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ORIGINAL ARTICLE

Prostate Cancer

The performance of ^{18}F-PSMA PET/CT in the detection of prostate cancer: a systematic review and meta-analysis

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This paper presents a meta-analysis regarding the detection rate (DR) of fluorine-18 (^{18}F)-labeled prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) in the management of patients with prostate cancer (PCa). Relevant studies regarding ^{18}F-PSMA PET/CT in the management of PCa published until June 1, 2021, were electronically searched in online databases including EMBASE, PubMed, and Web of Science. The primary outcome was the DR of ^{18}F-PSMA PET/CT in managing PCa patients, while the secondary outcome was the DR of ^{18}F-PSMA PET/CT according to Gleason scores and serum prostate-specific antigen (PSA) level. The pooled DR was calculated on a per-patient basis, with pooled odd ratios and 95% confidence intervals (CIs). In total, 17 observational studies evaluating 1019 patients with PCa met the inclusion criteria. The DR of ^{18}F-PSMA PET/CT was 0.83 (95% CI: 0.78–0.88), in the random-effects model. Subsequently, the analysis of DR of ^{18}F-PSMA PET/CT in PCa patients using Gleason score (≤7 *vs* ≥8), showed a significant difference in PCa patients. Based on the above results, the higher Gleason score of PCa patients, the higher DR of ^{18}F-PSMA PET/CT. The DR of ^{18}F-PSMA PET/CT in PCa was 0.57 for PSA <0.5 ng ml^{-1}; 0.75 for PSA ≥0.5 ng ml^{-1} and <1.0 ng ml^{-1}; 0.93 for PSA ≥1.0 ng ml^{-1} and <2.0 ng ml^{-1}; and 0.95 for PSA ≥2.0 ng ml^{-1}. Therefore, the significant diagnostic value was found in terms of the DR of ^{18}F-PSMA PET/CT in managing PCa patients and was associated with Gleason score and serum PSA level.

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INTRODUCTION

Prostate cancer (PCa) is one of the most frequently diagnosed cancers in men and the fifth leading cause of death worldwide. The incidence of PCa varies greatly depending on the continent.[1] In the recent past, incidences of PCa have been increasingly reported in regions like Asia, which were traditionally considered low-incidence areas.[1,2] Regardless of this, the diagnostic rate of PCa is still low due to the existing suboptimal imaging modalities used for diagnosis and treatment.[3] There have been efforts to develop novel imaging tools that will promote diagnostic and therapeutic strategies for PCa.[4] Therapeutic and management options for PCa are highly informed by the accurate staging of primary or recurrent PCa.[5,6] Various imaging tools and techniques have been employed to assess the progression of PCa.[7,8] They include transrectal ultrasound (TRUS), computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy (BS), which have been recommended for the diagnosis of primary and recurrence PCa by the European Association of Urology (EAU).[9,10] These imaging techniques are, however, not always effective for the early and reliable management of primary/recurrence PCa due to their low sensitivity and specificity.[10] Recently developed metabolic imaging techniques are aimed at improving the diagnosis of PCa when an increase in prostate-specific antigen (PSA) serum values is detected following curative primary treatments. In patients with low but rising values of PSA serum, after definitive local therapy, it is important to identify the sites of recurrence to maximize the effects of treatment. Therefore, imaging with radiotracers targeting the prostate-specific membrane antigen (PSMA) has received increasing attention as a promising novel technique for PCa detection.[6] The PSMA is a protein expressed in dysplastic prostate cells with expression levels of 100–1000 times that of normal cells. The overexpression of PSMA may further be caused by the advanced stage and grade of PCa.[11,12] It is important to note that PSMA is not prostate-specific, and it may be expressed in other tissues and tumors.[11] The physiological expression of PSMA has also been revealed in the kidneys, the lacrimal and salivary glands, parts of the small and large intestines, the liver, the spleen, the neuronal ganglia, and various solid malignant and benign tumors.[13,14]

The clinical breakthrough in PSMA-based imaging was achieved with the introduction of gallium-68 (^{68}Ga)-PSMA-11 in May 2011 as a PET tracer.[15,16] In addition to ^{68}Ga, several PSMA ligands, such as fluorine-18 (^{18}F) and copper-64 (^{64}Cu), can be radiolabeled with various positron-emitter isotopes to produce positron emission

