Original Article

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# Diagnostic Performance of $^{68}$Gallium Labelled Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography and Magnetic Resonance Imaging for Staging the Prostate Cancer with Intermediate or High Risk Prior to Radical Prostatectomy: A Systematic Review and Meta-Analysis

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**Purpose:** To compare the diagnostic efficiency of $^{68}$Gallium labelled prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA PET) and magnetic resonance imaging (MRI) for staging the lymph node metastases (LNMs) in the prostate cancer.

**Materials and Methods:** A broad search of scientific databases including PubMed, EMBASE, Web of Science, Cochrane Database, and Chinese Biomedicine Literature Database (updated prior to November 1st, 2018) was conducted systematically by two reviewers. In this paper, we evaluated the methodological quality of each included article independently and performed a systematic review and meta-analysis to reveal the summary of the diagnostic performance of $^{68}$Ga-PSMA PET and MRI in properly identifying LNMs of intermediate- and/or high-risk prostate cancer.

**Results:** Thirteen eligible articles comprising 1,597 patients were included. For LNMs detection, the pooled sensitivity and specificity of $^{68}$Ga-PSMA PET were 0.65 (95% confidence interval [CI]: 0.49–0.79) and 0.94 (95% CI: 0.88–0.97), respectively, while the corresponding values of MRI were 0.41 (95% CI: 0.26–0.57) and 0.92 (95% CI: 0.86–0.95). The area under the symmetric receiver-operating characteristic (SROC) curve for $^{68}$Ga-PSMA PET and MRI were 0.92 and 0.83, respectively.

**Conclusions:** In intermediate- or high-risk pre-treatment prostate cancer, $^{68}$Ga-PSMA PET had a higher sensitivity and a slightly different specificity in probing the LNMs when comparing with MRI. Moreover, the area under the SROC curve indicated that $^{68}$Ga-PSMA PET was a more effective weapon for predicting the LNMs prior to radical surgery.

**Keywords:** Magnetic resonance imaging; Metastasis; Meta-analysis; Positron-emission tomography; Prostate cancer



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## INTRODUCTION

Prostate cancer, the most frequent solid malignancy among men, has become the third leading cause of cancer-associated deaths worldwide [1,2]. An accurate preoperative assessment of the tumor stage plays an crucial role for therapy planning, and radical prostatectomy is a extensively used potentially curative strategy [3]. While the detection of serum prostate specific antigen (PSA) levels has led to earlier diagnosis of prostate cancer [4], the conventional imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), choline-based positron emission tomography (PET)/CT as well as $^{99}$mTc–methylene diphosphate bone scan, are more likely to be used for evaluating local tumor stage, seminal vesicle invasion, lymph node metastases (LNMs), and skeleton metastatic lesions. However, regardless of promising results that the conventional imaging techniques including MRI have performed, a wide range of reported sensitivities and specificities still exhibit their limitations in the current clinical scenarios [5].

Prostate-specific membrane antigen (PSMA), a transmembrane protein over-expressed in prostate cancer, has increasingly attracted the interest as a newly emerging approach for clinical imaging. Evidences have shown that the expression of PSMA in prostate cancer is 100- to 1,000-fold higher than that in normal tissues [6,7], and higher levels of PSMA expression have been demonstrated to be associated with increasing stage, Gleason grade and PSA level in prostate cancer [6,8]. To date, various PET ligands have been applied for the detection of prostate cancer [9], and despite the most common ligands 11 C- or 18 F-choline, a late-model probe named $^{68}$Gallium labelled prostate-PSMA ligands ($^{68}$Ga-PSMA) recently has drawn a concentration of researchers [10,11]. It has been well reported that $^{68}$Ga-PSMA-PET has superior sensitivity and specificity when comparing with choline-based PET [12]. Besides, a rising number of evidence has suggested that this targeted modality may provide more precise imaging for detecting prostate cancer [13,14].

Perera et al [15] have previously performed a systematic review and meta-analysis to identify the sensitivity and specificity in advanced prostate cancer, indicating its high level of accuracy as a predictor. However, no relevant systematical review and meta-analysis over the comparison between $^{68}$Ga-PSMA-PET and the conventional imaging modalities has been yet published. The utility of $^{68}$Ga-PSMA PET imaging in intermediate- and high-risk prostate cancer outlined in studies were systematically reviewed. Hence, we decided to perform this meta-analysis. Because the data from multi-central randomized control trials was rare, we collected as many literatures as possible to systematically evaluate the diagnostic accuracy of Ga-PSMA PET imaging and conventional imaging modalities. The aim of our study was to complete a meta-analysis comparing the diagnostic performance of $^{68}$Ga-PSMA-PET and the conventional imaging modalities MRI in the detection of LNMs in intermediate- and high-risk preoperative prostate cancer patients.

## MATERIALS AND METHODS

### 1. Data sources and search strategies

A systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [16].

The scientific databases (PubMed, EMBASE, Web of Science, Cochrane Database, Chinese Biomedicine Literature Database) were searched by two authors independently to pick out eligible published articles (up to November 2018) using the combination of several keywords, including: (1) "prostate neoplasms" or "prostatic neoplasm" or "prostate cancer" or "cancer of the prostate" or "prostate malignancy", (2) "prostate specific membrane antigen" or "PSMA", (3) "positron emission tomography" or "PET", (4) "magnetic resonance imaging" or "MRI". Besides, additional studies were identified from the references of original articles and reviews related to this topic.

### 2. Study selection criteria

Following were the inclusion criteria: (1) patients should have undergone $^{68}$Ga-PSMA PET and/or MRI. (2) Patients should not receive radical prostatectomy or other non-surgical treatment before accepting the imaging modalities above. (3) Patients should have been biopsy-proven intermediate- or high-risk prostate cancer. (4) Histopathology (treated with pelvic lymph node dissection or extended pelvic lymph node dissection) as a golden standard for lymph node detection. (5) A minimum of 10 patients should be included in the study. (6) The numbers of true-positive (TP), false-positive (FP),

true-negative (TN), and false-negative (FN) results can be calculated, (7) language of inclusion studies should be either English or Chinese.

