

Thoracic staging in patients with non-small cell lung cancer: A systematic review and meta-analysis on diagnostic accuracy of [¹⁸F]FDG PET/MRI and [¹⁸F]FDG PET/CT

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Abstract

Background: This study aimed to evaluate the diagnostic accuracy of [¹⁸F]FDG PET/MR versus [¹⁸F]FDG PET/CT in the thoracic staging of patients with non-small cell lung cancer (NSCLS).

Material and methods: The Preferred Reporting Items for Systematic Reviews (PRISMA) were followed in conducting the present study. All available research was collected through Embase (Elsevier), PubMed, as well as Cochrane Library databases up to June 2021. Only studies covering both [¹⁸F]FDG PET/MRI and [¹⁸F]FDG PET/CT techniques in the same group were included. Statistical analysis was done using Stata v.12.

Results: The overall accuracy of [¹⁸F]FDG PET/CT in T and N staging was 92% (95% CI: 89–95, I²: 93.4%) and 78% (95% CI: 74–82, I²: 98.5%) respectively. While, the corresponding rates for [¹⁸F]FDG PET/MRI were 91% (95% CI: 88–94, I²: 96.5%) and 89% (95% CI: 84–94, I²: 88.1%) respectively.

Conclusions: The present meta-analysis showed that [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI exhibit relatively the same performance in detecting N and T stages in patients with NSCLC. Thus, [¹⁸F]FDG PET/MRI can be a worthy alternative for [¹⁸F]FDG PET/CT in the diagnosis of advanced of NSCLC in the chest area, more specifically in N-staging, since it provides higher soft-tissue contrast. There is a need for more reliable research for comparing the diagnostic performance of these imaging techniques and various optimized [¹⁸F]FDG PET/MRI protocols.

KEY words: non-small cell lung cancer; [¹⁸F]FDG PET/MRI; [¹⁸F]FDG PET/CT; thoracic staging

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Introduction

[¹⁸F]FDG PET has been confirmed to be necessary for lymph node (N ratio) and distant metastases (M descriptor) staging in patients with non-small cell lung cancer (NSCLC) [1, 2]. However, the accurate evaluation of the size of local tumors is difficult due to the small space and the low descriptive accuracy of positron emission tomography (PET). On the other hand, the computerized

tomography (CT) scan is crucial for diagnosis, given the necessity for structural analysis images with high accuracy for the TNM staging system [3–5]. In this context, the combination of both techniques ([¹⁸F]FDG PET/CT) allows detecting the TNM in combined therapy and thereby is widely used in clinics and medical guidelines [6]. Predictions and therapies are strongly dependent on the early stage of cancer development. Thus, the accurate imaging of NSCLC development plays a critical role in the efficient management of the patient's condition and is crucial for restricting operations or multimodal treatments [7]. For patients with NSCLC and no advanced metastasis, the most predictive factor is the involvement of thoracic lymph nodes [8]. Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with

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computed tomography (^{18}F FDG PET/CT) is the first suggested tool for grading treatable NSCLCs given its high detection accuracy [9, 10]. In spite of the high negative predictive value (NPV) rate in detecting thoracic lymph node metastasis [11, 12], ^{18}F FDG PET/CT shows a limited specificity in detecting granulomatous lymph nodes as well as inflammatory lymph nodes [13–15]. Thus, Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) and/or ultrasound-guided needle biopsy and/or cervical mediastinoscopy are offered by the current therapy guidelines [8, 16–18]. Furthermore, thoracic staging can be challenging because of the parenchyma deformation after pulmonary obstruction and/or the tumor inflammation at the adjacent pleural cavity and mediastinal structures which can prevent accurate tumor detection by ^{18}F FDG PET/CT [19, 20]. Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with magnetic resonance imaging (^{18}F FDG PET/MRI), has been suggested as an accurate alternative for ^{18}F FDG PET/CT which can provide a higher soft tissue contrast as well as some important functional imaging data by diffusion-weighted imaging [18]. Despite the advantages of the ^{18}F FDG PET/CT, including more accessibility, higher specialty and skill of radiologists and nuclear physicians, and lower learning duration, the sensitivity of ^{18}F FDG PET/CT in detecting pulmonary nodes is still a doubtful issue. Since even 3D eco gradient residues fail to accurately detect pulmonary nodes lower than 10 mm in ^{18}F FDG PET/CT, it is probable to fail to detect small nodes and pulmonary nodes, which causes considerable

alterations in the management of the medical condition of these patients [21, 22]. An exact comparison of the accuracy of detection of the disease progress between both imaging techniques, ^{18}F FDG PET/CT and ^{18}F FDG PET/MRI. This study aimed to evaluate the diagnostic accuracy of ^{18}F FDG PET/MRI versus ^{18}F FDG PET/CT in the thoracic staging of patients with NSCLS.

