochemically recurrent prostate cancer (PSA 2.3) and disease located to the prostate bed only (B,E,H). A third patient, also with biochemically recurrent disease (PSA 21), but with extensive bone metastases (C,F,I).

Fig. 2 PRISMA flow-diagram showing the selection of studies.

Fig. 3A-C Forest plots of sensitivity and specificity (mean values, 95%CI) for localization of primary prostate cancer tumor, EPE and SVI (A), primary lymph node metastases (B) and recurrent lymph node metastases (C).

Fig. 4 Summarized receiver operating characteristic (SROC) curves for localization of primary tumor within the prostate (upper), primary lymph node metastases (middle), and recurrent lymph node metastases (lower).

Table 1 Study characteristics

Author (year)	Journal	Country	PET tracer	Design	Setting	Anatomy
Abufaraj *et al.* (2019)	EJNMMI	Austria	^{68}Ga-PSMA-11	Prospective	Recurrence	Nodes
Berger *et al.* (2018)	Prostate Cancer Prostatic Dis	Australia	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Prostate
Bettermann *et al.* (2019)	Radiat Oncol	Germany	^{68}Ga-PSMA-11	Prospective	Primary	Prostate
Budäus *et al.* (2016)	Eur Urol	Germany	^{68}Ga-PSMA	Retrospective	Primary	Nodes
Cytawa *et al.* (2020)	EJNMMI	Germany	^{68}Ga-PSMA I&T	Retrospective	Primary	Nodes
Dekalo *et al.* (2019)	Urol Oncol-Semin Ori	Israel	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Prostate
Dundee *et al.* (2018)	Urology	Australia	^{68}Ga-PSMA-HBED-CC	Prospective	Recurrence	Nodes
Eiber *et al.* (2016)[*]	Eur Urol	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Prostate
El Hajj *et al.* (2019)	Medicine	Lebanon	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate
Fendler *et al.* (2016)	JNM	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Prostate
Gorin *et al.* (2018)	J Urol	USA	^{18}F-DCFPyL	Prospective	Primary	Nodes
Gupta *et al.* (2018)	World J Nucl Med	India	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate + nodes
Hanske *et al.* (2019)	Urol Oncol-Semin Ori	Germany	^{68}Ga-PSMA	Retrospective	Recurrence	Nodes
Herlemann *et al.* (2016)[&]	Eur Urol	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Nodes
Hicks *et al.* (2018)[*]	Radiology	USA	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate
Jilg *et al.* (2017)	Theranostics	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Recurrence	Nodes
Jilg *et al.* (2020)	EJNMMI Research	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Recurrence	Nodes
Kopp *et al.* (2020)	World J Urol	Germany	^{68}Ga-PSMA	Retrospective	Primary	Nodes
Kroenke *et al.* (2020)[#]	JNM	Germany	^{18}F-rhPSMA-7	Retrospective	Primary	Nodes
Liu *et al.* (2020)	JNM	China	^{68}Ga-PSMA-617	Prospective	Pre-diagnostic	Prostate
Mandel *et al.* (2020)	Eur Urol Focus	Germany	^{68}Ga-PSMA	Retrospective	Recurrence	Nodes
Maurer *et al.* (2016)[#]	J Urol	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Primary	Nodes
Muhlematter *et al.* (2019)	Radiology	Switzerland	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate
Park *et al.* (2018)[*]	Radiology	USA	^{68}Ga-PSMA-11	Prospective	Primary	Prostate + nodes
Petersen *et al.* (2020)	World J Urol	Denmark	^{68}Ga-PSMA-11	Prospective	Primary	Nodes
Pfister *et al.* (2016)	EJNMMI	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Recurrence	Nodes
Rauscher *et al.* (2016)	JNM	Germany	^{68}Ga-PSMA-HBED-CC	Retrospective	Recurrence	Nodes

