^{68}Ga-PSMA PET/CT for the evaluation of metastasis in patients with prostate cancer: A systematic review and meta-analysis

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Abstract

Objective: The aim of this study was to assess the diagnostic value of gallium-68-prostate specific membrane antigen (6^{8}Ga-PSMA) positron emission tomography/computed tomography (PET/CT) in detecting metastases in prostate cancer (PCa) patients. **Materials and Methods:** A comprehensive literature search of studies published before August 2021 in PubMed, Embase and Cochrane Library databases was conducted. The methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Studies investigating the diagnostic value of ^{68}Ga-PSMA PET/CT were selected for qualitative and quantitative analysis. **Results:** Twenty-five articles using ^{68}Ga-PSMA PET/CT for detecting metastases in PCa patients were selected for qualitative analysis, 16 of which were selected for meta-analysis. The sensitivities of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases ranged from 33.3% to 96.08%, with high specificities ranged from 82% to 100%. Gallium-68-PSMA PET/CT demonstrated outstanding diagnostic performance in PCa patients with bone metastases. Only two articles about ^{68}Ga-PSMA PET/CT for lung metastases showed that the detection value was limited. It was difficult to distinguish lung metastases in PCa patients from benign lesions or primary lung cancer. There was only one article about ^{68}Ga-PSMA PET/CT for liver metastases, which showed that about 77.7% of metastatic lesions will be ^{68}Ga-PSMA-positive and 22.3% will be false negatives. Due to the lack of articles on PCa visceral metastases, we only conducted a meta-analysis on lymph node metastases and bone metastases. In our meta-analysis, the per-patient pooled sensitivity, specificity, positive likelihood ratio (LR^{+}), negative likelihood ratio (LR^{-}), diagnostic odds ratio (DOR), and the area under the ROC curve (AUC) of lymph node metastases were 0.61, 0.96, 14.4, 0.41, 35, and 0.95, respectively. The per-lesion pooled sensitivity, specificity, LR^{+}, LR^{-}, DOR, and AUC of V were 0.74, 0.99, 76.0, 0.26, 289 and 0.99, respectively. The per-patient pooled sensitivity, specificity, LR^{+}, LR^{-}, DOR, and AUC of bone metastases were 0.97, 1.00, 1100.1, 0.03, 37490 and 0.98, respectively. **Conclusion:** Gallium-68-PSMA PET/CT demonstrated outstanding diagnostic performance for bone metastases in PCa patients. The majority of lymph node metastases, lung metastases, and liver metastases overexpressed PSMA, which could be directly detected. However, a considerable number of lesions were false negatives.

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Introduction

Sung H et al. (2021) provided a status report on cancer as a global burden in 185 countries and presented that prostate cancer (PCa) ranked as the second most common type of cancer and the fifth leading cause of cancer-related deaths in men [1]. Lymph node metastases and hematogenous were mainly present in PCa patients. Lymph node metastases are characterized as adverse prognostic factors and are associated with bone or visceral metastases [2]. Common hematogenous metastases include the bone, lung, and liver [3]. Bone metastases was detected in more than 80% of PCa patients with a high risk of morbidity [4]. Recurrent metastases could occur at multiple sites, mainly in the lymphoid tissue (30.5%), bone (42.1%), and retroperitoneal (13.7%) and visceral (13.7%) sites [5]. Therefore, patients need to be accurately staged to undergo the most appropriate treatment. Early detection through screening and appropriate treatment can increase the expected 5-year survival rate to 100% before cancer cell metastases [6]. Conventional modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) to detect metastases rely on morphological features. However, most metastases could not be detected by conventional modalities. Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is overexpressed in prostate epithelial cells. It is a potential target for prostate cancer-specific imaging. In recent years, the use of gallium-68 (^{68}Ga)-PSMA positron emission tomography/computed tomography (PET/CT) has been widely reported and has become the focus of research [7, 8]. Thus, we aimed to evaluate the role of ^{68}Ga-PSMA PET/CT in detecting metastases in PCa patients.

Materials and Methods

Search strategy

Literature searches of the PubMed, Embase, and Cochrane Library databases were performed to collect relevant articles published between January 1990 and August 2020 using the following search algorithm: (prostate cancer OR prostate carcinoma) AND (metastases OR recurrence) AND (PET/CT OR positron emission tomography/computed tomography) AND (prostate-specific membrane antigen OR PSMA). The studies were limited to English-language articles. The search and article selection were independently assessed by two experienced nuclear medicine physicians without any discrepancies.

Study selection

The main topics of the included articles for analysis were the diagnostic value of ^{68}Ga-PSMA PET/CT in detecting metastases from PCa, including primary staging and recurrent PCa patients. Prostate cancer was confirmed by histopathology or biopsy. Metastases from PCa were confirmed by histopathology, biopsy or imaging findings, and clinical follow-up. The exclusion criteria were as follows: abstracts, case reports, reviews, notes, letters, comments, animal experiments, other unrelated imaging modalities, articles where the number of cases was less than 10, and original articles with incomplete data. When the same data were used in more than one article, two investigators evaluated them to make the most suitable choice for our analysis.

Data extraction

Data were extracted from each included study by two reviewers independently. Data recorded were as follows: author's name, year of publication, and country of origin; study design, patient sample size, patient characteristics such as age, and type of patients evaluated; location of metastases, prostate-specific antigen (PSA) level, GS, and analysis methods; technical aspects such as imaging modality, mean injected activity, time interval between radiotracer injection and image acquisition, image analysis, and other imaging modalities used for comparison. The results compiled included sensitivity, specificity, or the number of true positives, true negatives, false positives, and false negatives.

Quality assessment

The methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool which evaluates four sections: the risk of bias in patient selection, index test, reference standard, and flow and timing. The degree of applicability in the first three domains was also evaluated.

Statistical analysis

Based on the bivariate random-effects model, the extracted data were analysed using the Midas command in Stata 15.1 software (StataCorp, College Station, Texas) to calculate the pooled sensitivity, specificity, positive likelihood ratio (LR^+), negative likelihood ratio (LR^-), and diagnostic odds ratio (DOR), to draw the summary receiver operating characteristic (SROC) curve, and to calculate the area under the curve (AUC), Q*value, and 95% confidence interval (CI) as our primary outcome measures. If I2>50% and P<0.05, heterogeneity was considered to exist. The publication bias was evaluated using Deeks' funnel plot and was indicated if P< 0.1.

Results

Literature search

According to the flow diagram (Figure 1), 1057 articles (739 articles in PubMed, 240 articles in Embase, and 78 articles in Cochrane) were identified. A total of 135 duplicate articles and 816 articles were excluded by reading the titles and abstracts (conference abstracts, case reports, reviews, notes, letters, and editorials). Furthermore, there are 106 articles left, and some articles were read but failed to meet the inclusion criteria. Finally, 25 articles met the inclusion criteria in this systematic review and meta-analysis [9-33]. All participants were eligible for qualitative analysis [9-33] and 16 of them for meta-analysis [9-24]. The characteristics of the included studies are shown in Tables 1 and 2.

Quality assessment

The quality assessment results presented in Figure 2 shows some high risks and unclear risks in each section. However, the applicability was acceptable.