Material and methods

Literature Search

The Preferred Reporting Items for Systematic Reviews (PRISMA) was followed in conducting the present study. All available research was collected through Embase (Elsevier), PubMed, as well as Cochrane Library databases up to June 2021. The PRISMA flow diagram in Figure 1 summarized the process of study search and study selection.

Eligibility criteria

Participants were selected with the least risk of bias. All the studies had a low risk of bias according to the standard reference, because of performing histology examinations and follow-up programs for six to twelve months as well as blinded interpretation of the imaging results. Studies could not be evaluated given the risk of bias in trends and schedules, because no time interferences were reported between index tests and standard references. QUADAS-2 examination results are shown in Figures 1 and 2.

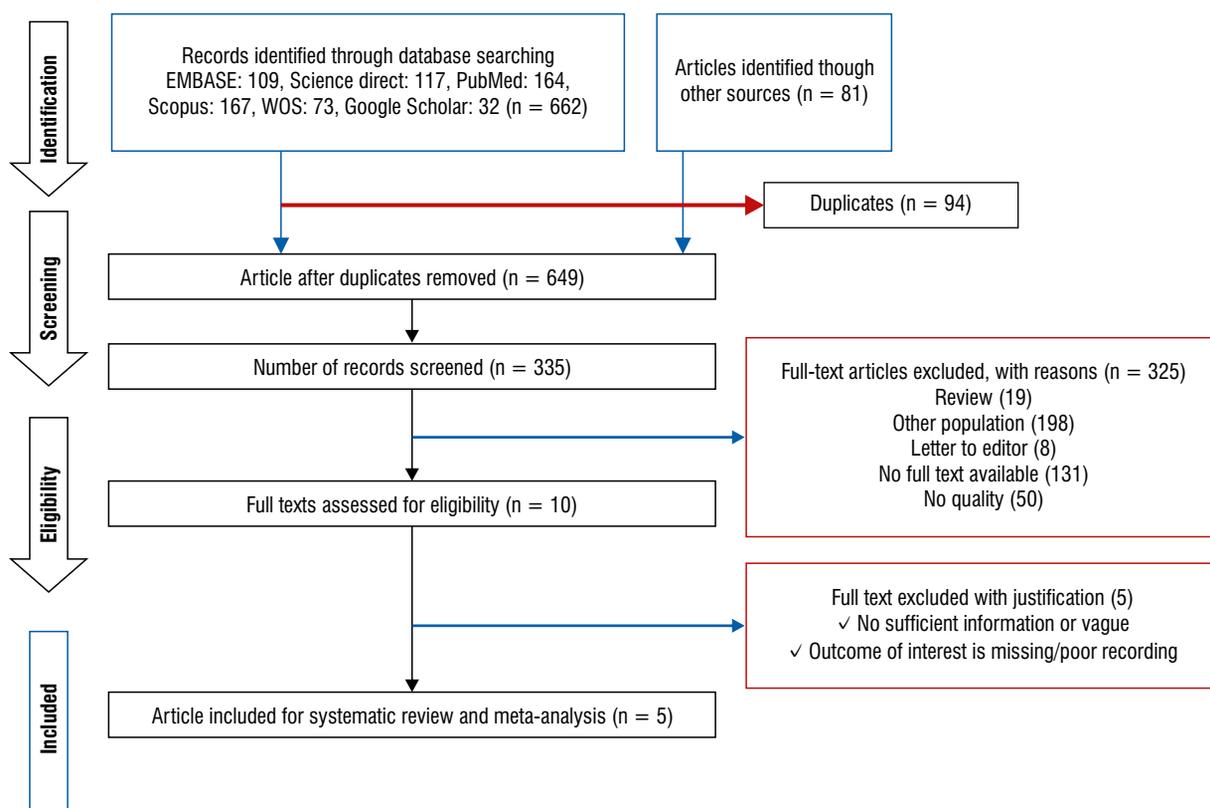


Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram

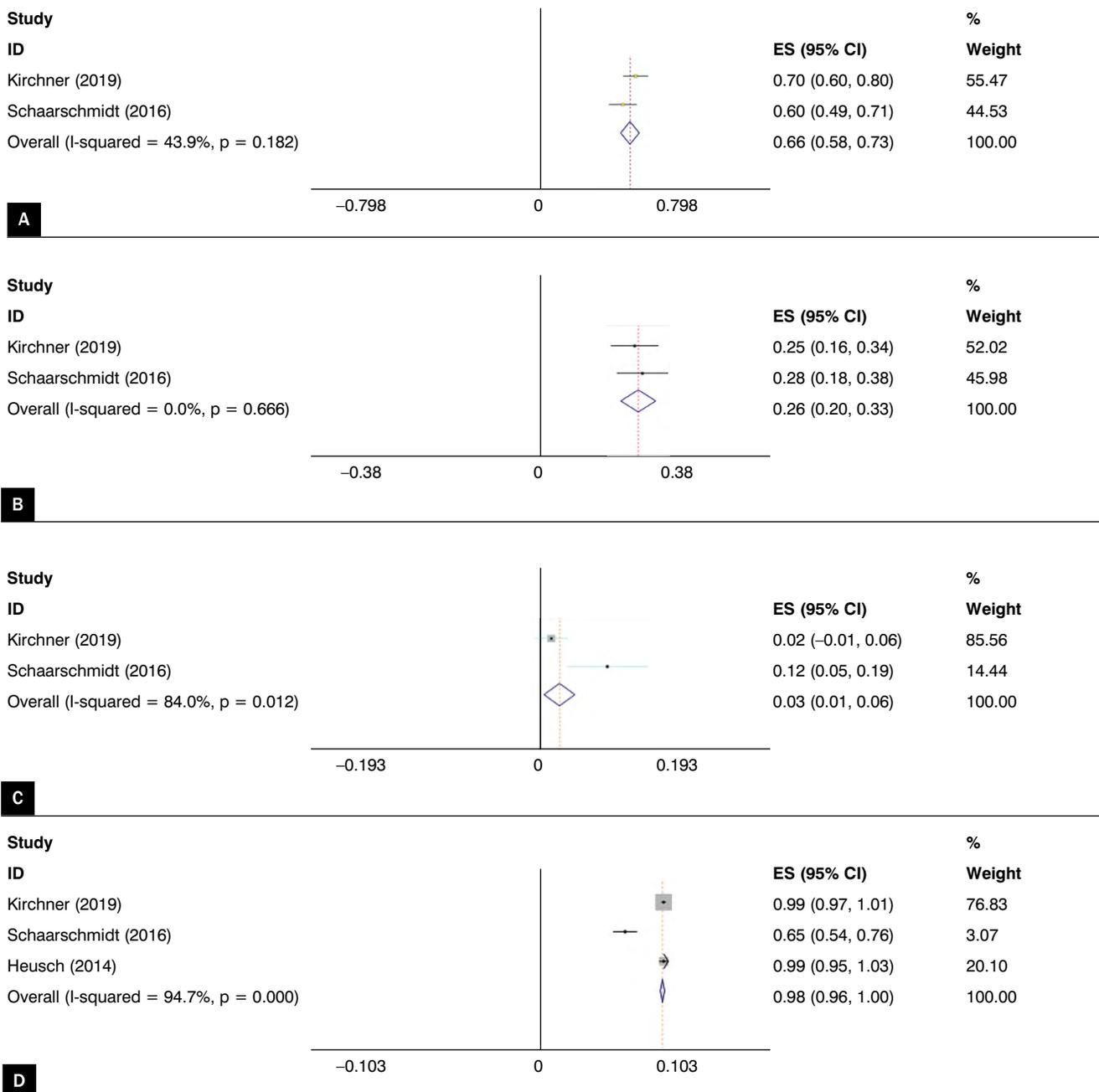


Figure 2. Prevalence of adenocarcinoma (A), squamous cell carcinoma (B), and large cell carcinoma (C), and the concordance rate between PET/CT and PET/MRI findings (D)

Inclusion and exclusion criteria

The criteria covered in this study included 1) the evaluation of the performance of [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI at the advanced stages of cancer; 2) the use of histology assessments or step-by-step imaging as a standard reference; and 3) including clear values for true positive (TP), false positive (FP), false negative (FN), and true negative (TN). The exclusion criteria considered when selecting studies included 1) concentrating on predictions or therapy responses against progress M; 2) having participants less than 10; 3) being published in an abstract of a conference, a letter, research, research on animals (*in vivo*

examinations), an opinion, or a report; 4) being not published in English; 5) using [¹⁸F]FDG PET separately from CT scan; 6) using radio probes except for [¹⁸F]FDG. The three researchers evaluated the titles and abstracts of articles and inclusion and exclusion criteria applied in this study. The full text of the articles was obtained and evaluated for reliability confirmation.