Rhee *et al.* (2016)	J Urol	Australia	^{68}Ga-PSMA-HBED-CC	Prospective	Primary	Prostate
Scheltema *et al.* (2019)	BJUI	The Netherlands	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate
van Kalmthout *et al.* (2020)	J Urol	The Netherlands	^{68}Ga-PSMA-11	Prospective	Primary	Nodes
van Leuween *et al.* (2017)	BJUI	Australia	^{68}Ga-PSMA-HBED-CC	Prospective	Primary	Nodes
von Klot *et al.* (2017)	Nucl Med Mol Imaging	Germany	^{68}Ga-PSMA I&T	Retrospective	Primary	Prostate
Yilmaz *et al*. (2019)	The Prostate	Turkey	^{68}Ga-PSMA-11	Retrospective	Primary	Prostate
Zhang *et al.* (2017)	J Transl Med	China	^{68}Ga-PSMA-11	Retrospective	Primary	Nodes

PET/CT was used unless otherwise notified. [*]PET/MRI. [#]Mixed PET/CT and PET/MRI. [&]Patients with recurrent disease were excluded due to number of patients <15.

Table 2A Patient characteristics: primary prostate tumor

Author (year)	Patients	Age (years)		PSA (ng/mL)		Gleason score (%)	pT category (%)
		Median	Range	Median	Range		
Berger *et al.* (2018)	50[*]	65	5.6[#]	10.6	8.1[#]	6 (2), 7a (36), 7b (30), 8 (12), 9 (20)	T2 (46), T3a (36) T3b (18)
Bettermann *et al.* (2019)	17	67	48-76	17.4	6.1-218	7a (35), 7b (29), 8 (18), 9 (18)	T2 (41), T3a (29), T3b (29)
Dekalo *et al.* (2019)	59/61[&]	65	7.0[#]	13.0	11.9[#]	7a (37), 7b (36), 8 (17), 9 (10)	T2 (51), T3a (29), T3b (20)
Eiber *et al.* (2016)	53/66[&]	66	62-72[§]	12.0	6.9-18.8[§]	6 (6), 7 (66), 8 (19), 9 (8), 10 (2)	T2 (43), T3a (34), T3b (21) T4 (2)
El Hajj *et al.* (2019)	23	69	8.7[#]	10.8	7.5[#]	7a (26), 7b (48), 8 (13), 9 (9), 10 (4)	T2 (70), T3a (4), T3b (26)
Fendler *et al.* (2016)	21	71	59-80	31.0	3-363	6 (14), 7a (10), 7b (29), 8 (14), 9 (33)	T2 (24), T3a (24), T3b (48), T4 (5)
Gupta *et al.* (2018)	23	66	50-77	36.1	5.5-200	6 (4), 7a (13), 7b (22), 8 (39), 9 (22)	T2 (17), T3a (22), T3b (61)
Hicks *et al.* (2018)	32	68	62-71[§]	13.4	8.4-19.7[§]	7a (6), 7b (56), 8 (3), 9 (28), 10 (6)	T2 (31), T3a (41), T3b (22), T4 (6)
Liu *et al.* (2020)	31	65	53-81	18.0	5.5-49.8	no cancer (52), 6 (10), ≥7a (39)	NR
Muhlematter *et al.* (2019)	40	63	6[#]	8.1	7 -56 [§]	7a (5), 7b (15), 8 (53), 9 (28)	T2 (68), T3a (20), T3b (13)
Park *et al.* (2018)	33	66	55-74	9.6	3.7-34.5	7 (55), 8 (24), 9 (21)	T1c (45), T2 (48), T3a (6)[+]
Rhee *et al.* (2016)	20	62	41-71	6.1	3.5- 45	7a (60), 7b (20), 9 (20)	T2 (65), T3a (20), T3b (15)
Scheltema *et al.* (2019)	54	64	59-6[§]	7.7	4.4-11[§]	7a (41), 7b (59)	T1c (46), T2 (50), T3 (4)[+]
von Klot *et al.* (2017)	21	68	56-77	11.9	1.8-58	6 (10), 7a (48), 7b (19), 8 (14), 9 (10)	T2 (52), T3a (29), T3b (19)
Yilmaz *et al.* (2019)	24	63	49-73	12.0	2.4-32	6 (13), 7a (25), 7b (42), 8 (8), 9 (13)	NR

NR = not reported. [*]Two patients with recurrent disease after definite radiotherapy included. [&]Patients with histology/total number of patients. [#]Standard deviation. [§]Inter-quartile range. [+]Clinical T-category.