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tomography (PET) radiopharmaceuticals for PCa therapy. The ^{68}Ga PSMA PET/CT method of imaging has rapidly spread worldwide and is regarded as a significant step forward in the detection of PCa.[16] It is characterized by excellent tumor uptake, low background signal, high specificity, and very fast pharmacokinetics. These features enhance superior tumor visibility compared with other imagings.[17,18] Currently available ^{18}F-labeled PSMA agents (^{18}F-PSMA-1007, ^{18}F-DCFPyL, and ^{18}F-DCFBC) provide a more accurate and earlier detection of prostate disease than conventional imaging.[2,19-21] The labeling of PSMA agents as ^{18}F has several advantages over ^{68}Ga. They include a larger amount of activity from ^{18}F production by cyclotron, compared with the limited activity of ^{68}Ga derived from the elution of Germanium-68 (^{68}Ge)/^{68}Ga generators.[18,19] This is in addition to improved image resolution and a longer half-life.[19] Due to the lower positron energy, the theoretical achievable resolution of ^{18}F is relatively better compared to that of ^{68}Ga.

To date, numerous studies have explored the detection rate (DR) of ^{68}Ga-labeled PSMA PET/CT in PCa patients. Conversely, this study aimed to perform a meta-analysis concerning the DR of ^{18}F-PSMA PET/CT in the management of patients with PCa.

MATERIALS AND METHODS

Research question

A meta-analysis was performed to explore the DR of ^{18}F-PSMA PET/CT for PCa patients in the management of localized or metastatic PCa.

Search strategy

This study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[22] The existing studies from EMBASE, PubMed, and Web of Science electronic databases were searched from the inception of the databases to June 1, 2021. The search query was formulated based on the following keywords: "^{18}F-PSMA" or "^{18}F-prostate-specific membrane antigen" and "diagnosis accuracy" or "detection" and "management" and "PCa" or "prostate cancer". Besides, we also hand-searched the relevant studies from the reference lists of the selected articles, to identify more relevant publications and avoid relevant information being missing. The search was only limited to human studies and no language restrictions were posted in the setting.

Inclusion and exclusion criteria

Studies were included based on "Patient/Intervention/Outcome/Study design" criteria:[22] (1) "patients" with PCa, regardless of the clinical setting of primary staging or biochemical failure (BCF; biochemical persistence or recurrence); (2) studies using ^{18}F-PSMA PET/CT as an "intervention"; (3) patient-specific overall detection rate or proportion of PCa patients who experience change as an "outcome"; and (4) "study design" of clinical trials and prospective or retrospective studies published as original articles or brief communications.

The following were the exclusion criteria: (1) small number of patients (<10); (2) other publication types, including conference abstracts, review articles, editorials, and letters; (3) papers irrelevant

Table 1: Characteristics and methodology assessment of individual studies included in the meta-analysis