Methodology assessment

Studies complying with the inclusion criteria were assessed by the two researchers using the QUADAS-2 tool for evaluating the diagnostic accuracy of studies. The quality control tool included

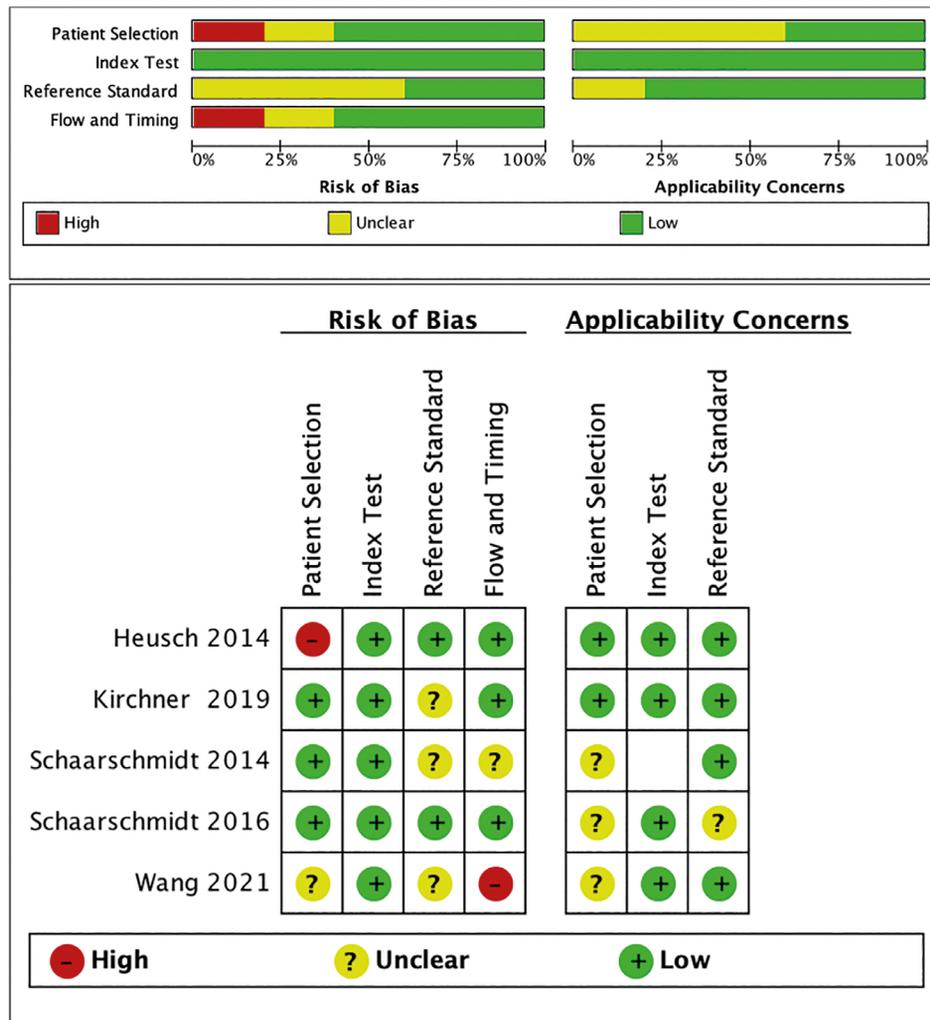


Figure 3. QUADS-2 for publication bias

four sections, namely the patient's selection, index testing, standard reference, and schedule and flow. The last index was based on the risk of bias with the capacity for implementation. The score of bias risk was evaluated at high, low, and unknown ranges. Only studies with a low risk of bias were used in this study. Conflicts were solved by consensus (Fig. 3).

Data extraction

The confirmed studies were evaluated by the two researchers using the PRISMA guideline tool. Data obtained from studies included affiliation, the year of publication, study designs, the country, patient registration, particular technical items, standard reference, and covers. Data were collected from each article considering the trend of progress and the number of FP, TN, TP, and FN.