Duplicated articles, case reports, review articles, editorials, clinical conference abstracts, cell and animal articles, meta-analysis were excluded to ensure the accuracy of the data.

## 3. Quality assessment

In order to evaluate the methodological quality of the eligible studies, the Quality Assessment Tool for Diagnostic Accuracy Studies version 2 (QUADAS-2) were used by two evaluators independently [17], and any discrepancies were discussed and resolved. The tool assesses the following four domains: patient selection, index test, reference standard, as well as the timing of reference test. The four domains above are all assessed in terms of risk of bias when we also assessed the degree of applicability of first three. Finally, we used Review Manager 5.3 software to evaluate the methodological quality and draw the figures.

## 4. Data extraction and statistical analysis

The extracted data from the enrolled studies should obtain following basal characteristics: author, year of publication, location, study design, the number of patients, age, pre-PET PSA level, Gleason scores, histopathologic data, rates of imaging modalities ($^{68}$Ga-PSMA PET and MRI) positivity, the stage and size of tumor. If available, the numbers of TP, FP, FN, and TN from each paper would also be calculated. The numbers were used to measure sensitivity, specificity as well as a corresponding confidence interval (CI). If needed, we would contact the corresponding author for further details and the study would be excluded if there was no response.

To synthesize the data extracted, we used the bivariate mixed-effects regression model [18] in our meta-analysis. Based on the two-dimensional model, we obtained logit sensitivity and specificity with their 95% CIs. Then, pooled analysis of sensitivity, specificity and diagnostic odds ratios (DORs) for $^{68}$Ga-PSMA PET and MRI with corresponding 95% CIs was performed. Next, a summary receiver-operating characteristic (SROC) curve was back-transformed from the obtaining summary sensitivity, specificity and DORs. All the data was analyzed through MIDAS module for Stata software version 14.0.

## 5. Heterogeneity and publication bias

The chi-square test were used to analyze the heterogeneity between the eligible studies. $I^2$ were measured as it lies between 0% and 100%. The respective value were approximately divided into 0%, 25%, 50%, 75%,

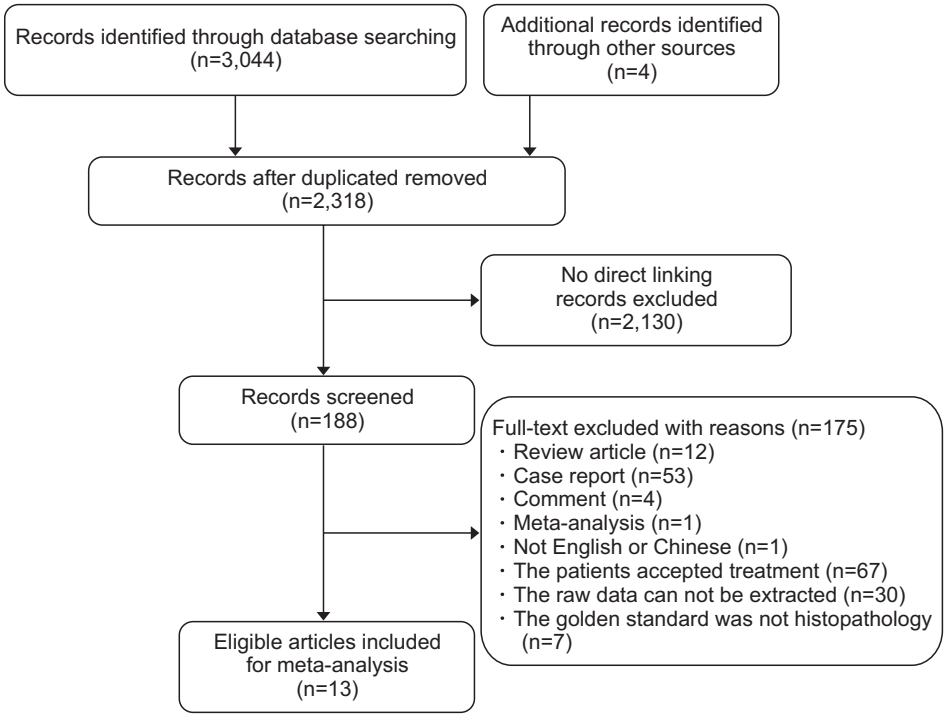


Fig. 1. Flow diagram of the literature search.