Publication year	*Study*	*Country/region*	*Patient enrolment period*	*Institution*	*Prospective or retrospective*	*Responding entity*	*Prior imaging*
2020	Dietlein *et al*.[32]	Germany	04/2017–03/2018	University Hospital of Cologne	R	The institutional review board	NR
2020	Kuten *et al*.[36]	Israel	NR	Tel Aviv Sourasky Medical Center	P	The institutional ethical committee	NR
2020	Witkowska-Patena *et al*.[37]	Poland	NR	Military Institute of Medicine	P	Military Medical Chamber ethics committee	NR
2020	Sachpekidis *et al*.[38]	Germany	NR	German Cancer Research Center	R	Ethical Committee of the University of Heidelberg	NR
2020	Rowe *et al*.[48]	USA	NR	Johns Hopkins University School of Medicine	P	Institutional Review Board of Johns Hopkins Medicine	NR
2020	Rowe *et al*.[34]	USA	05/2016–11/2016	Johns Hopkins University School of Medicine	P	Institutional Review Board of Johns Hopkins Medicine	NR
2020	Rauscher *et al*.[33]	Germany	08/2017–02/2018	Klinikum rechts der Isar Technical University Munich	R	Ethics Committee of the Technical University Munich	NR
2020	Dietlein *et al*.[35]	Germany	03/2017–12/2017	University Hospital of Cologne	R	The ethics committee	NR
2019	Rousseau *et al*.[31]	Canada	NR	University of British Columbia, Vancouver	P	UBC/BC Cancer Research Ethics Board	NR
2019	Giesel *et al*.[24]	Germany Chile	02/2017–01/2018	Technical University of Munich University of Heidelberg FALP, Santiago de Chile	R	The ethics committee	NR
2018	Rahbar *et al*.[23]	Germany Switzerland	10/2017–05/2018	University Hospital Münster University Hospital Bern	R	NR	CT/MRI/BS
2018	Rahbar *et al*.[25]	Germany Switzerland	10/2017–01/2018	University Hospital Münster University Hospital Bern	R	NR	NR
2018	Giesel *et al*.[26]	Germany	05/2016–07/2017	University Hospital Heidelberg German Cancer Research Center	R	The Institutional review board	NR
2018	Giesel *et al*.[27]	Germany South Africa	NR	Heidelberg University Hospital/ German Cancer Research Center University of Pretoria and Steve Biko Academic Hospital	P	The Institutional Ethics Committee	NR
2017	Kesch *et al*.[28]	Germany	2016	University Hospital Heidelberg German Cancer Research Center	R	The institutional review board	MRI
2017	Wondergem *et al*.[29]	The Netherlands	11/2016–03/2017	Noordwest Ziekenhuisgroep locatie Alkmaar	R	The institutional review board	NR
2018	Mena *et al*.[30]	USA	07/2014–11/2016	National Cancer Institute, NIH	P	The institutional review board	MRI

NR: not reported; P: prospective; R: retrospective; CT: computed tomography; MRI: magnetic resonance imaging; BS: bone scintigraphy

to the research question; (4) insufficient information provided in the study to calculate the DR of ^{18}F-PSMA PET/CT in the management of PCa; and (5) overlapping study population. In the case of overlapping study populations, the article that provided more comprehensive information required for this meta-analysis was included.

Data extraction and quality assessment

Data extraction and study quality assessment were conducted blindly by two researchers (ZQQ and GJP). In the case of any inconsistency occurring in the results, a third reviewer (ZX) was consulted to reach a consensus. For each eligible article, clinicopathological and ^{18}F-PSMA PET/CT characteristics were extracted using a standardized form, as follows:

1. Basic studies: origin (first author, publication year, patient enrolment period, institution, and country), design (prospective *vs* retrospective, and consecutive enrolment *vs* nonconsecutive), and methods for data acquisition (review of medical records *vs* questionnaires)
2. Clinicopathological: number of patients, age, and level of serum PSA at initial diagnosis and before ^{18}F-PSMA PET/CT, Gleason score, and clinical setting (primary staging *vs* BCF)
3. PET: vendor, scanner model, ligands, injected dose, uptake time, acquisition time, and PET positivity (proportion of patients with positive ^{68}Ga-PSMA PET scans).

Statistical analyses

The primary outcome of this meta-analysis was "the impact of ^{18}F-PSMA PET/CT on the detection of PCa" according to the proportion of patients who had their PCa care changed following imaging findings detected on ^{18}F-PSMA PET/CT. The secondary outcomes compared the DR of ^{18}F-PSMA PET/CT in PCa patients, based on Gleason scores and the level of serum PSA. Pooled odds ratios (ORs) analyses were carried out using data retrieved from individual studies about the DR of ^{18}F-PSMA PET/CT in the management of PCa. Pooled data were plotted with its specific 95% confidence interval (95% CI) values. A fixed-effects model (the Mantel–Haenszel method) or a random-effects model (the DerSimonian and Laird method) was used for statistical pooling of the data. During pooling, consideration was given to heterogeneity between the selected studies. The heterogeneity was assessed among studies using the χ^2 test and the I^2 statistic. The I^2 value typically ranges from 0 (no observed heterogeneity) to 100% (maximal heterogeneity). If the heterogeneity across studies was not identified, then the fixed-effects model was used; otherwise, the random-effects model was used in the meta-analysis. All statistical analyses were performed using STATA software (version 12.0; StataCorp LP, College Station, TX, USA). $P < 0.05$ was regarded as statistically significant.