Qualitative analysis (systematic review)

Lymph node metastasis

There were 14 articles (1377 patients) about the diagnostic performance of lymph node metastases in PCa patients by ^{68}Ga-PSMA PET/CT [9, 11-15, 17, 19, 20, 22, 28-31]. The diagnosis of lymph node metastases was mainly based on the pathological criteria. Only two articles were judged by histological correlation and clinical follow-up [12, 13]. We performed analyses in patients with intermediate- and high-risk features or those with recurrent clinical diseases. The range of sensitivities of the articles was large and the specificities were high. The sensitivities of the three studies were low [9, 11, 15], ranging from 33.3%-41.5%. Two studies showed moderate sensitivities [12, 14], ranging from 56%-64%. The sensitivities of six studies were high [13, 17, 19, 20, 22, 28, 29], ranging from 82%-96.08%. The range of specificities ranged from 82% to 100%, and all of them were high [9, 11-15, 17, 19, 20, 22, 28, 29].

Except for different sensitivities and specificities, Budäus et al. (2016) found that the detection rate of lymph node metastases was related to the size of metastatic lymph node [11]. Leeuwen et al. (2017) presented that the size of 91% of undetected metastatic lymph node was <5mm [14]. This is mainly because the current spatial resolution of PET/CT is between 4.9 and 5.1mm. To detect lesions below this size, a stronger PSMA signal activity that overcomes the influence of "partial volume effect" on current PET/CT technology is needed. In the study by Leeuwen et al. (2017), there was a

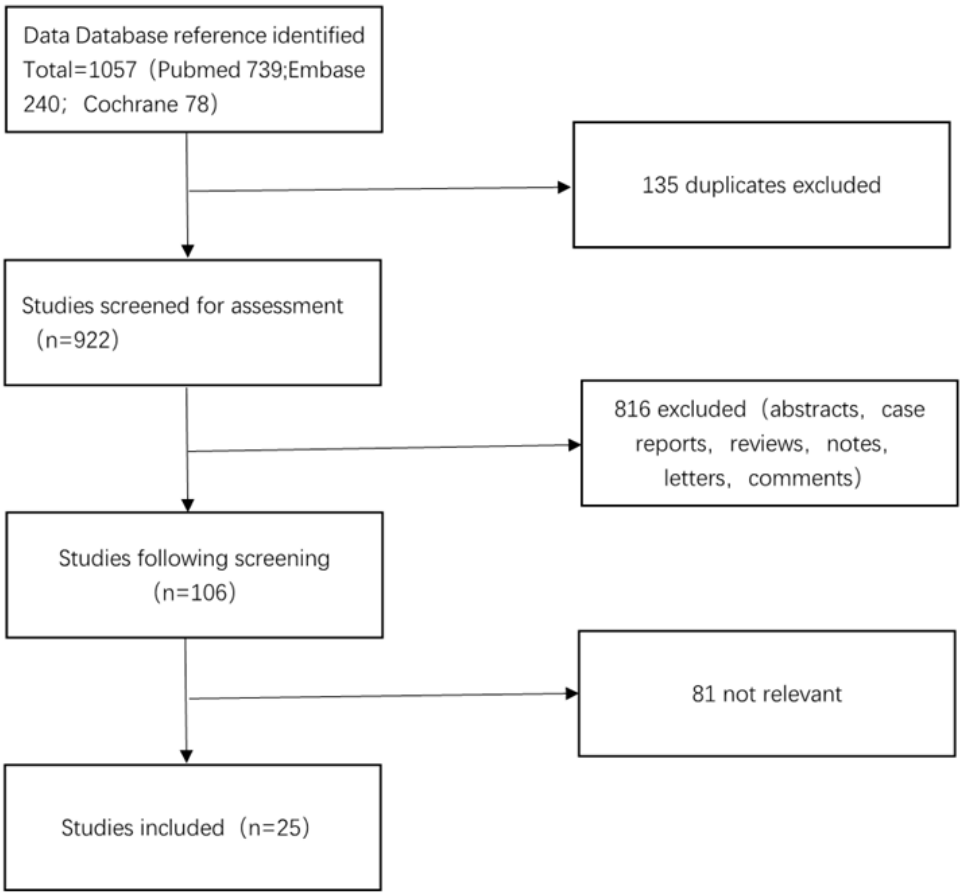

Figure 1. Summary of the study selection process of ^{68}Ga-PSMA PET/CT in detecting metastases in PCa patients.

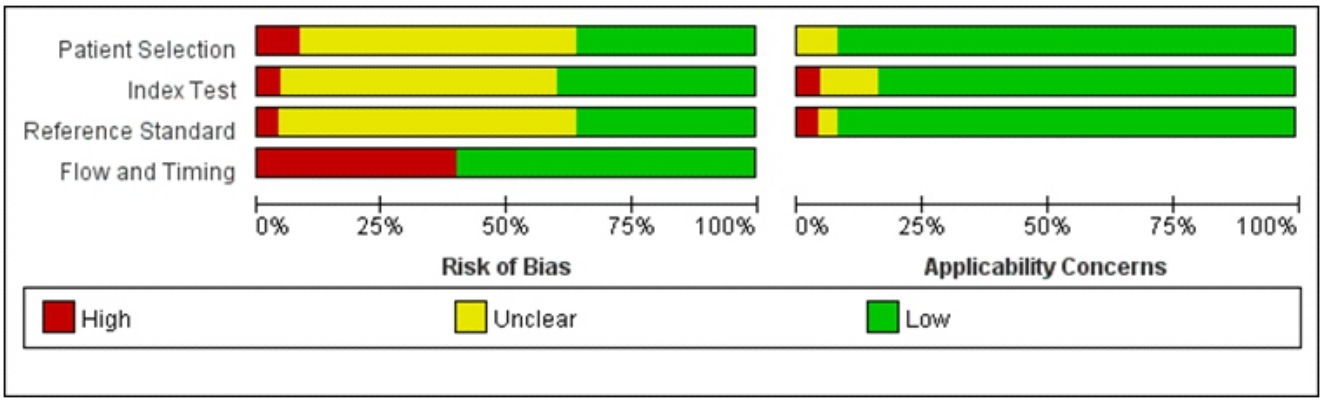

Figure 2. Summary of QUADAS-2 risk of bias and summary of QUADAS-2 applicability concerns

Table 1.*Basic studies and patients characteristics.*

Authors	Year	Country	Study design	No. of patients	Age (years)	Type of patients evaluated	Locations of tumor	Analysis methods
Yaxley [9] . et al.	2019	Australia	Retrospective single centre	208	68 (44-80)	Primary staging prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Lengana [10] et al.	2018	South Africa	Prospective single centre	113	66 (43–88)	Primary staging prostate cancer	Bone metastases	Qualitative and quantitative analysis
Budaus [11] et al.	2015	Germany	Retrospective single centre	30	63.0 (44–75)	Primary staging prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Oromieh [12] et al.	2014	Germany	Retrospective single centre	319	68 (46-86)	Recurrent prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Hofman [13] et al.	2020	Australia	Prospective multi-centre	302	70 (64–74)	High-risk prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Leeuwen [14] et al.	2016	Australia	Prospective single centre	30	65 (60–71)	Intermediate- and high-risk prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Kalmthout [15] et al.	2019	Netherlands	Prospective single centre	103	69 (53-82)	Primary Staging of Prostate Cancer	Lymph node metastasis	Qualitative and quantitative analysis
Zacho [16] et al.	2018	Denmark	Prospective single centre	68	67 (47–80) 67 (53–74) 70 (64–77)	Biochemically recurrent prostate cancer	Bone metastases	Qualitative and quantitative analysis
Hijazi [17] et al.	2015	Germany	Retrospective single centre	35	71 (49–77)	Biochemically recurrent and high-risk primary staging prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis

(continued)

Simsek [18] et al.	2020	Turkey	Retrospective single centre	138	66 (49–92)	Primary staging and biochemically recurrent prostate cancer	Bone metastases	Qualitative and quantitative analysis
Jilg [19]et al.	2017	Germany	Retrospective single centre	30	65.7 (52.4 - 70)	Recurrent Prostate Cancer	Lymph node metastasis	Qualitative and quantitative analysis
Pfister [20] et al.	2016	Germany	Retrospective single centre	66	67 (46–79)	Recurrent prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Janssen [21] et al.	2017	Germany	Retrospective single centre	54	70 ± 6.5	Prostate cancer	Bone metastasis	Qualitative and quantitative analysis
Zhang [22] et al.	2017	China	Retrospective single centre	42	69 (55–82)	Intermediate to high-risk prostate cancer	Lymph node metastasis	Qualitative and quantitative analysis
Schwenck [23] et al.	2016	Germany	Retrospective single centre	123	NA		Bone metastasis	Qualitative and quantitative analysis
Dyrberg [24] et al.	2018	Denmark	Prospective single centre	55	75 (54–91)	Prostate cancer	Bbone metastasis	Qualitative and quantitative analysis
Damjanovic [25] et al.	2019	Germany	Retrospective single centre	739	71.0 (54.5–81.4)	Prostate cancer	Liver metastasis	Qualitative analysis
Damjanovic [26] et al.	2018	Germany	Retrospective single centre	34	71.7 (50.6 - 82.5)	Prostate cancer	Lung metastasis	Qualitative analysis
Pyka [27] et al.	2016	Germany	Retrospective single centre	1889	68.8 (50 – 83)	Staging or restaging of PC	Lung metastasis	Qualitative analysis
Vinsensia [28] et al.	2017	Germany	Retrospective single centre	147	68(44-87)	Biochemical recurrence of prostate cancer	Lymph node metastasis	Qualitative analysis
Herlemann [29] et al.	2015	Germany	Retrospective single centre	24	NA	Patients with Prostate Cancer	Lymph node metastasis	Qualitative analysis

(continued)

Giesel [30] et al.	2015	Germany	Retrospec-tive single centre	147	71 (59-87)	Biochemical recurrence of prostate cancer	Lymph node metastasis	Qualitative analysis
Rauscher [31] et al.	2016	Germany	Retrospec-tive single centre	48	71 (66-74)	Recurrent prostate cancer	Lymph node metastasis	Qualitative analysis
Schmidkonz [32] et al.	2019	Retrospe ctive single centre	NA	177	70(54 – 85)	Biochemical recurrence of prostate cancer	Bone metastasis	Qualitative analysis
Lawal [33] et al.	2020	Germany	Prospec-tive single centre	18	68 (48-80)	Patients with advanced prostate cancer	Bone metastasis	Qualitative analysis

Table 2. *Technical aspects of ^{68}Ga-PSMA PET/CT in the included studies.*

Authors	Mean injected activity	Time interval between radiotracer injection and image acquisition	Image analysis	Other imaging modalities used for comparison
Yaxley [9] et al.	200 MBq	45 to 60 minutes	Visual and semi-quantitative	NA
Hirmas [6] et al.	3 MBq/kg	60 min	Visual and semi-quantitative	NA
Lengana [10] et al.	3.7mCi (1.24-8.25mCi)	60 minutes	Visual and semi-quantitative	BS
Budaus [11] et al.	NA	NA	Visual and semi-quantitative	NA
Oromieh [12] et al.	161 Mbq (40-400MBq)	60min	Visual and semi-quantitative	NA
Hofman [13] et al.	NA	NA	Visual and semi-quantitative	CT with intravenous contrast and SPECT/CT
Leeuwen [14] et al.	NA	60min	visual and semi-quantitative	NA
Kalmthout [15] et al.	1.5 MBq/kg	60min	Visual and semi-quantitative	NA
Zacho [6] et al.	2 MBq/kg	60min	Visual and semi-quantitative	^{18}F-NaF PET/CT MRI (DW600-MRI)
Hijazi [17] et al.	300 MBq (140–392 MBq)	60min	Visual and semi-quantitative	NA

(continued)

Simsek [18] et al.	185 MBq	45–60 min	Visual and semi-quantitative	Bone scintigraphy and SPECT/CT
Jilg [19] et al.	198 MBq	60min	Visual and semi-quantitative	NA
Pfister [20] et al.	2 MBq/kg	45min	Visual and semi-quantitative	^{18}FEC PET/CT
Janssen [21] et al.	120.3±20.35 MBq	61.7 min (±32.2 mins)	Visual and semi-quantitative	SPECT/CT and CT
Zhang [22] et al.	131.72 Mbq, (130.6-177.6 MBq)	60min	Visual and semi-quantitative	MRI
Schwenck [23] et al.	169 ± 12 MBq	60min	Visual and semi-quantitative	^{11}C-Choline PET/CT
Dyrberg [24] et al.	NA	NA	Visual and semi-quantitative	^{18}F-NaF/CT-MRI
Damjanovic [25] et al.	120.5 ± 25.7MBq	75.8 ± 18.2 min	visual and semi-quantitative	NA
Damjanovic [26] et al.	125.9±26.9 MBq	67.0±33.1 min	visual and semi-quantitative	NA
Vinsensia [28] et al.	mean 176 MBq	60±10 min	Visual and semi-quantitative	NA
Herlemann [29] et al.	NA	60 min	Visual and semi-quantitative	NA
Giesel [30] et al.	mean 176 MBq	60±10 min	Visual and semi-quantitative	NA
Rauscher [31] et al.	154 MBq, (133-179 MBq)	57 min 49-63	Visual and semi-quantitative	NA
Schmidkonz [32] et al.	131 ± 29 MBq	56 min (range 51 – 64 min)	Visual and semi-quantitative	NA
Lawal [33] et al.	147.32	60 min	Visual and semi-quantitative	[^{68}Ga]Ga-NODAGAZOL PET/CT, and [^{99m}Tc]Tc-MDP bone scintigraphy