Table 1. Study characteristics

| First author (year) | Country | Study type | Subject | Median age (y) | Median PSA (ng/mL) | HP | Index test | TP | FP | TN | FN | SS | SP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LNMs | | | | | | | | | | | | | |
| Maurer (2016) [14] | Germany | Retrospective | 130 | 66.5 (45–84) | 11.55 (0.57–244.00) | Yes | $^{68}$Ga PET, | 27 | 1 | 88 | 14 | 0.66 | 0.99 |
| | | | | | | | MRI | 18 | 13 | 76 | 23 | 0.44 | 0.85 |
| van Leeuwen (2018) [21] | Australia | Retrospective | 140 | NR | 9.4 (NR) | Yes | $^{68}$Ga PET, | 27 | 11 | 78 | 24 | 0.53 | 0.88 |
| | | | | | | | MRI | 7 | 1 | 88 | 44 | 0.14 | 0.99 |
| Öbek (2017) [22] | Turkey | Prospective | 51 | 64 (58–70) | 26.5 (4.1–47.9) | Yes | $^{68}$Ga PET, | 8 | 5 | 31 | 7 | 0.53 | 0.86 |
| | | | | | | | MRI | 1 | 9 | 31 | 3 | 0.25 | 0.76 |
| Zhang (2017) [23] | China | Retrospective | 42 | 69 (55–82) | 37.25 (7.2–348.0) | Yes | $^{68}$Ga PET, | 14 | 1 | 26 | 1 | 0.93 | 0.96 |
| | | | | | | | MRI | 14 | 2 | 25 | 1 | 0.93 | 0.96 |
| Gupta (2017) [24] | India | Retrospective | 12 | NR | NR | Yes | $^{68}$Ga PET, | 7 | 1 | 4 | 0 | 1 | 0.8 |
| | | | | | | | MRI | 4 | 1 | 4 | 3 | 0.57 | 0.8 |
| Budäus (2016) [25] | Germany | Retrospective | 30 | 62 (44–75) | 8.8 (1.4–376.0) | Yes | $^{68}$Ga PET | 4 | 0 | 18 | 8 | 0.33 | 1 |
| Berger (2018) [26] | Australia | Retrospective | 50 | NR | NR | Yes | $^{68}$Ga PET | 1 | 4 | 44 | 1 | 0.5 | 0.92 |
| van Leeuwen (2017) [27] | Australia | Prospective | 30 | 65 (60–71) | 8.1 (5.2–10.1) | Yes | $^{68}$Ga PET | 7 | 1 | 18 | 4 | 0.64 | 0.95 |
| Jeong (2013) [28] | Korea | Retrospective | 922 | 67 (42–85) | 10.7 (0.3–737.0) | Yes | MRI | 8 | 27 | 837 | 50 | 0.14 | 0.97 |
| Pinaquy (2015) [29] | France | Prospective | 47 | 63 (50–79) | 24 (5–371) | Yes | MRI | 3 | 3 | 32 | 6 | 0.33 | 0.84 |
| Selnæs (2018) [30] | Norway | Prospective | 28 | 66.1 (55–72) | 16.7 (6.3–56.9) | Yes | MRI | 4 | 2 | 14 | 6 | 0.4 | 0.88 |
| von Below (2016) [31] | Sweden | Prospective | 40 | NR | NR | Yes | MRI | 11 | 2 | 18 | 9 | 0.55 | 0.9 |
| Van den Bergh (2015) [32] | Belgium | Prospective | 75 | 64.6 (49–74) | 10.4 (52–71) | Yes | MRI | 13 | 2 | 36 | 23 | 0.36 | 0.95 |

Values are presented as number only, median (range), or percent only.
PSA: prostate specific antigen, HP: histopathology, TP: true positive, FP: false positive, TN: true negative, FN: false negative, SS: sensitivity, SP: specificity, LNMs: lymph node metastases, NR: not reported, $^{68}$Ga PET: $^{68}$Gallium positron emission tomography, MRI: magnetic resonance imaging.

which indicate no, low, moderate and high heterogeneity [19]. We would choose the random-effects models when $I^2$ was superior to 50%; on the contrary, we preferred to choose the fixed-effects models when $I^2$ was less than 50%. To validate if there existed a threshold which was thought as one of main source of heterogeneity, we performed Spearman correlation coefficients. If the p-value >0.05, there was no threshold.

To test the publication bias in each study, we used the Stata 14.0 software (STATA Corp., College Station, TX, USA) to analyze all included studies according to the Deek's test [20].

## 6. Ethics statement

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

# RESULTS

## 1. Study selection and the characteristics

We systematically retrieved through the scientific database (PubMed, EMBASE, Web of Science, Cochrane Database, Chinese Biomedicine Literature Database), which identified 3,044 citations. Additional 4 citations were from the references of the eligible articles. Then, 730 duplicated and 2,130 irrelevant studies were excluded by the abstracts screening. The remaining 188 studies were assessed in detail and 175 of them were excluded because (1) the study type was review, case report, comment or meta-analysis (n=70); (2) the language was not English or Chinese (n=1); (3) the raw data could not be extracted from the articles (n=30); (4) the golden standard was not histopathology (n=7); (5) the patients accepted surgery or hormone therapy (n=67). Finally, 13 eligible articles met the inclusion cri-