RESULTS

Literature search

In total, 486 articles were initially identified through a primary search of the relevant online databases and reference lists. After reviewing titles and abstracts, 424 articles were excluded. The remaining 62 articles were selected and reviewed in full-text version. Consequently, 45 full-text articles were excluded due to the following reasons: no original available data ($n = 13$), meta-analysis ($n = 9$), review articles ($n = 20$), and overlapping articles ($n = 3$). Ultimately, 17 full-text studies met the inclusion criteria and were involved in the present meta-analysis. The studies were accrued from May 2017 to June 2021.[23-38] The literature search and selection procedure is presented in **Figure 1**.

Table 2: Characteristics about fluorine-18-labeled prostate-specific membrane antigen positron emission tomography/computed tomography of individual studies included in the meta-analysis

Publication year	*First author*	*Vendor*	*Model*	*Ligand*	*Dose (MBq)*	*Uptake time (min)*	*Acquisition time (min per bed)*
2020	Dietlein *et al*.[32]	Siemens	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	986.91±358.97[a]	NR	NR
2020	Kuten *et al*.[36]	NR	NR	^{18}F-PSMA-1007	NR	60	NR
2020	Witkowska-Patena *et al*.[37]	Siemens	Biograph mCT	^{18}F-PSMA-1007	295.5±14.1[a]	95±12[a]	NR
2020	Sachpekidis *et al*.[38]	Siemens	Biograph mCT	^{18}F-PSMA-1007	237 (131–266)[b]	70	2
2020	Rowe *et al*.[48]	Siemens	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	≤333[c]	60	NR
2020	Rowe *et al*.[34]	Siemens	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	≤333[c]	60	NR
2020	Rauscher *et al*.[33]	Siemens	Biograph mCT	^{18}F-PSMA-1007	325±40[a]	94±22[a]	NR
2020	Dietlein *et al*.[35]	Siemens	Biograph mCT	^{18}F-JK-PSMA	141±30[a]	230	NR
2019	Rousseau *et al*.[31]	NR	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	237–474[c]	120	2–4[c]
2019	Giesel *et al*.[24]	Siemens	Biograph mCT	^{18}F-PSMA-1007	301±46[a]	92±26[a]	3–4[c]
2018	Rahbar *et al*.[23]	Siemens	Siemens mCT	^{18}F-PSMA-1007	338±44.31[a]	120	3
2018	Rahbar *et al*.[25]	Siemens	Siemens mCT	^{18}F-PSMA-1007	336.7±46[a]	120/60	3
2018	Giesel *et al*.[26]	Siemens	Biograph mCT	^{18}F-PSMA-1007	251.5 (154–326)[b]	180±5[a]	NR
2018	Giesel *et al*.[27]	Siemens	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	240-260[a]	120	3
2017	Kesch *et al*.[28]	Siemens	Biograph mCT	^{18}F-PSMA-1007	15.9 (10.6–54.9)/27.5 (14.8–76.2)[b]	60/180	NR
2017	Wondergem *et al*.[29]	Siemens	Biograph mCT	^{18}F-DCFPyL ^{18}F-PSMA-1007	314 (243–369)[b]	120/60	NR
2018	Mena *et al*.[30]	NR	Biograph mCT	^{18}F-DCFBC ^{18}F-PSMA-1007	292.3 (255.3–299.7)[b]	120/60	2

[a]Data are shown as mean±s.d.; [b]data are shown as mean (range); [c]data are shown as range. NR: not reported; CT: computed tomography; PSMA: prostate-specific membrane antigen; ^{18}F: fluorine-18; s.d.: standard deviation

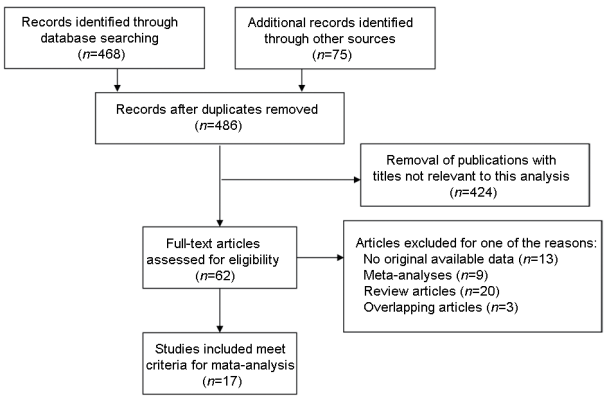

Figure 1: A flowchart showing the selection process.