Table 2B Patient characteristics: primary lymph nodes

Author (year)	Patients	Age (years)		PSA (ng/mL)		Gleason score (%)*	pT category (%)*
		Median	Range	Median	Range		
Budäus *et al.* (2016)	30	63	44-75	8.8	1.4-376	7a (30), 7b (33), ≥8 (37)	T2 (37), T3a (13), T3b (40) T4 (10)
Cytawa *et al.* (2020)	40/82[&]	67	53-83	11.0	0.7-872	median 7, range 6-10	NR
Gorin *et al.* (2018)	25	61	49-75	9.3	3.6-125.5	7b (20), 8 (8), 9 (72)	T2 (20), T3a (52), T3b (28)
Gupta *et al.* (2018)	23	66	50-77	36.1	5.5 - 200	6 (4), 7a (13), 7b (22), 8 (39), 9 (22)	T2 (17), T3a (22), T3b (61)
Herlemann *et al.* (2016)	20	71	59-80	55.9	3.3-363	6 (10), 7 (40), 8 (15), 9 (35)	T2 (15), T3a (25), T3b (60)
Kopp *et al.* (2020)	90	65	60-71[§]	7.4	5.5-12.5[§]	6 (1), 7a (43), 7b (33), ≥8 (24)	T2 (55), T3a (27), T3b (18)
Kroenke *et al.* (2020)	58	68	48-80	12.2	1.2-81.6	7a (19), 7b (43), 8 (7), 9 (31)	≤T2 (45), T3a (21), ≥T3b (35)
Maurer *et al.* (2016)	130	67	45-84	11.6	0.6-244	median 7, 7-8[§], range 6-10	≤T2 (43), T3a (23), ≥T3b (34)
Park *et al.* (2018)	33	66	55-74	9.6	3.7-34.5	7 (55), 8 (24), 9 (21)	T1c (45), T2 (48), T3a (6)[+]
Petersen *et al.* (2020)	20	71	58-76	12.5	2.8-66.0	7a (10), 7b (30), 8 (15), 9 (45)	T1c (10), T2 (40), T3 (50)[+]
van Kalmthout *et al.* (2020)	97/103[&]	69	53-82	21.8	1.7-298	6 (4), 7a (16), 7b (30), 8 (34), 9 (15), 10(2)	T2 (32), T3a (42), T3b (26)
van Leuween *et al.* (2017)	30	65	60-71[§]	8.1	5.2- 10.1	7b (17), 8 (17), 9 (67)	T2 (30), T3a (43), T3b (27)
Zhang *et al.* (2017)	42	69	55-82	52.3	7.2-348	7a (21), 7b (21), ≥8 (57)	T2 (26), T3a (19), T3b (55)

NR = not reported. [&]Patients with histology/total number of patients. [§]Inter-quartile range. *Gleason score and pT category from the primary tumor. [+]Clinical T-category.

Table 2C Patient characteristics: recurrent lymph nodes

Author (year)	Patients	Age (years)		PSA (ng/mL)		Gleason score (%)*	pT category (%)*
		Median	Range	Median	Range		
Abufaraj *et al.* (2019)	65	65	63 -69§	1.4	0.8 - 2.9§	6 (2), 7a (22), 7b (31), ≥8 (46)	T2 (19), T3a (47), T3b (31)
Dundee *et al.* (2018)	17	66	60-70§	1.6	0.8-2.7§	7a (6), 7b (35), 8 (35), 9 (24)	T2 (24), T3a (41), T3b (35)
Hanske *et al.* (2019)	22/43&	62	55-66§	0.8	0.4-1.7§	≤6 (7), 7a (23), 7b (26), 8 (19), 9 (25)	T2 (30), T3a (28), T3b (42)
Jilg *et al.* (2017)	30	66	52.4-70	1.7	0.1-12-2	7 (40), ≥8 (60)	NR
Jilg *et al.* (2020)	23£	67	52-78	1.8	0.03-56.2	7a (17), 7b (31), 8 (22), 9 (30)	NR
Mandel *et al.* (2020)	23	64¥	NR	3.9¥	NR	NR	NR
Pfister *et al.* (2016)	28	67	46-79	2.4	0.04-8.0	≤7 (57), >7 (32), NR (11)	NR
Rauscher *et al.* (2016)	48	71	66-74§	1.3	0.75-2.6§	median 7, 7-9§	NR