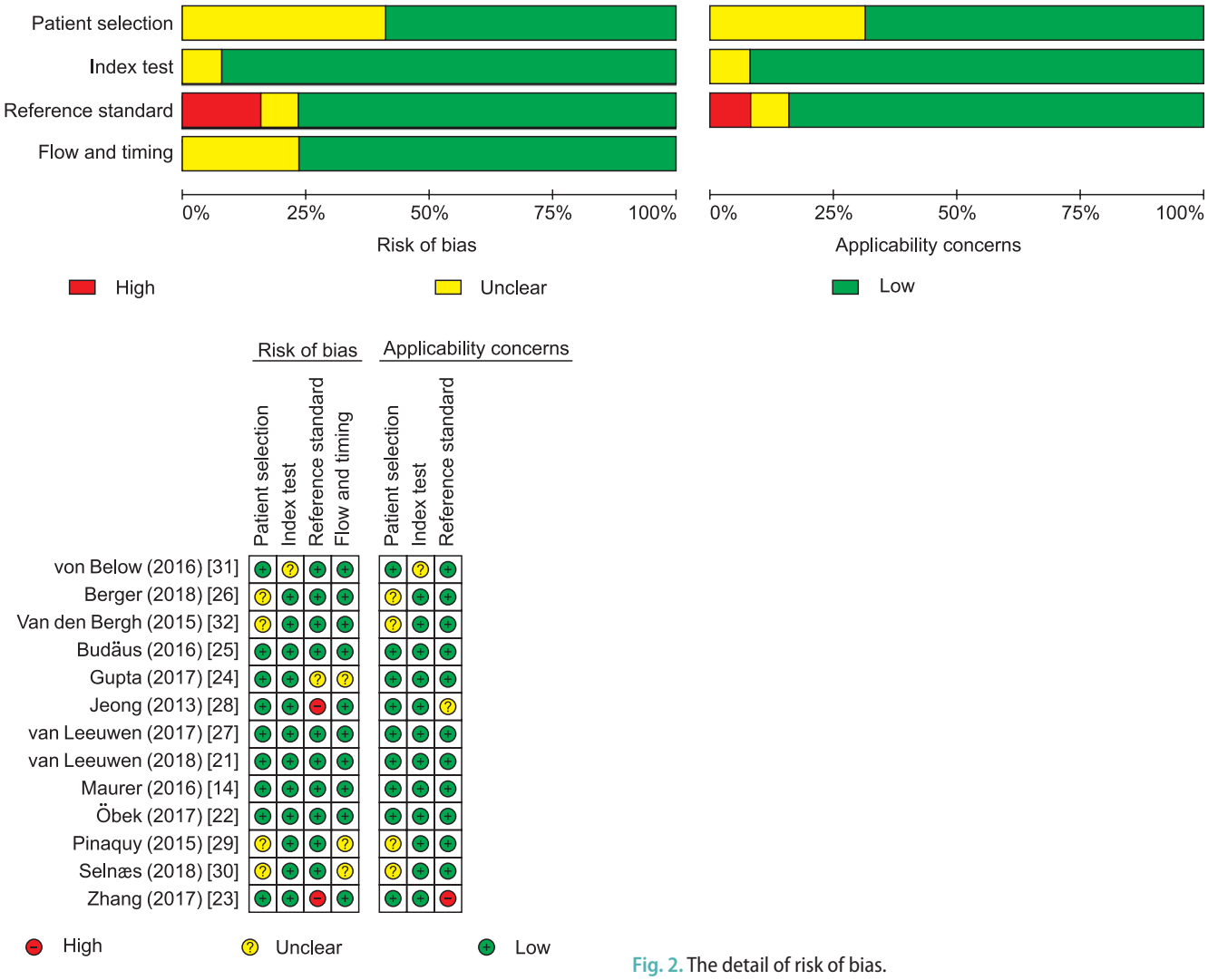


Fig. 2. The detail of risk of bias.

teria. The flow diagram of the study selection process was shown in Fig. 1.

Thirteen eligible studies containing 1,597 patients who suffered biopsy-proven intermediate- or high-risk prostate cancer were included in our meta-analysis. All the patients were prior to surgery and non-treated with hormone therapy when undergoing the imaging examination method. The age of the patients was ranging from 42 to 84 years; the PSA level from 0.3 to 737 ng/mL; and the patient number ranged from 12 to 922. In total, seven of the eligible studies were retrospective, and the remaining five studies were prospective. Among these studies, 3 were from Australia, 2 were from Germany, and 1 of each was from China, Turkey,

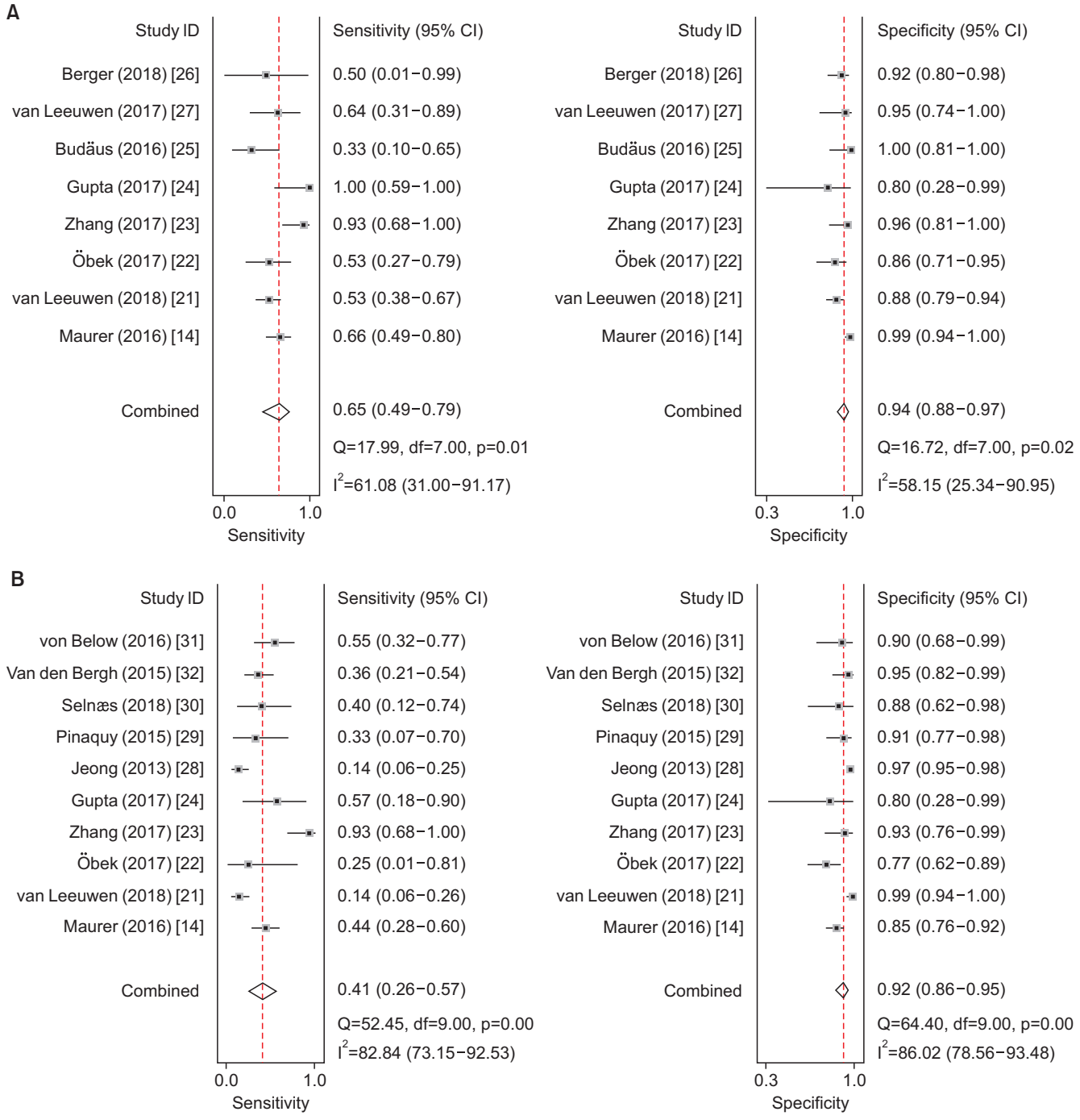


Fig. 3. Forest plot concluded the sensitivity and specificity of the two modalities. (A) the diagnostic performance of $^{68}$Gallium positron emission tomography group; (B) the diagnostic performance of magnetic resonance imaging. CI: confidence interval, df: degree of freedom.

Korea, India, France, Sweden, Norway and Belgium. Other critical information is summarized in Table 1.