strong PSMA activity of 60% in 2.0-mm to 4.9-mm metastatic lymph node, but a considerable number of metastatic lymph node of less than 5mm (and all <2mm) were not detected [14]. The median short diameter of tumour deposits in metastatic lymph node from false negatives (1.3mm) was significantly smaller than that from true positives (5.5mm, P<0.0001). When anatomical sub-regions contain only one metastatic lymph node, the median short diameter of tumour deposits in metastatic lymph node was estimated to be ≥2.3mm and ≥4.5mm if the detection rate of lymph node metastases was 50% and 90%, respectively [19]. Therefore, the size of metastases is very important for accurate detection of lesions. In a multicentre, two-arm, randomised study, ^{68}Ga-PSMA PET/CT had higher diagnostic value than traditional imaging in high-risk Pca patients [13]. In the low GS group, only 38 (34%) of 113 PSMA-positive lymph nodes were morphologically positive. In the intermediate GS cohort, 69 (56%) of 122 PSMA-positive lymph nodes were morphologically positive. Among 127 PSMA-positive lymph nodes in the high GS group, 67 (53%) were morphologically positive. Further, 52% of lymph nodes did not exceed the size standard of CT diagnosis of metastases. Finally, 61% of patients were reclassified from cN0 to cN1 by ^{68}Ga-PSMA PET/CT [28]. In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of ^{68}Ga-PSMA PET criteria for diagnosing lymph node metastases were 84%, 82%, 84%, and 82%, respectively, and the CT criteria were 65%, 76%, 75%, and 67%, respectively. Compared with CT, PET was more accurate than pelvic lymph node dissection (PLND) (88% vs. 75%) and salvage lymphadenectomy (sLAD) (77% vs. 65%). Therefore, with combined PET and CT, 68Ga-PSMA PET/CT can provide more accurate lymph node staging before PLND and sLAD of PCa [29]. Of the 179 lymph nodes resected during the operation, 68 metastatic lymph node were found (38.0%). The specificities of ^{68}Ga-PSMA PET and morphological imaging were 97.3% and 99.1%, respectively. However, ^{68}Ga-PSMA PET detected metastatic lymph node in 53 of 68 pathologically confirmed metastatic regions (77.9%), while only 18 of 67 (26.9%) had positive morphological imaging [31]. In 21 patients with recurrent PCa and rising PSA, 31 PSMA-positive nodules were found in seven patients (33.3%), and only 11 nodules with a >8-mm diameter were found on CT scan. Among the other 14 patients (66.7%), the diameters of 18 (37%) PSMA-positive lymph nodes were <8mm. The mean short axis diameter was 5.0 mm (range, 2.4-7.9mm). As a result, ^{68}Ga-PSMA PET/CT found lymph node recurrence in two-thirds of cases missed by routine morphological examination. The use of ^{68}Ga-PSMA PET/CT imaging may lead to reclassification from cN0 to cN1 [30]. However, there was also a different result. Gallium-68-PSMA PET/CT and MRI can both perform to detect lymph node metastases in patients with intermediate- and high-risk PCa, with no significant difference (P>0.05) [20].

Bone metastasis

There were 8 articles (751 patients) on the diagnostic performance of BM metastases in PCa patients by ^{68}Ga-PSMA PET/CT [10, 16, 18, 21, 23, 24, 32, 33]. Bone metastases were identified in various studies including imaging technique, histological correlations, and clinical follow-up. The sensitivities and specificities of ^{68}Ga-PSMA PET/CT in detecting bone metastasis were excellent, ranging from 80%-100% and 95.6%-100%, respectively.

Gallium-68-PSMA PET/CT can accurately detect most of the false positive and false negative findings on bone scintigraphy (BS) [10, 21]. Simsek et al. (2020) presented that ^{68}Ga-PSMA PET/CT was still superior to BS + single photon emission computed tomography (SPECT)/CT due to the limited number of false positives [18]. Zachoet al. (2018) also found that both ^{68}Ga-PSMA PET/CT and fluorine-18-sodium fluoride (^{18}F-NaF) PET/CT have excellent diagnostic accuracy for bone metastases, while MRI had poor diagnostic efficiency [16, 24]. In a retrospective study of 177 PCa patients, the ^{68}Ga-PSMA uptake in PET-positive/CT-negative bone metastases was significantly lower than that in PET-positive/CT-positive bone metastases (P<0.05). The maximum of standard uptake value (SUVmax), the mean of standard uptake value(SUVmean), PSMA-tumour volume, and PSMA-total lesion of patients with a GS of>7 were significantly higher than those with a GS≤7 (P<0.05). There was no significant correlation between changes of bone density and CT-derived volume measurements of metastatic bone lesions and changes of serum PSA levels before and after treatment (P>0.05) [32]. Carbon-11 (^{11}C)-choline is also commonly used in the metastasis detection of PCa. A retrospective analysis by Schwenck et al. (2017) showed that ^{68}Ga-PSMA PET/CT can detect more suspicious bone metastases than ^{11}C-choline PET/CT in both primary and recurrent PCa. Carbon-11-choline-positive and ^{68}Ga-PSMA-negative tumours/metastases were also found in this study [23]. A study by Lawal et al. (2020) suggested that reducing more uncertain lesions may detect more lesions in patients with advanced PCa by ^{68}Ga-PSMA PET/CTthan ^{68}Ga-NODAGA PET/CT and technetium-99m-methyl diphosphonate (^{99m}Tc-MDP) BS. However, ^{68}Ga-NODAGA PET/CT may be a more suitable imaging method for detecting bone lesions without expressing PSMA in patients with PSA progression [33].

Other distant metastases

At present, there are few articles about ^{68}Ga-PSMA PET/CT for liver and lung metastases of PCa. A total of 739 PCa patients were included in the study by Damjanovic et al. (2019), with 91 confirmed lung metastases in 20 patients. The results showed that 72.5% of lung metastases were PSMA-positive and 27.5% were PSMA-negative. PSMA was highly expressed in the majority of lung metastases, buta considerable number of metastatic tumours were PSMA-negative. Benign pulmonary lesions showed a moderate tracer uptake, which was significantly lower than that of PSMA-positive lung metastases, but significantly higher than that of PSMA-negative metastases. Therefore, according to the SUVmax of ^{68}Ga-PSMA PET, it is impossible to distinguish pulmonary metastases from benign lung lesions [25]. This conclusion is consistent with that of the study by Pyka et al. (2016), which showed that lung metastasis of PCa was also difficult to differentiate from primary lung cancer based on the SUVmax of ^{68}Ga-PSMA PET [26].

Damjanovic et al. (2019) studied 739 PCa patients with 103 liver metastases confirmed by CT, MRI, ^{68}Ga-PSMA PET/ CT, and follow-up in 18 patients. The results showed that 77.7%

of the lesions were PSMA-positive and 22.3% were PSMA-negative. The SUVmean of PSMA-positive lesions was significantly higher than that of normal liver tissues. The SUVmean of PSMA-negative lesions was significantly lower than that of normal liver tissues. The CT attenuation value of liver metastases was significantly lower than that of normal liver tissues, especially PSMA-negative lesions. Thus, it was demonstrated that the majority of liver metastases highly overexpress PSMA and can be directly detected by ^{68}Ga-PSMA PET/CT [27].

Quantitative analysis (meta-analysis)

A total of 16 studies including 1567 patients were included in the meta-analysis.