NR = not reported. &Patients with histology/total number of patients. £Two patients with primary prostate cancer included. §Inter-quartile range. ¥Mean. *Gleason score and pT category from the primary tumor.

Table 3 Quality of the included studies using QUADAS-2

Author (year)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abufaraj *et al.* (2019)	Low	Low	Low	Unclear	Low	Low	Low
Berger *et al.* (2018)	Low	Low	Low	Low	Low	Low	Low
Bettermann *et al.* (2019)	Low	Low	Low	Unclear	Low	Low	Low
Budäus *et al.* (2016)	High	Unclear	Unclear	Unclear	Low	Low	Low
Cytawa *et al.* (2020)	Low	Low	Low	Unclear	Low	Low	Low
Dekalo *et al.* (2019)	Low	Low	Unclear	Unclear	Low	Low	Low
Dundee *et al.* (2018)	Low	Low	Low	Unclear	Low	Low	Low
Eiber *et al.* (2016)	Low	Low	Low	Low	Low	Low	Low
El Hajj *et al.* (2019)	Low	Low	Low	Low	Low	Low	Low
Fendler *et al.* (2016)	Low	Low	Low	Low	Low	Low	Low
Gorin *et al.* (2018)	Low	Low	Low	Unclear	Low	Low	Low
Gupta *et al.* (2018)	Low	Low	Unclear	Low	Low	Low	Low
Hanske *et al.* (2019)	High	Unclear	Low	Unclear	Unclear	Low	Low
Herlemann *et al.* (2016)	Low	Low	Unclear	Low	Low	Low	Low
Hicks *et al.* (2018)	Low	Low	Low	Low	Low	Low	Low
Jilg *et al.* (2017)	Low	Low	Low	Low	Low	Low	Low
Jilg *et al.* (2020)	Low	Low	Unclear	Unclear	Low	Low	Unclear
Kopp *et al.* (2020)	Low	Low	Low	Unclear	Low	Low	Low
Kroenke *et al.* (2020)	Low	Unclear	Low	Unclear	Low	Unclear	Low
Liu *et al.* (2020)	High	Low	Low	Low	Low	Low	Low
Mandel *et al.* (2020)	Unclear	Unclear	Low	Unclear	Unclear	Low	Low
Maurer *et al.* (2016)	Low	Unclear	Low	Low	Low	Low	Low
Muhlematter *et al.* (2019)	Low	Low	Low	Unclear	Low	Low	Low
Park *et al.* (2018)	Low	Low	Low	Low	Low	Low	Low
Petersen *et al.* (2020)	Low	Low	Low	Low	Low	Low	Low
Pfister *et al.* (2016)	Low	Low	Low	Unclear	Low	Low	Low
Rauscher *et al.* (2016)	Low	Unclear	Low	Low	Low	Low	Low
Rhee *et al.* (2016)	Low	Low	Low	Low	Low	Low	Low
Scheltema *et al.* (2019)	Low	Low	Low	Low	Low	Low	Low
van Kalmthout *et al.*	Low	Low	Low	Low	Low	Low	Low
van Leuween *et al.* (2017)	Low	Low	Low	Low	Low	Low	Low
von Klot *et al.* (2017)	Low	Low	Unclear	Unclear	Low	Low	Low
Yilmaz *et al*. (2019)	Low	Low	Low	Low	Unclear	Low	Low
Zhang *et al.* (2017)	Low	Low	Low	Unclear	Low	Low	Low