Characteristics of included studies

The characteristics and methodology assessment of individual studies included in the meta-analysis are described in **Table 1**. Briefly, seven prospective and ten retrospective studies were included. To ensure homogenous calibration between sites, all articles were approved by the Ethics Committee of each university or hospital. The patients from the included studies were consecutive enrolment. Besides, the data acquisition was based on the review of medical records in all these studies. **Table 2** and **3** show the clinicopathologic features and PET characteristics of individual studies included in this meta-analysis. The number of PCa patients ranged from 10 to 251, with ages of 45–86 years. Median levels of PSA reported before ^{18}F-PSMA PET/CT in all the included studies ranged between 0.03 ng ml^{-1} and 1481 ng ml^{-1}. Of the total studies, only six studies reported the outcomes separately for primary staging and BCF; ten studies reported outcomes for BCF; and one study reported outcomes for primary staging. Besides, PET positivity was reported in all studies,[23-38] with values ranging from 60% to 100% (overall, 82.8%).

Quality assessment

A total of 17 articles, enrolling 1019 patients, were identified and included in the analysis. According to the random-effects model, the DR of ^{18}F-PSMA PET/CT was 0.83 (95% CI: 0.78–0.88) increase in the odds of the management of PCa (**Figure 2a**). Subsequently, the performance of ^{18}F-PSMA PET/CT on the detection of PCa patients was compared with the DR of ^{18}F-PSMA PET/CT based on Gleason scores and serum PSA level. The results of Gleason score showed that there was a statistically significant diagnostic value in two groups of PCa patients when using ^{18}F-PSMA PET/CT in the management of PCa patients. In the PCa patients with Gleason scores ≤7, the DR of ^{18}F-PSMA PET/CT in PCa management changes was 0.83 (95% CI: 0.72–0.93; **Figure 2b**). Moreover, in the PCa patients with Gleason scores ≥8, the DR of ^{18}F-PSMA PET/CT prominently increased (OR: 0.89, 95% CI: 0.83–0.94; **Figure 2c**). In the subgroup analysis using serum PSA level, the DR of ^{18}F-PSMA PET/CT in PCa was 0.57 for PSA <0.5 ng ml^{-1} (95% CI: 0.37–0.77; **Figure 3a**); 0.75 for PSA ≥0.5 ng ml^{-1} and <1.0 ng ml^{-1} (95% CI: 0.68–0.83; **Figure 3b**); 0.93 for PSA ≥1.0 ng ml^{-1} and <2.0 ng ml^{-1} (95% CI: 0.89–0.98; **Figure 3c**); and 0.95 for PSA ≥2.0 ng ml^{-1} (95% CI: 0.93–0.98; **Figure 3d**). It was therefore revealed that, the Gleason score or serum PSA level of PCa patients correlated with DR of ^{18}F-PSMA PET/CT in the management of PCa.

DISCUSSION

In recent years, increased studies in cancer research have focused on the diagnosis of tumors, which includes but is not limited to serum biomarkers, tissue pathology examination, and imaging tools.[9,10] It has emerged that the most ideal methods in the field of cancer screening should be specific, noninvasive, and convenient, especially at an early stage.[39] Screening tools such as PSA, DRE, TRUS, CT, and MRI are significant in the clinical diagnosis and management of PCa.[9,10,39] Previous studies have, however, found that morphologic imaging, such as TRUS and CT, is limited in terms of diagnostic value (management rate <5%), especially when the PSA levels are <20 ng ml^{-1} or the PSA velocity is <2 ng ml^{-1} per year. Their sensitivity to detecting local PCa relapse remains relatively low (25%–54%) and is only moderately improved with functional MRI techniques.[40,41] Moreover, the sensitivity of CT and MRI for the management of lymph node metastases of PCa is reported to be 30%–80%.[42] In view of the low sensitivity of morphologic imaging, there has been an urgent need to find more effective and reliable diagnostic methods to better manage primary/recurrence PCa.[9,10,39] As a new method of staging and restaging PCa patients, recent studies have recommended ^{18}F-PSMA PET/CT. This method has the potential to improve the management of approximately half of PCa patients.[23-38] Elsewhere, studies have reported overexpression of PSMA in PCa tissue compared with normal tissue, which increased even further at advanced stage and grade of PCa.[15,20] These findings suggest that PSMA is a novel and promising biomarker.[5,20] Thus, this meta-analysis aimed to evaluate the DR of ^{18}F-PSMA PET/CT in the management of patients with PCa.