The diagnostic performance of ^{68}Ga-PSMA PET/CT in patients with suspected metastasis was analysed by visual analysis. Among them, 10 studies were used for meta-analysis of lymph node metastases [9, 11-15, 17, 19, 20, 22], and 6 were used for meta-analysis of bone metastasis [10, 16, 18, 21, 23, 24]. Results of the meta-analysis are presented in Figures 3-8.The per-patient pooled sensitivity, specificity, LR^+, LR^-,DOR, and AUC of lymph node metastases were 0.61 [0.39, 0.79], 0.96 [0.92, 0.98], 14.4 [6.0, 34.3], 0.41 [0.23, 0.71], 35 [9, 138], and 0.95 [0.93-0.97], respectively, and the per-lesion pooled sensitivity, specificity, LR^+, LR^-, DOR, and AUC of lymph node metastases were 0.74 [0.50, 0.89], 0.99 [0.98, 1.00], 76.0 [27.5, 209.9], 0.26 [0.12, 0.56], 289 [65, 1277], and 0.99 [0.97-0.99], respectively. The per-patient pooled sensitivity, specificity, LR^+, LR^-, DOR, and AUC of bone metastasis were 0.97 [0.93, 0.99], 1.00 [0.69, 1.00], 1100.1 [2.2, 560481.2], 0.03 [0.01, 0.07], 37490 [74,19003392], and 0.98 [0.97-0.99], respectively.

Due to insufficient data, it is impossible to perform a meta-analysis on the per-lesion diagnostic performance of bone metastasis. Because there are few articles about ^{68}Ga-PSMA PET/CT for liver and lung metastases of PCa, it was difficult to perform a meta-analysis.

Publication bias and heterogeneity exploration

No significant publication bias was detected by the Deeks' funnel plot asymmetry test (P>0.1).

The per-patient pooled sensitivity and specificity I2 values of ^{68}Ga-PSMA PET/CTon the diagnostic performance of lymph node metastases in PCa patients were 85.67 and 49.91, respectively. The per-lesion pooled sensitivity and specificity I2 values of ^{68}Ga-PSMA PET/CT on the diagnostic performance of lymph node metastases in PCa patients were 96.99 and 98.34, respectively. The per-patient pooled sensitivity and specificity I2 values of ^{68}Ga-PSMA PET/CTon the diagnostic performance of bone metastasis in PCa patients were 63.41 and 65.84, respectively. All data were highly heterogeneous. We could not determine which study had a greatest impact on heterogeneity by the method of removing single studies. Due to the lack of research data, it was impossible to analyse the source of heterogeneity using subgroup analysis. In this study, the bivariate mixed effects model was used to merge and analyse the data. The bivariate mixed effects model is an essential random-effects model, which can reduce the impact of data heterogeneity on the accuracy of the research results.

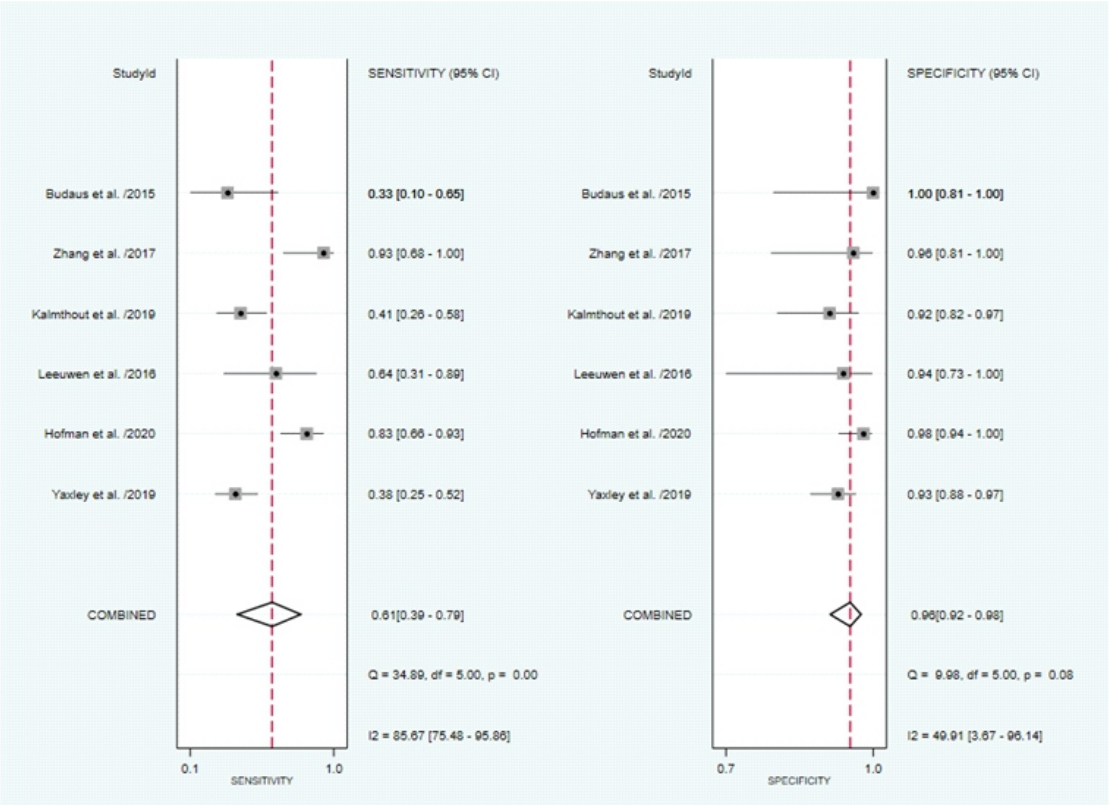

Figure 3. The per-patient forest plots of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases in PCa patients.

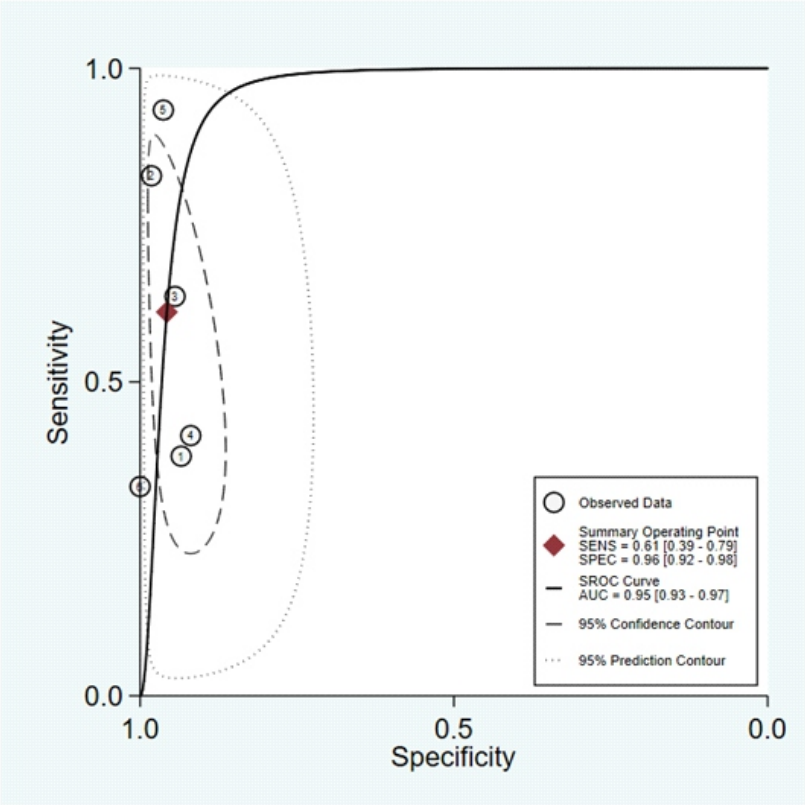

Figure 4. The per-patient SROC curves of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases in PCa patients.