## 2. Methodological quality assessment

Referring to the QUADAS-2 quality assessment tool, seven studies enrolled consecutive patients. The index test was prior to surgery, while postoperative pathology was the only golden standard in all eligible articles, which indicated the reference standard barely influenced the result of the index test. According to the result of assessment, the overall quality of included research was credible. The summary of risk of bias and quality assessment is shown in Fig. 2.

## 3. Findings

In $^{68}$Ga-PSMA PET/CT group, we included eight studies [14,21-27] which represented 485 patients to identify its efficiency. The forest plot exhibited the results that the sensitivity for $^{68}$Ga-PSMA PET/CT ranged from 0.33 to 1.00, as the specificity ranged from 0.69 to 1.00 (Fig. 3A). The summary pooled parameters in $^{68}$Ga-PSMA PET/CT group were as follows: sensitivity: 0.65 (95% CI: 0.49–0.79); specificity: 0.94 (95% CI: 0.88–0.97); positive likelihood ratio (LR+): 10.6 (95% CI: 5.1–21.9); negative likelihood ratio (LR-): 0.37 (95% CI: 0.24–0.58); DOR: 29 (95% CI: 10–80).

Meanwhile, in MRI group, ten articles [14,21-24,28-32] represented 1,487 patients were evaluated. The corresponding values in the forest plot ranged from 0.14 to 0.93 and 0.57 to 0.96 (Fig. 3B). The summary pooled parameters in MRI group were as follows: sensitivity: 0.41 (95% CI: 0.26–0.57); specificity: 0.92 (95% CI: 0.86–0.95); LR+: 4.9 (95% CI: 3.1–7.6); LR-: 0.65 (95% CI: 0.51–0.83); DOR: 8 (95% CI: 4–13).

Comparing the pooled data between $^{68}$Ga-PSMA PET/CT and MRI, the overall sensitivity was 0.65 (95% CI: 0.49–0.79) *versus* 0.41 (95% CI: 0.26–0.57); the overall specificity was 0.94 (95% CI: 0.88–0.97) *versus* 0.92 (95% CI: 0.86–0.95), respectively; the overall LR+ was 10.6 (95% CI: 5.1–21.9) *versus* 4.9 (95% CI: 3.1–7.6); the overall LR- was 0.37 (95% CI: 0.24–0.58) *versus* 0.65 (95% CI: 0.51–0.83); and the DOR was 29 (95% CI: 10–80) *versus* 8 (95% CI: 4–13). $^{68}$Ga-PSMA PET/CT had a higher pooled sensitivity (0.65 *versus* 0.41) and a close pooled specificity (0.94 *versus* 0.92) when comparing with MRI. The results above were shown in Fig. 3 and Table 2.

Moreover, we performed the SROC curve of $^{68}$Ga-PSMA PET/CT and MRI (Fig. 4). The area under the curve (AUC) of $^{68}$Ga-PSMA PET/CT was larger than that of MRI (0.92 *versus* 0.83), which suggested $^{68}$Ga-PSMA PET/CT a more efficient imaging modality when comparing with MRI.

## 4. Heterogeneity test

According to the result of the forest plot, the heterogeneity of $^{68}$Ga-PSMA PET/CT and MRI was high in both sensitivity ($I^2$=61.08% and 82.84%, respectively) and specificity ($I^2$=58.15% and 86.02%, respectively). For MRI group, meta-regression was used to find out the source of heterogeneity. Subsequently, we found the heterogeneity of specificity might come from the electric field strength (1.5 T or 3.0 T), and the results of meta-regression showed the p-value of specificity in electric field strength was 0.03. However, there was no significant differences between the 1.5 T group and 3.0 T group when we performed a sub-group analysis. Therefore, our results of MRI were reliable. As for $^{68}$Ga-PSMA PET/CT, lacking enough included studies (n=8) for meta-regression, we decided to choose a random effects model to pool the data of $^{68}$Ga-PSMA PET/CT.

Stata 14.0 software was used to analyze the diagnostic threshold, indicating that the Spearman correlation coefficient was 0.26 and the p-value was 0.07 for $^{68}$Ga-

Table 2. Summary of the parameters in $^{68}$Ga-PSMA PET/CT and MRI groups

| Modality | Study | Patient | Threshold effects (p-value) | Sensitivity (95% CI) | Specificity (95% CI) | LR+ (95% CI) | LR- (95% CI) | DOR (95% CI) | AUC |
|---|---|---|---|---|---|---|---|---|---|
| $^{68}$Ga-PSMA | 8 | 485 | 0.07 | 0.65 (0.49–0.79) | 0.94 (0.88–0.97) | 10.6 (5.1–21.9) | 0.37 (0.24–0.58) | 29 (10–80) | 0.92 |
| MRI | 10 | 1,487 | 0.73 | 0.41 (0.26–0.57) | 0.92 (0.86–0.95) | 4.9 (3.1–7.6) | 0.65 (0.51–0.83) | 8 (4–13) | 0.83 |

Values are presented as number only, median (range), or index only.
$^{68}$Ga-PSMA PET/CT: $^{68}$Gallium–prostate-specific membrane antigen positron emission tomography/computed tomography, MRI: magnetic resonance imaging, CI: confidence interval, LR+: positive likelihood ratio, LR-: negative likelihood ratio, DOR: diagnostic odds ratio, AUC: area under the curve.