Statistical analysis

Only studies covering both [¹⁸F]FDG PET/MRI and [¹⁸F]FDG PET/CT techniques in the same group were studied to allow minimizing inconsistency between methodological and clinical studies. Sensitivity and accuracy data with the CI of 95% were calculated by the Reitsma bivariate random-effects analysis. The inconsistency

between studies was obtained by chi-squared (χ^2) test results, with $p < 0.05$ which indicates the magnitude of inconsistency. The inconsistency estimated by DORs was then calculated to test if the inconsistency is due to the threshold effect or not. Variations among studies were mostly due to inconsistency, rather than the rate of chance obtained by calculating the value of I^2 . Statistical analysis was done using Stata v.12.

Results

Research for studies

The initial research covered a total of 743 articles, of which 10 articles were assessed and five articles were ultimately included in this study. Figure 1 provides a summary of searching for articles and the reason for excluding articles. These five articles included a total of 263 patients (Fig. 1).

Characteristics of included studies

A total of 5 studies consisting of 263 patients were included. Out of 5 studies 4 were in retrospective design and only one was prospective. Four studies were conducted in Germany and the remaining one was from China. The overall mean age and male-to-female

Table 1. General characteristics of included studies

Parameters	Kirchner [29]	Heusch [30]	Wang [31]	Schaarschmidt [32]	Schaarschmidt [33]
Year	2019	2014	2021	2015	2016
Country	Germany	Germany	China	Germany	Germany
Study design	Prospective	Prospective		Retro	Retro
Study duration	N/A	N/A	Prospective	2012–2014	N/A
Patient enrollment	84	22	52	28	77
Men/women	51/33	10/12	N/A	15/13	43/34
Mean age (range)	62.5 ± 9.1 years	65.1 ± 9.1 years	N/A	65.1 ± 8.2 years	61 ± 10 years
Reference standard	Histopathology	Histopathology	Histopathology	Histopathology	Histopathology
Blinding	Yes	Yes	N/A	Yes	Yes

ratio were 63.42, and 1.21, respectively. All studies used histopathology as the reference standard. Only two studies reported the prevalence of different types of NSCC. Based on those two articles, the most common type of NSCC was adenocarcinoma; 66% (95% CI : 58.73), followed by SCC 26% (95% CI : 20.33), and large cell carcinoma 3% (95% CI : 1.6) (Tab. 1, Fig. 2).

Meta-analysis of the overall concordance of [¹⁸F]FDG PET/MRI and [¹⁸F]FDG PET/CT

According to the results of three included studies the overall concordance of [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI in the thoracic staging of NSCC was 98% (95% CI : 96–100, I² : 94.7%) and the rate of discrepancy between these two methods was 2.3% (95% CI : 2–4.4, I² : 97.3%) (Tab. 2).

Comparison of the accuracy of [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI in thoracic T and N staging

The overall accuracy of [¹⁸F]FDG PET/CT in T and N staging was 92% (95% CI: 89–95, I² : 93.4%) and 78% (95% CI: 74–82, I² : 98.5%) respectively. While the corresponding rates for [¹⁸F]FDG PET/MRI were 91% (95% CI: 88–94, I² : 96.5%) and 89% (95% CI: 84–94, I² : 88.1%) respectively. The overall accuracy of [¹⁸F]FDG PET/MRI in the detection of mediastinal lymph node metastasis was 90% (95% CI: 85–96, I² : 85.7%) based on three studies. However, we did not have enough data to analyze the sensitivity and specificity measures (Tab. 2, Fig. 4–6).

Meta-analysis of the mean SUV max for the thoracic staging of NSCC

The overall mean SUVmax for the staging of NSCC was measured at 11.1 ± 6.8 for [¹⁸F]FDG PET/CT and 12.3 ± 7.2 for [¹⁸F]FDG PET/MRI, based on 2 included articles (Tab. 2).

Discussion

For patients with NSCLC who are qualified for surgery, the exact estimation of T and N stages is crucial. It has recently been observed that the accuracy of [¹⁸F]FDG PET/MRI is equal to that of [¹⁸F]FDG PET/CT in detecting the advancement of the disease and evaluating the volume of metastatic lymph nodes in the pulmonary pleural cavity. The basis for treating patients with NSCLC is surgery, while the initial biopsy is recommended only for stages I and II of the disease and for some specific cases of