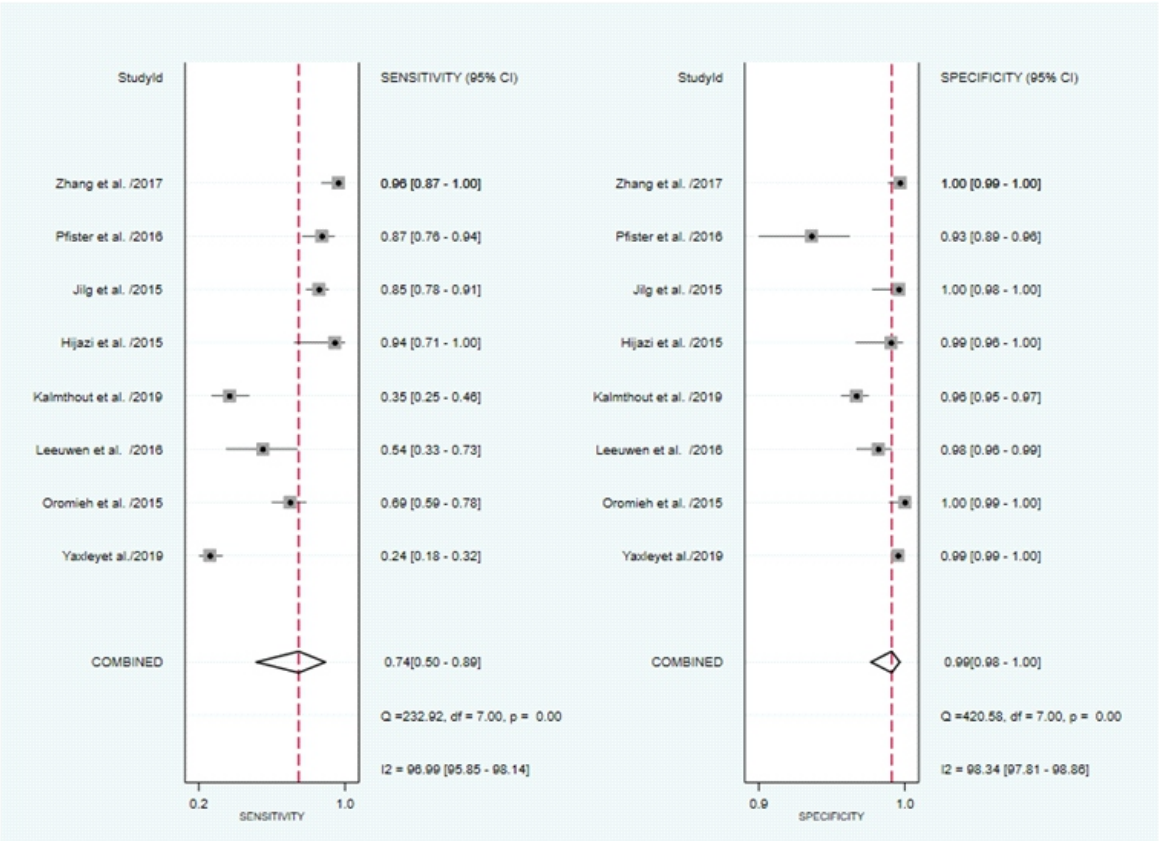

Figure 5. The per-lesion forest plots of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases in PCa patients.

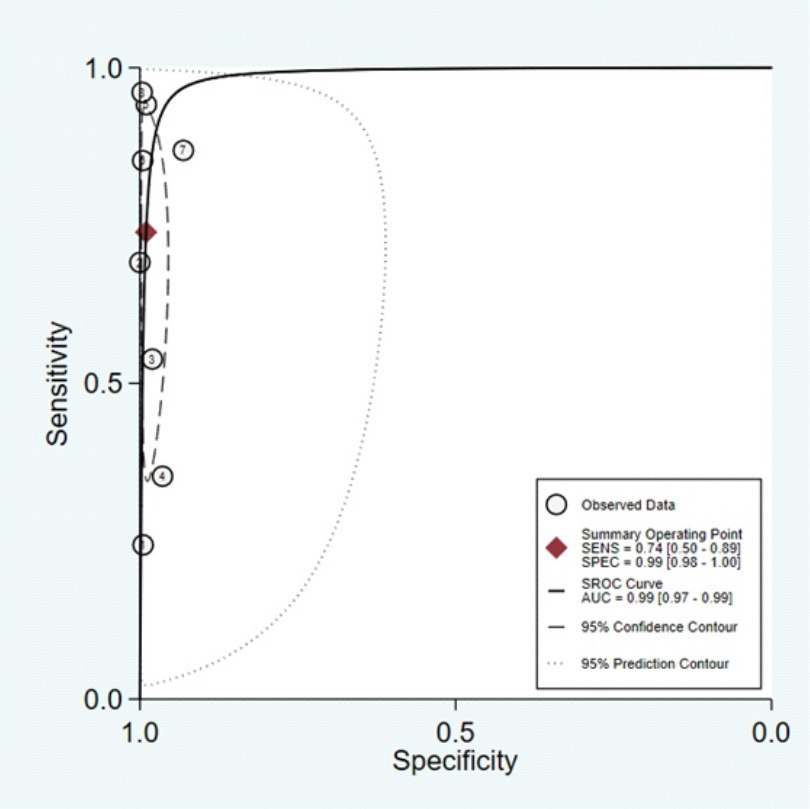

Figure 6. The per-lesion SROC curves of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases in PCa patients.