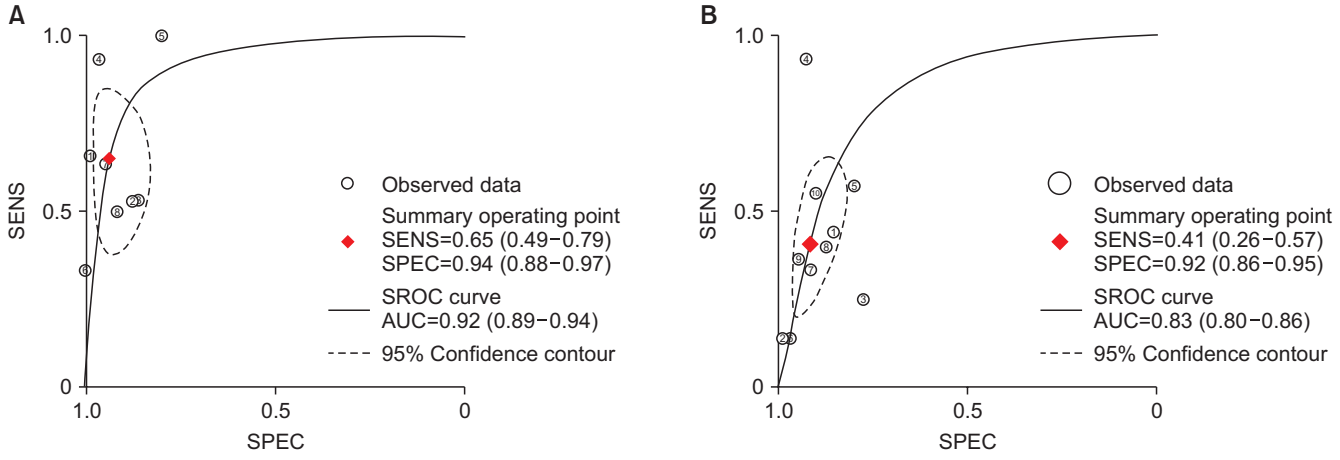


Fig. 4. Symmetric receiver-operating characteristic (SROC) curve. (A) $^{68}$Gallium–prostate-specific membrane antigen positron emission tomography/computed tomography; (B) magnetic resonance imaging group. SENS: sensitivity, SPEC: specificity, AUC: area under the curve.

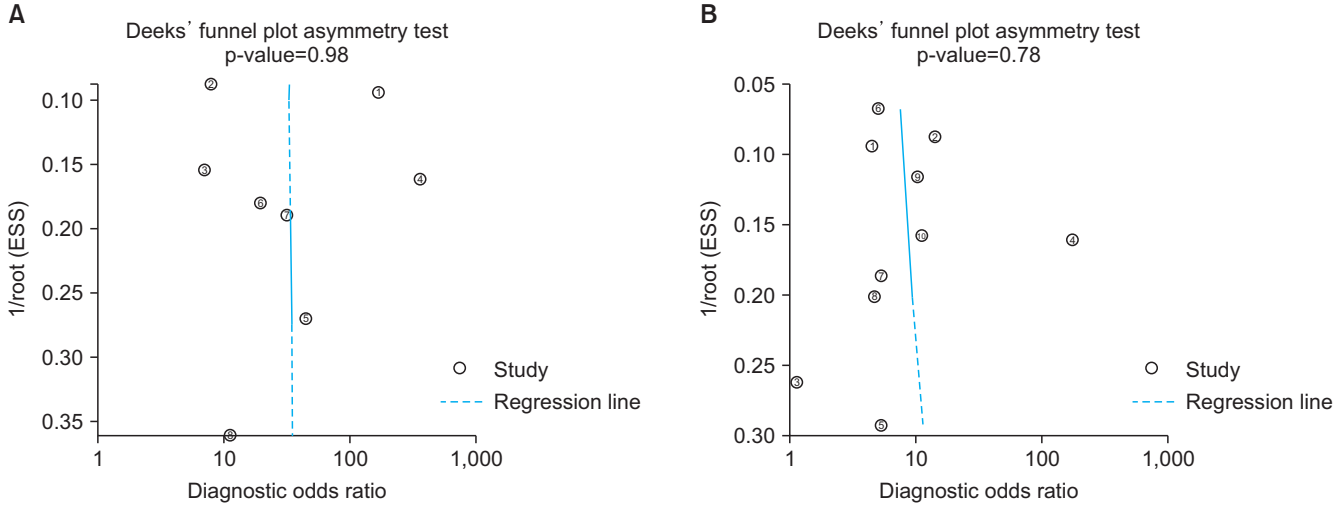


Fig. 5. Funnel Plot of publication bias. (A) $^{68}$Gallium–prostate-specific membrane antigen positron emission tomography/computed tomography; (B) magnetic resonance imaging. ESS: effective sample size.

PSMA PET/CT. Meanwhile, the corresponding index for MRI was -0.85 and 0.73. No evidence revealed a significant threshold effect existing in our meta-analysis.

## 5. Publication bias

The results of Deek's funnel plot test revealed that the p-values for $^{68}$Ga-PSMA PET/CT and MRI were 0.98 and 0.78, which indicated that there existed no severe publication bias. The results of Deek's funnel plot was shown in Fig. 5.

# DISCUSSION

Appropriate preoperative evaluation for the LNMs is critical for planning the most efficient prostate-cancer therapy strategy [33]. In the recent clinical scenarios, MRI has been widely applied to predict the primary staging of the patients with prostate cancer. As a standard modality, MRI is indispensable in current practice guidelines, but it still has many deficiencies. In general, MRI excessively relies on pathological changes such as morphological information and the sizes of lymph nodes. By defining pelvic lymph nodes lager than 8 to 10 mm as suspicious lesions [34,35], the fact that approximately 80% of them in prostate cancer are smaller than 8 mm [36] results in the low sensitivity of LNMs detection for MRI. Hence, there is an urgent need for a more accurate implement.

As a novel targeted imaging modality, $^{68}$Ga-PSMA PET/CT has been well used in numerous published

studies. However, in most of outlined data, the utility of $^{68}$Ga-PSMA PET just served as a predictor for the secondary staging with biochemical recurrence (BCR). The published studies setting of primary staging without therapy are still limited. Budäus et al [25] previously reported the initial experience on $^{68}$Ga-PSMA PET/CT predicting the LNMs in the patients with prostate cancer who were prior to radical surgery. The authors retrospectively analyzed 30 patients and concluded the sensitivity and specificity of 0.33 and 1.00. Later on, in 2017, Gupta et al [24] published a research, indicating the sensitivity and specificity for detection of metastatic lymph nodes were 66.7% and 98.9%. In the same year, Zhang et al [23], a research team from China, delivered the results that the corresponding values changed into 93.3% and 96.6%. However, there are few multicentre prospective randomized studies. A clinical trial protocol for the comparation between $^{68}$Ga-PSMA PET and the conventional imaging modalities, which was published by Hofman et al [37], may help promote more research and offer beneficial evidence. According to the varied results, we performed this meta-analysis to identify the true efficiency of $^{68}$Ga-PSMA PET/CT.