Table 4A 2x2 contingency data for PSMA PET/CT assessment of primary prostate tumor

Author (year)	Patients	TP	FN	FP	TN	Total
Berger *et al.* (2018)	50	79	2	2	317	400
Bettermann *et al.* (2019)	17	356	58	46	312	772
Dekalo *et al.* (2019)	59	90	18	0	10	118
Eiber *et al.* (2016)[*]	53	153	49	3	113	318
El Hajj *et al.* (2019)	23	150	204	54	420	828
Fendler *et al.* (2016)	21	67	33	2	24	126
Gupta *et al.* (2018)[#]	23	17	7	4	18	46
Hicks *et al.* (2018)[*]	32	275	137	159	389	960
Liu *et al.* (2020)[£]	31	88	17	38	297	440
Muhlematter *et al.* (2019)[§]	40	10	10	18	282	320
Muhlematter *et al.* (2019)[¥]	40	36	40	55	509	640
Park *et al.* (2018)[*]	33	52	8	1	5	66
Rhee *et al.* (2016)	20	92	97	16	335	540
Scheltema *et al.* (2019)	54	NR	NR	NR	NR	648
von Klot *et al.* (2017)	21	36	2	1	3	42
von Klot *et al.* (2017)[#]	21	3	1	0	38	42
Yilmaz *et al.* (2019)[#]	24	NR	NR	NR	NR	48

NR = not reported. TP = true-positives. FN = false-negatives. FP = false-positives. TN = true-negatives. [*]PET/MRI. [#]SVI. [§]SVI pooled data for four different readers. [£]pre-diagnostic data with template and targeted biopsies. [¥]EPE pooled data for four different readers.

Table 4B 2x2 contingency data for PSMA PET/CT assessment of primary lymph node metastases

Author (year)	Patients	TP	FN	FP	TN	Total
Budäus *et al.* (2016)	30	34	19	40	515	608
Cytawa *et al.* (2020)	40	7	13	4	246	270
Gorin *et al.* (2018)	25	NR	NR	NR	NR	50
Gupta *et al.* (2018)	23	12	3	3	28	46
Herlemann *et al.* (2016)	20	12	2	3	23	40
Kopp *et al.* (2020)	90	10	11	5	432	458
Kroenke *et al.* (2020)[#]	58	28	24	10	313	375
Maurer *et al.* (2016)[#]	130	86	31	5	612	734
Park *et al.* (2018)[*]	33	3	1	6	56	66
Petersen *et al.* (2020)	20	4	22	3	102	131
van Kalmthout *et al.* (2020)	97	NR	NR	NR	NR	NR
van Leuween *et al.* (2017)	30	15	11	1	509	536
Zhang *et al.* (2017)	42	49	2	2	568	621

NR = not reported. TP = true-positives. FN = false-negatives. FP = false-positives. TN = true-negatives. [#]Mixed PET/CT and PET/MRI. *PET/MRI.

Table 4C 2x2 contingency data for PSMA PET/CT assessment of recurrent lymph node metastases

Author (year)	Patients	TP	FN	FP	TN	Total
Abufaraj *et al.* (2019)[§]	65	NR	NR	NR	NR	NR
Dundee *et al.* (2018)	17	NR	NR	NR	NR	NR
Hanske *et al.* (2019)	22	NR	NR	NR	NR	NR
Jilg *et al.* (2017)	30	69	16	1	203	289
Jilg *et al*. (2020)[£]	23	83	21	5	158	267
Mandel *et al.* (2020)	23	22	7	10	70	109
Pfister *et al.* (2016)	28	53	8	17	230	308
Rauscher *et al.* (2016)	48	53	3	15	108	179

NR = not reported. TP = true-positives. FN = false-negatives. FP = false-positives. TN = true-negatives.
[§]2x2 data for subregions. [£]Radio-guided surgery (RGS) used for ex situ measurement of surgically removed lymph nodes.