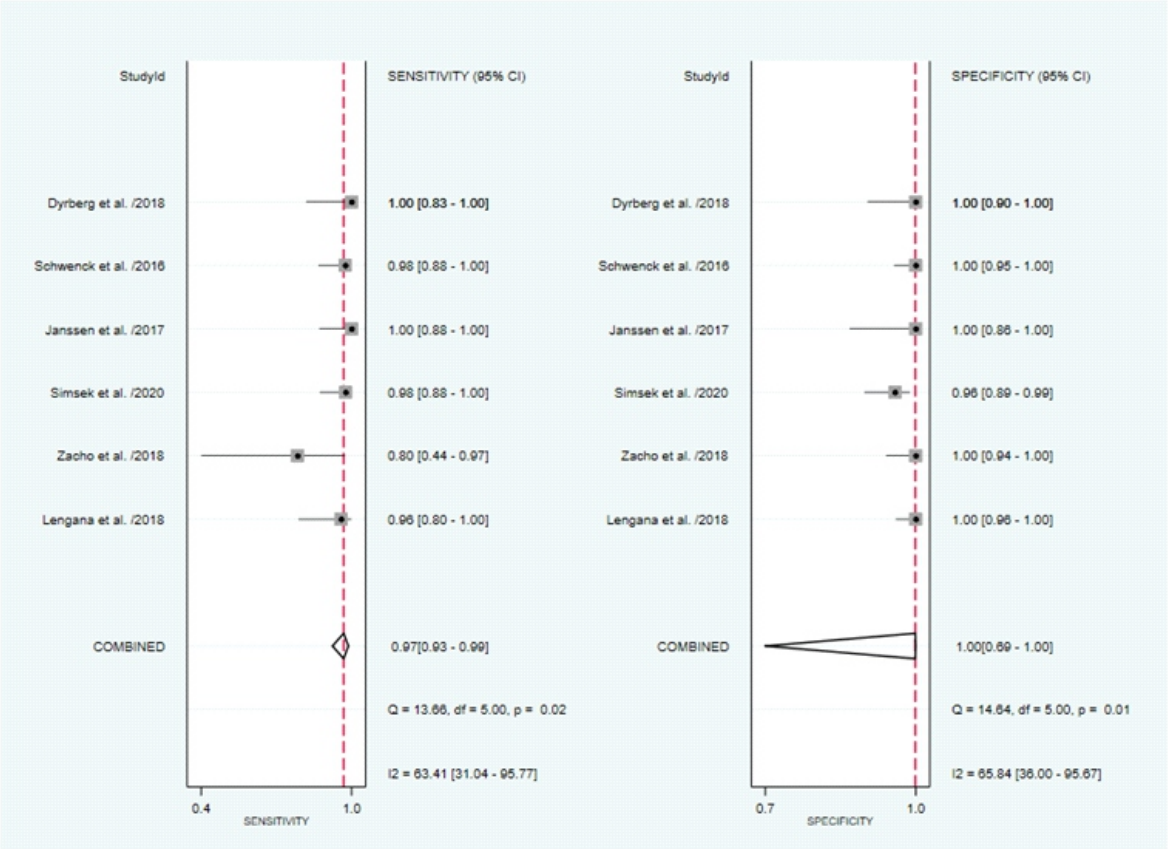

Figure 7. The per-patient forest plots of ^{68}Ga-PSMA PET/CT in detecting bone metastases in PCapatients.

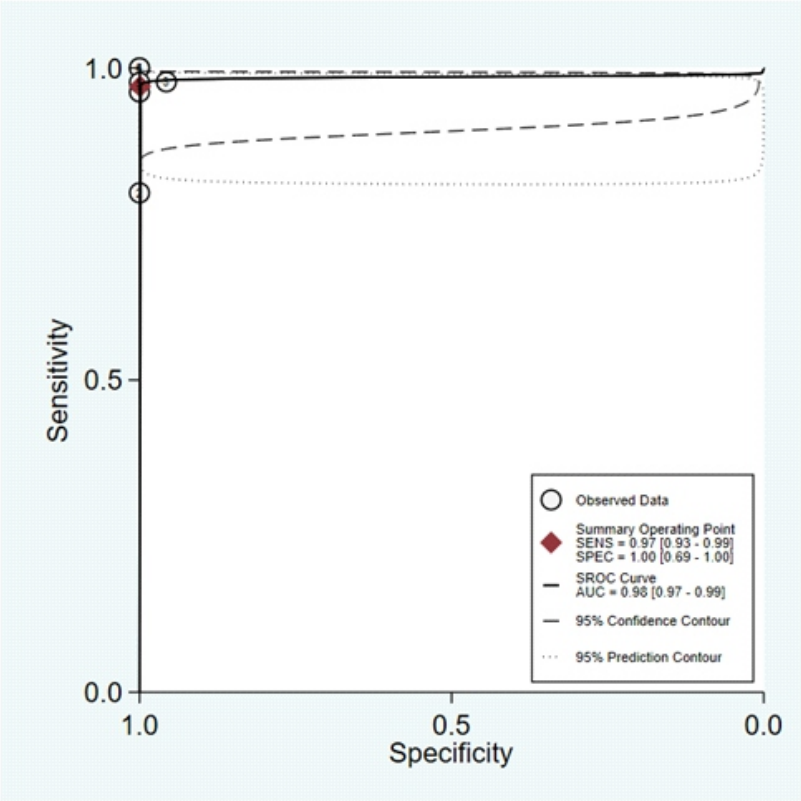

Figure 8. The per-patient SROC curves of ^{68}Ga-PSMA PET/CT in detecting bone metastases in PCapatients.

Discussion

Prostate cancer is one of the most common malignant tumours. Lymph node metastases and bone metastases are the most common, followed by lung and liver metastases. Although some PCa patients receive timely and effective treatment, they still have a high risk of recurrence. Up to 50% of patients have biochemical recurrence and metastases. The risk of PCa increases in 15 years, and the mortality rate is as high as 35% [34, 35].

Therefore, a precise method to detect metastases is needed. Gallium-68-PSMA PET/CT is a new and promising imaging technique. However, due to the limited ^{68}Ga-PSMA PET/CT-related literature, data regarding detection rate of metastases was heterogeneous. In particular, for lymph node metastases, the sensitivity ranges from 33.3% to 96.08%. Therefore, it is imperative to conduct a big data analysis.

At present, bilateral extended PLND is still the standard for staging [36]. In intermediate- to high-risk PCa patients, bilateral extended PLND is recommended if the estimated risk of lymph node metastases is more than 5% [37, 38]. Salvage lymphadenectomy can be considered a palliative treatment in patients with recurrent PCa or with lymph node metastases in the pelvic or paraaortic region that slows down the progression of the disease and delays systemic treatment [39, 40]. However, extended PLND or sLAD is an invasive diagnostic intervention that can cause severe complications (such as lymphocysts and lower extremity oedema) [41]. Early detection of PSA after PCa surgery or radiotherapy can be used to identify PCa recurrence. However, it has been proven difficult to locate the site of recurrence, so empirical therapies such as pelvic irradiation and androgen-deprivation therapy have been used [42], which may lead to overtreatment. Therefore, a reliable imaging method is urgently needed before treatment. Traditional methods for detecting lymph node metastases, such as CT and MRI, depend on morphological features, that is, size and shape. In particular, the detection of small metastatic lymph node is challenging in recurrent PCa. The lymphnodelarger than 8-10mm are considered suspicious metastases. However, more than 80% of lymph node metastases of PCa are less than 8mm. Large lymph nodes above the size threshold may simply represent nodal hyperplasia. Therefore, CT and MRI are not considered reliable for routine nodal staging [43]. Gallium-68-PSMA PET imaging successfully detected two-thirds of lymph node recurrence, which may be missed by traditional CT morphological criteria [14]. Some studies have also shown that PSMA-targeted radio-guided surgery techniques may further improve the value of PLND [44, 45]. However, our results showed that the pooled sensitivities of ^{68}Ga-PSMA PET/CT in detecting lymph node metastases were 0.61 based on per-patient and 0.74 based on per-lesion, which were in the middle level. The pooled specificities were good, and they were consistent with the results of the chosen studies. There were some differences in the inclusion criteria of the chosen articles. The possible causes of the low sensitivity are as follows. First, it is possible that the presence