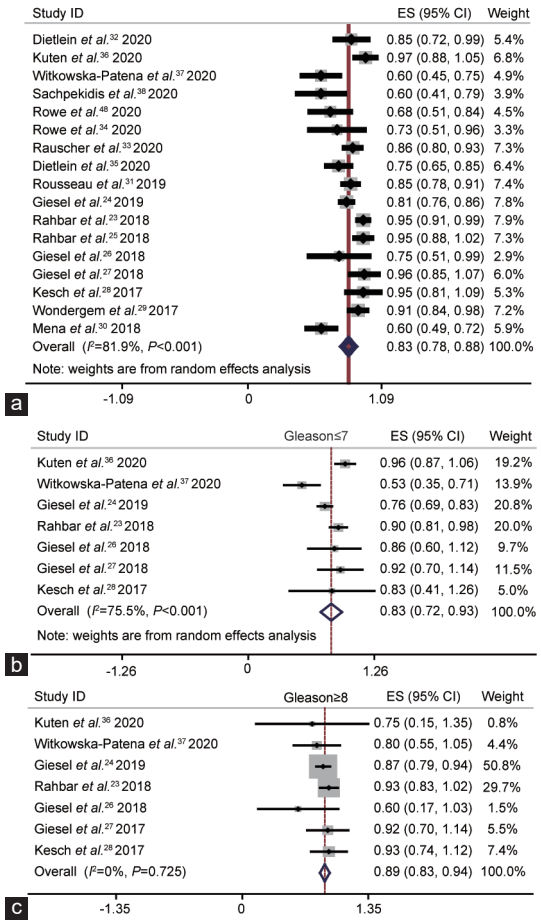

Figure 2: Forest plots showing the detection rate of ^{18}F-labeled prostate-specific membrane antigen positron emission tomography/computed tomography for prostate cancer based on Gleason scores. (**a**) All PCa-suspected patients; (**b**) Gleason scores ≤7; (**c**) Gleason scores ≥8. PCa: prostate cancer; ^{18}F: fluorine-18; PCa: prostate cancer; CI: confidence interval; ES: Elastic Search.

Table 3: Patient characteristics of individual studies included in the meta-analysis