In our meta-analysis which included 13 studies comprising 1,597 patients, we compared the sensitivity and specificity of $^{68}$Ga-PSMA PET/CT and MRI. Previous studies reported the varied sensitivity and specificity of $^{68}$Ga-PSMA PET/CT and MRI. For $^{68}$Ga-PSMA PET/CT, sensitivity and specificity ranged from 0.33 to 1.00 and 0.82 to 1.00, respectively. The corresponding values of MRI ranged from 0.14 to 0.93 and 0.76 to 0.99, respectively. The pooled results of the eligible studies highlighted that $^{68}$Ga-PSMA PET/CT has a higher sensitivity than that of MRI (0.65 *versus* 0.39), and a comparable specificity (0.94 *versus* 0.92). When comparing the SROC curve, the results of AUC indicated that $^{68}$Ga-PSMA PET/CT was a more effective predictor for LNMs detection in intermediate- and high-risk prostate cancer.

Our results of $^{68}$Ga-PSMA PET/CT are different from those of a previously published meta-analysis performed by Perera et al [15]. In this article, they enrolled 16 articles with 1,309 patients, obtaining a pooled sensitivity and specificity of 0.86 and 0.86 for $^{68}$Ga-PSMA PET/CT, respectively. Moreover, they constructed the SROC curve, indicating $^{68}$Ga-PSMA PET/CT a valuable diagnostic method.

Despite the similar result of AUC, we are not surprised by the difference between the two meta-analysis, because the different inclusion criteria resulted in the different pooled data. Specifically, in the patient selection, we only enrolled the preoperative patients without hormone therapy, however, Perera et al [15] included a result of mixed staging patients including primary staging and secondary staging patients with BCR. With regard to the patients with BCR, several previous articles revealed a high sensitivity of LNMs detection, ranging from 77.9% to 98.8% [38-40]. The results above prompted us that $^{68}$Ga-PSMA PET/CT probably had a superior detection rate in the patients with BCR. Therefore, there is no doubt that the pooled sensitivity of Perera's study [15] is higher than that of our meta-analysis. In addition, referring to the results mentioned above, we conferred that hormone therapy and surgery might influence the exploration ability of $^{68}$Ga-PSMA. Hence, we excluded the patients who accepted hormone therapy or radical prostatectomy to dispel the confounding factors which might lead to a potentially rising bias.

As for MRI, dating back to 2008, Hövels et al [34] had already reported a meta-analysis which included 10 studies comprising 628 patients, with a result that the pooled sensitivity and specificity of LNMs detection in prostate cancer were 0.39 (95% CI: 0.19–0.56) and 0.82 (95% CI: 0.73–0.83), respectively. The outlined results above are similar to those in our study, suggesting MRI possess bounded ability in LNMs detection in prostate cancer. Also, MRI has its own advantages when comparing with $^{68}$Ga-PSMA PET/CT. On the one hand, the anatomic discriminative resolution of MRI is higher than that of $^{68}$Ga-PSMA PET/CT. On the other hand, the price of the two imaging techniques are not comparable. A modest price of MRI makes it a more acceptable diagnostic method for Chinese patients.

In addition, according to the result of $I^2$ value, the heterogeneity of $^{68}$Ga-PSMA PET/CT and MRI is high in our study. Therefore, we performed meta-regression and sub-group analysis for MRI, dividing it into 1.5 T MRI and 3.0 T MRI groups, finding no significant differences between the patients receiving 3.0 T MRI and 1.5 T MRI, which demonstrated our results reliable for MRI. As for $^{68}$Ga-PSMA PET/CT group, as a result of limited statistical method to explore heterogeneity, we finally choose a random-effect model. Besides, the differences between included studies in both $^{68}$Ga-PSMA PET/CT and MRI thresholds for positivity may become

the potential source of heterogeneity.

There are a few limitations in our study.

First, without a sufficient evidence from prospective studies, a majority of the included studies for the meta-analysis were providing a small, retrospective data. As what was mentioned above, the multicentre prospective randomized studies will help accelerate the research. Meanwhile, there was still limited data for more sub-group analysis of different characteristics, such as race (black, white and yellow race) or PSA level. Undoubtedly, additional data will be of benefit for consummating the sub-group analysis.

Second, some criteria or definition in our included literature may not conform the same standard, such as imaging protocol or the definition of sensitivity.

Third, we only enrolled published English articles, leaving out non-English or unpublished studies, which might give rise to selection bias.

## CONCLUSIONS

Our meta-analysis suggested that, when comparing with MRI, $^{68}$Ga-PSMA PET had a higher sensitivity and a comparable specificity for staging the preoperative LNMs in the intermediate- and high-risk prostate cancer. The area under the SROC curve indicated that $^{68}$Ga-PSMA PET was potentially a more effective and appropriate imaging modality to predict the LNMs prior to a surgery strategy.

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### Disclosure

The authors have no potential conflicts of interest to disclose.

### Author Contribution

Conceptualization: HW, TX. Data curation: XW, YBY, ZYF. Formal analysis: DXL, LL, XCY. Funding acquisition: HTN. Investigation: YBY. Methodology: WJ. Project administration: HTN, WJ. Resources: HW, TX. Software: HW. Supervision: HTN, WJ. Validation: XW, ZYF. Visualization: DXL. Writing–original draft: HW, TX. Writing–review & editing: HTN, WJ.