of ^{68}Ga-PSMA PET/CT imaging is the main focus of the primary prostate before operation, which may lead to insufficient uptake of an imaging agent in other metastatic lesions, thus reducing the sensitivity [11]. A semi-quantitative study demonstrated that immunohistochemical PSMA staining was strongest in primary PCa and lowest in lymph node metastases [46]. Another explanation may be that a critical size or vascularisation threshold limits the exposure and binding of the ^{68}Ga-labelled PSMA ligand, restricting perfusion in lymph node metastases.It may also have an impact on different levels of image acquisition technology and readers. A recent meta-analysis similarly evaluated five studies comparing ^{68}Ga-PSMA PET/CT to histopathology in 266 patients newly diagnosed with PCa. For lymph node metastases detection, the pooled sensitivity was 0.74 (95% CI: 0.51-0.81) and specificity was 0.96 (95% CI: 0.85-0.99) [47], similar to our results.

The sensitivities and specificities were high in some studies. In Jilg et al. (2017) study patients diagnosed with biochemical recurrence but negative ^{68}Ga-PSMA PET/CT imaging (i.e., false negative) were excluded [19]. Therefore, the sensitivity may increase unreasonably.

Other tumours or sites, such as the thyroid, colon, kidney, brain, neck, abdominal cavity, and sacral ganglion, also showed PSMA uptake; thus, false positives were added [48, 49]. Therefore, Vinsenia et al. (2017) intended to exclude other patients of this type to reduce false positives [28]. False positives have been reduced, but the overall results seem less reliable.

Our results showed that ^{68}Ga-PSMA PET/CT has a good performance in detecting bone metastases. The sensitivity of BS for the detection of osteoblast bone metastases was high, but the specificity, sensitivity of osteolysis, and bone marrow metastases detection were low [50]. Pyka et al. (2016) showed that the detection of bone metastasis of PCa by ^{68}Ga-PSMA PET is more sensitive and specific than BS. If PET is combined with CT, it will be more sensitive and specific, and the accuracy will be higher [51]. According to the European Association of Urology (EAU) guidelines, BS should not be used in BCR until PSA levels reach 10ng/mL due to inadequate sensitivity [52]. Although SPECT/CT can improve the accuracy of BS, small lesions and osteolytic lesions can still be overlooked. The flare phenomenon may be diagnosed as bone metastases on BS, which increases the false positive rate [10, 53]. Gallium-68-PSMA PET/CT can detect bone and bone marrow metastases in clinical and experimental environments, and it is superior to BS and can potentially replace BS. Gallium-68-PSMA PET/CT has a significant detection rate for PCa metastases, even at low PSA levels [54]. However, BS is the most widely used method in clinical practice due to its low price. It can also detect bone metastases with good sensitivity and can carry out whole-body skeletal examination. The latest EAU guidelines recommend ^{68}Ga-PSMA PET/CT only for patients with BCR, and they still recommend BS for intermediate- and high-risk PCa staging or restaging of symptomatic patients, regardless of serum PSA levels [55]. Zacho et al. (2018) also found that both ^{68}Ga-PSMA PET/CT and ^{18}F-NaF PET/CT have excellent diagnostic accuracy for bone metastases, but while MRI had poor diagnostic efficiency [16, 24]. Particularly, ^{18}F-NaF PET/CT has excellent advantages in investigating bone metastasis. Our team's research demonstrated ^{18}F-NaF PET/CT good sensitivity and specificity for detecting bone metastases [56]. Carbon-11-choline is also commonly used in the metastases detection of PCa. Schwenck et al. (2017) showed that ^{68}Ga-PSMA PET/CT can detect more suspicious bone metastases than ^{11}C-choline PET/CT in both primary and recurrent PCa [23]. Oromieh et al. (2014) showed that ^{68}Ga-PSMA PET/CT could better detect bone metastases than ^{11}C-choline PET/CT, especially in cases where PSA levels are low [57]. Carbon-11-choline-positive and ^{68}Ga-PSMA-negative tumours/metastases were also found in this study. This may be due to the influence of the tumour/metastases environment and the habits of PCa cells to decide whether to express PSMA or choline transporter [23].

Some bone metastases can be detected by BS but were negative using ^{68}Ga-PSMA PET/CT. Maybe it's because cellular PSMA expression is increased with increasing Pca aggressiveness, it is anticipated that with higher GS, there may be a down regulation of PSMA cellular expression as cells become more poorly differentiated. In the course of PCa, 10%-15% of the patients may show a lack of PSMA expression [58, 59]. Therefore, every method of inspection is not perfect. If we can combine the advantages of various examinations, we can improve the accuracy of disease diagnosis. Some bone metastases can be identified by bone scan, but PSMA is negative

According to Bubendorf et al. (2000), pulmonary metastases were regarded as the second most common extranodal metastases in PCa (46%), after bone metastases (90%) [60]. The PSMA imaging agent can be moderately uptaken in pulmonary opacities. In addition, PSMA-negative status existed in a considerable number of PCa metastases. It is difficult to differentiate metastases and benign pulmonary opacities based on the SUVmax in ^{68}Ga-PSMA PET alone [25]. Pykaet al. (2016) investigated the imaging and differentiation of pulmonary PCa metastases, primary lung cancer, and tuberculosis in 45 patients using ^{68}Ga-PSMA PET. In their study, it was not possible to differentiate pulmonary metastases from lung cancer and tuberculosis. Using immunohistochemistry, they showed PSMA expression in the neo-vasculature of several PSMA PET-positive lung cancers and tuberculous lesions [26]. As mentioned, her types of tumours or sites may uptake PSMA, such as lung, colorectal, gastric, renal, and thyroid cancer, particularly within the tumour neovasculature [25]. It may be that PSMA is not expressed in some lung metastases, which leads to false negative imaging.

Liver metastases is considered the third most common type after bone and lungmetastases. Damjanovic et al. (2018) found that the majority of liver metastases highly overexpress PSMA and can be directly detectable. However, a considerable number of metastases are PSMA-negative [27]. Poussel et al. (2007) reported that liver metastases are often associated with neuroendocrine characteristics in PCa [61]. Neuroendocrine trans-differentiation may lead to the loss of PSMA expression, thus hindering liver metastasis uptake in ^{68}Ga-PSMA PET. It is thought that the degree of neuroendocrine trans-differentiation increases with disease progression and in response to androgen-deprivation therapy [62]. In

addition, the relatively high background of the liver may also affect the uptake of ^{68}Ga-PSMA in liver metastases [63].

In conclusion, ^{68}Ga-PSMA PET/CT showed a good diagnostic performance in bone metastasis in PCa patients. However, a considerable number of lesions were false negatives. All analyses were based on limited data, especially on liver and lung metastases. Therefore, the conclusions are not completely reliable. Prostate cancer metastases are not completely analysed in this study because a relevant research lacks. Therefore, further studies are necessary on the diagnosis of PCa metastases using ^{68}Ga-PSMA PET/CT.

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