Publication year	*First author*	*Patients (n)*	*Age (year)*	*PSA (ng ml^{-1})*	*Clinical setting*	*PSMA-positive patients (n)*	*Gleason score ≥7 (%)*	*Gleason score, n/total*		*PSA (ng ml^{-1}), n/total*			
								≤7	*≥8*	*<0.5*	*≥0.5 and <1.0*	*≥1.0 and <2.0*	*≥2.0*
2020	Dietlein *et al.*[32]	27	NR	NR	BCF	23	NR	NA	NA	NA	NA	NA	NA
2020	Kuten *et al.*[36]	16	56.0–72.0[a]	3.5–14.4[a]	Primary staging/BCF	16	87.5	14/14	2/2	NA	NA	NA	16/16
2020	Witkowska-Patena *et al.*[37]	40	68.6±6.5[b]	0.75±0.6[b]	BCF	24	62.5	16/30	8/10	7/18	6/11	10/10	1/1
2020	Sachpekidis *et al.*[38]	25	66.0 (48.0–84.0)[c]	1.2 (0.2–237.3)[c]	BCF	15	68.0	NA	NA	NA	NA	NA	NA
2020	Rowe *et al.*[48]	31	63.0 (45.0–74.0)[c]	0.4 (0.2–28.3)[c]	BCF	21	NR	NA	NA	NA	NA	NA	NA
2020	Rowe *et al.*[34]	15	65.8 (52.0–77.0)[c]	4.4 (0.2–224.5)[c]	Primary staging/BCF	11	NR	NA	NA	NA	NA	NA	NA
2020	Rauscher *et al.*[33]	102	71.0±8.0[b]	0.87 (0.2–13.6)[c]	BCF	88	NR	NA	NA	NA	NA	NA	NA
2020	Dietlein *et al.*[35]	75	69.2±8.1[b]	0.5–14.9[a]	BCF	56	NR	NA	NA	6/11	14/16		36/39
2019	Rousseau *et al.*[31]	130	69.1±6.5[b]	5.2±6.5[b]	BCF	110	86.2	NA	NA	3/5	18/23	18/23	71/77
2019	Giesel *et al.*[24]	251	70.0 (48.0–86.0)[c]	10.9 (0.6–250.0)[c]	Primary staging/BCF	204	83.7	106/139	72/83	40/65	35/47	50/55	79/84
2018	Rahbar *et al.*[23]	100	68.7±7.6[b]	3.4±6.1[b]	BCF	95	71.0	44/49	26/28	18/21	16/18	22/22	39/39
2018	Rahbar *et al.*[25]	40	68.7±8.1[b]	35.4 (0.03–939.0)[c]	Primary staging/BCF	38	60.0	NA	NA	6/8		32/32	
2018	Giesel *et al.*[26]	12	70.0 (54.0–79.0)[c]	0.60 (0.08–6.50)[c]	BCF	9	91.6	6/7	3/5	5/6	1/1	1/1	2/4
2018	Giesel *et al.*[27]	12	66.0 (54.0–82.0)[c]	85.0 (10.0–279.8)[c]	Primary staging/BCF	12	91.6	6/6	6/6	0/0	0/0	0/0	12/12
2017	Kesch *et al.*[28]	10	67.0 (62.0–77.0)[c]	13.1 (5.8–40.0)[c]	Primary staging	10	100.0	3/3	7/7	0/0	0/0	0/0	10/10
2017	Wondergem *et al.*[29]	65	62.0 (52.0–84.0)[c]	56.0 (0.1–1481.0)[c]	Primary staging/BCF	59	67.7	NA	NA	NA	NA	NA	NA
2018	Mena *et al.*[30]	68	64.0 (51.0–74.0)[c]	4.4±7.3[b]	BCF	41	NR	NA	NA	2/13	6/13	10/12	23/30

[a]Data are shown as range; [b]data are shown as mean±s.d.; [c]data are shown as median (range). NR: not reported; BCF: biochemical failure; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; NA: not available; s.d.: standard deviation