## REFERENCES

1. Babb C, Urban M, Kielkowski D, Kellett P. Prostate cancer in South Africa: pathology based national cancer registry data (1986-2006) and mortality rates (1997-2009). Prostate Cancer 2014;2014:419801.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. Loeb S, Smith ND, Roehl KA, Catalona WJ. Intermediate-term potency, continence, and survival outcomes of radical prostatectomy for clinically high-risk or locally advanced prostate cancer. Urology 2007;69:1170-5.
4. Bartsch G, Horninger W, Klocker H, Reissigl A, Oberaigner W, Schönitzer D, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001;58:417-24.
5. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70:233-45.
6. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998;82:2256-61.
7. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 1997;3:81-5.
8. Minner S, Wittmer C, Graefen M, Salomon G, Steuber T, Haese A, et al. High level PSMA expression is associated with early PSA recurrence in surgically treated prostate cancer. Prostate 2011;71:281-8.
9. Jadvar H. positron emission tomography in prostate cancer: summary of systematic reviews and meta-analysis. Tomography 2015;1:18-22.
10. Pfob CH, Ziegler S, Graner FP, Köhner M, Schachoff S, Blechert B, et al. Biodistribution and radiation dosimetry of (68) Ga-PSMA HBED CC-a PSMA specific probe for PET imag-

ing of prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:1962-70.
11. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester HJ, Czernin J, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med 2015;56:855-61.
12. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2014;41:11-20.
13. Herlemann A, Wenter V, Kretschmer A, Thierfelder KM, Bartenstein P, Faber C, et al. (68)Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. Eur Urol 2016;70:553-7.
14. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic efficacy of (68)Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 2016;195:1436-43.
15. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, specificity, and predictors of positive (68)Ga-Prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:926-37.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-36.
18. Van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. Stat Med 1993;12:2273-84.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
20. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882-93.
21. van Leeuwen PJ, Donswijk M, Nandurkar R, Stricker P, Ho B, Heijmink S, et al. 68Ga PSMA PET/CT predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate and high-risk prostate cancer. BJU Int 2018. doi: 10.1111/bju.14506 [Epub].
22. Öbek C, Doğanca T, Demirci E, Ocak M, Kural AR, Yıldırım A, et al. The accuracy of 68Ga-PSMA PET/CT in primary lymph node staging in high-risk prostate cancer. Eur J Nucl Med Mol Imaging 2017;44:1806-12.
23. Zhang Q, Zang S, Zhang C, Fu Y, Lv X, Zhang Q, et al. Comparison of 68Ga-PSMA-11 PET-CT with mpMRI for preoperative lymph node staging in patients with intermediate to high-risk prostate cancer. J Transl Med 2017;15:230.
24. Gupta M, Choudhury PS, Hazarika D, Rawal S. A comparative study of 68gallium-prostate specific membrane antigen positron emission tomography-computed tomography and magnetic resonance imaging for lymph node staging in high risk prostate cancer patients: an initial experience. World J Nucl Med 2017;16:186-91.
25. Budäus L, Leyh-Bannurah SR, Salomon G, Michl U, Heinzer H, Huland H, et al. Initial experience of (68)Ga-PSMA PET/ct imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol 2016;69:393-6.
26. Berger I, Annabattula C, Lewis J, Shetty DV, Kam J, Maclean F, et al. 68Ga-PSMA PET/CT vs. mpMRI for locoregional prostate cancer staging: correlation with final histopathology. Prostate Cancer Prostatic Dis 2018;21:204-11.
27. van Leeuwen PJ, Emmett L, Ho B, Delprado W, Ting F, Nguyen Q, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. BJU Int 2017;119:209-15.
28. Jeong IG, Lim JH, You D, Kim MH, Choi HJ, Kim JK, et al. Incremental value of magnetic resonance imaging for clinically high risk prostate cancer in 922 radical prostatectomies. J Urol 2013;190:2054-60.
29. Pinaquy JB, De Clermont-Galleran H, Pasticier G, Rigou G, Alberti N, Hindie E, et al. Comparative effectiveness of [(18)F]-fluorocholine PET-CT and pelvic MRI with diffusion-weighted imaging for staging in patients with high-risk prostate cancer. Prostate 2015;75:323-31.
30. Selnæs KM, Krüger-Stokke B, Elschot M, Willoch F, Størkersen Ø, Sandsmark E, et al. 18F-Fluciclovine PET/MRI for preoperative lymph node staging in high-risk prostate cancer patients. Eur Radiol 2018;28:3151-9.
31. von Below C, Daouacher G, Wassberg C, Grzegorek R, Gestblom C, Sörensen J, et al. Validation of 3 T MRI including diffusion-weighted imaging for nodal staging of newly diagnosed intermediate- and high-risk prostate cancer. Clin Radiol 2016;71:328-34.
32. Van den Bergh L, Lerut E, Haustermans K, Deroose CM, Oyen R, Isebaert S, et al. Final analysis of a prospective trial

on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. Urol Oncol 2015;33:109.e23-31.
33. Van Poppel H, Joniau S. An analysis of radical prostatectomy in advanced stage and high-grade prostate cancer. Eur Urol 2008;53:253-9.
34. Hövels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 2008;63:387-95.
35. Hricak H, Dooms GC, Jeffrey RB, Avallone A, Jacobs D, Benton WK, et al. Prostatic carcinoma: staging by clinical assessment, CT, and MR imaging. Radiology 1987;162:331-6.
36. Heesakkers RA, Hövels AM, Jager GJ, van den Bosch HC, Witjes JA, Raat HP, et al. MRI with a lymph-node-specific contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study. Lancet Oncol 2008;9:850-6.
37. Hofman MS, Murphy DG, Williams SG, Nzenza T, Herschtal A, Lourenco RA, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. BJU Int 2018;122:783-93.
38. Hijazi S, Meller B, Leitsmann C, Strauss A, Meller J, Ritter CO, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by 68Ga-PSMA-positron emission tomography/computerized tomography. Prostate 2015;75:1934-40.
39. Hamed MAG, Basha MAA, Ahmed H, Obaya AA, Afifi AHM, Abdelbary EH. 68Ga-PSMA PET/CT in patients with rising prostatic-specific antigen after definitive treatment of prostate cancer: detection efficacy and diagnostic accuracy. Acad Radiol 2018. doi: 10.1016/j.acra.2018.05.020 [Epub].
40. Rauscher I, Maurer T, Beer AJ, Graner FP, Haller B, Weirich G, et al. Value of 68Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med 2016;57:1713-9.