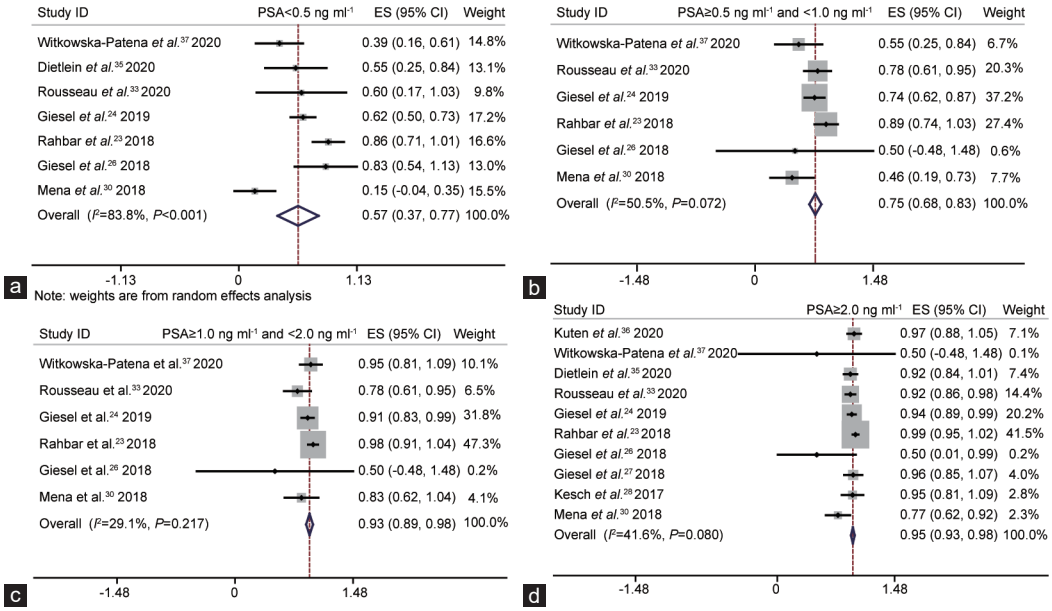

Figure 3: Forest plots showing the detection rate of ^{18}F-labeled prostate-specific membrane antigen positron emission tomography/computed tomography for prostate cancer based on serum PSA level. (**a**) PSA <0.5 ng ml^{-1}; (**b**) 0.5 ng ml^{-1}≤ PSA <1.0 ng ml^{-1}; (**c**) 1.0 ng ml^{-1}≤ PSA <2.0 ng ml^{-1}; (**d**) PSA ≥2.0 ng ml^{-1}. PSA: prostate-specific antigen; ^{18}F: fluorine-18; CI: confidence interval; ES: Elastic Search.

Recently, some studies have evaluated the clinicopathologic characteristics of ^{18}F-PSMA PET/CT in the management of PCa.[23-38] Nevertheless, the study's outcomes remain inconsistent due to the relatively small sample size, the different ethnicities, and the possible limited effect of individual patient data in the ^{18}F-PSMA PET/CT. The meta-analysis had explored the results of the DR of ^{18}F-PSMA PET/CT in the management of biochemical recurrent PCa, but such studies remain unreliable due to the disparity between the individual studies involved.[43,44] Limited research on ^{18}F-PSMA PET/CT limits comprehensive understanding of the disparity in the management of PCa, based on Gleason scores and serum PSA level. The present study pooled data reported in various studies to explore the DR of ^{18}F- PSMA PET/CT in the management of patients with PCa.

According to the current meta-analysis findings, the DR of ^{18}F-PSMA PET/CT significantly increased in patients with PCa. The meta-analysis could also provide the most comprehensive information about different subgroups. Results of the stratified analysis using Gleason scores (≤7 or ≥8), suggested that higher DR of ^{18}F-PSMA PET/CT was found in PCa patients with Gleason scores ≥8. In addition, the DR of ^{18}F-PSMA PET/CT in PCa increased with the increase in the serum PSA level.

The present meta-analysis was not without limitations. First, there were a limited number of studies and an insufficient number of PCa patients for the meta-analysis. Thus, the results were based on unadjusted estimates due to slight variations in the inclusion criteria for each individual patient.[45,46] Second, many factors could affect the DR of ^{18}F-PSMA PET/CT, such as reagent resources, tumor size, assay type, cutoff value, and the proficiency of a particular physician. These factors were, however, not considered in the subgroup analysis. Prospect studies should focus on exploring better diagnostic strategies for PCa. Third, there were no studies reporting on adverse events in ^{18}F-PSMA PET/CT in all the included trials. As a result, additional exploration to determine adverse events should be prospected for and studied. In addition, the PET/CT scan may underestimate the burden of the recurrence of PCa patients with a PSA below 1.5 ng ml^{-1} and a limited nodal tumor load. This may be so regardless of the tracer used.[47] All of the studies included in this study were conducted in the Caucasian population and cannot be generalized to the situation among other races. Thus, future studies should consider the influence of ethnicity-related factors. Overall, this meta-analysis demonstrated a good DR of ^{18}F-PSMA PET/CT in patients with PCa, but large prospective multicentric studies, and in particular, the influence of different factors such as ethnicity, are warranted.

CONCLUSIONS

In summary, ^{18}F-labeled PSMA PET/CT demonstrated a good DR in patients with PCa compared to those reported in the literature with ^{68}Ga-labeled PSMA PET/CT. Based on the Gleason score, the DR of ^{18}F-labeled PSMA PET/CT is correlated with PSA values whereby significantly lower DR is recorded in patients having PSA <0.5 ng ml^{-1}. Prospective multicentric trials with a large sample size are needed to justify these results. Nevertheless, ^{18}F-labeled PSMA PET/CT is significantly important in the management of PCa.

AUTHOR CONTRIBUTIONS

RPJ, ZQQ, and GJP designed the study, collected, analyzed, and interpreted the clinical data, and wrote the manuscript. GJP, ZX, LWX, and HW analyzed part of the data. RPJ and ZQQ supervised the project and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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