stage III [23]. Along with neoadjuvant chemoradiotherapy and radiotherapy, full tumor removal is possible, even at the advanced local steps of the disease. For patients where a full biopsy is not achievable, alleviating therapies are administered. Thus, the accurate diagnosis of advanced phases of the disease (N and T) is crucial, as it provides important data on the size of the tumor, selecting the appropriate procedure for therapy, and identifying the status of the patient [23, 24]. The current meta-analysis showed high diagnostic accuracy of [¹⁸F]FDG PET/MRI for advanced stages of the thoracic NSCLC and its comparable concordance rate with [¹⁸F]FDG PET/CT as the current imaging standard. Contrary to [¹⁸F]FDG PET/CT, [¹⁸F]FDG PET/MRI allows us to simultaneously assess the whole body in terms of NSCLC advancement and even perform brain imaging. Since NSCLC metastases mostly occur in the brain, liver, and/or bones, [¹⁸F]FDG PET/MRI is expected to deliver better diagnostic results. Thus, [¹⁸F]FDG PET/MRI can be a comprehensive and useful tool for detecting the TNM advancement stage in the body [25, 26].

In line with our study Lee et al reported a complete (32/32) agreement between [¹⁸F]FDG PET/MRI and [¹⁸F]FDG PET/CT in T-stage. They also reported that out of 24 cases, [¹⁸F]FDG PET MRI predicted the correct N-stage in all of them while [¹⁸F]FDG PET/CT missed 2 [27]. These data are in line with our study reporting accuracy of 89% for [¹⁸F]FDG PET/MRI in N-staging in comparison to the corresponding rate of 78% for [¹⁸F]FDG PET/CT. However, a recent review by Dahlsgaard-Wallenius et al. [28] concluded that [¹⁸F]FDG PET/MRI did not have any advantages in N and T staging of NSCLC. They also indicated that although [¹⁸F]FDG PET/MRI had a comparable sensitivity for detection of lung nodules over 10 mm, it remains inferior to [¹⁸F]FDG PET/CT in the evaluation of nodules under 5 mm [28]. Regarding the SUVmax in thoracic staging, only two of our included studies provided the required data, both of which reported a high correlation between these two methods [29, 30]. However, Lee et al. [29] in their study evaluating the diagnostic accuracy of [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI in overall staging of NSCLC reported a significantly higher SUVmax of primary lesions for [¹⁸F]FDG PET/CT compared to [¹⁸F]FDG PET/MRI [27]. The number of articles and included patients was fewer than we expected. In diagnostic imaging studies, the small sample size and inconsistent techniques can affect the quality of meta-analysis. The other explanation for inconsistency is the impact of assessing the patient instead

Table 2. Diagnostic accuracy data of included studies

Subtype		Kirchner [29]	Heusch [30]	Wang [31]	Schaarschmidt [32]	Schaarschmidt [33]	
Adenocarcinoma		59	N/A	N/A	N/A	46	
Squamous cell carcinoma		21	N/A	N/A	N/A	22	
Large cell carcinoma		2	N/A	N/A	N/A	9	
Not otherwise specified NSCLC		2	N/A	N/A	N/A		
Total		84	N/A	N/A	N/A	77	
M-stage		N/A	N/A	N/A	N/A	1% (n = 1)	
Patient therapy management was changed		N/A	N/A	N/A	N/A	Six patients (8%)	
Concordant staging results were observed between thoracic [¹⁸ F]FDG PET/CT and [¹⁸ F]FDG PET/MR		83 of 84 patients (98.8%)	100%	N/A	N/A	65% (50 patients)	
Discrepancies in thoracic tumor staging were observed		1 of 84	0	N/A	N/A	35% (27 patients)	
[¹⁸ F]FDG PET/CT accuracy	T stage	92.3	16 of 16	84.6%	73%	19% (n = 11) while in 20	
	N stage	78 of 84 patients (92.9%)	18 of 22 (82%)	88.5% (46/52)	N/A	16% (n = 9) in all 57	
[¹⁸ F]FDG PET/MRI accuracy	T stage	89.7%	16 of 16	82.7%	69%	15% (n = 3) in 20	
	N stage	77 of 84 patients (91.7%)	20 of 22 (91%)	N/A	N/A	45% (n = 9) in 20	
Mediastinal lymph node metastases	[¹⁸ F]FDG PET/CT	Sen	N/A	75%	63.6%	N/A	N/A
		Spe	N/A	86%	95.1%	N/A	N/A
		Acc	N/A	82%	88.5%	N/A	N/A
		Ppv	N/A	75%	N/A	N/A	N/A
		Npv	N/A	86%	N/A	N/A	N/A
	[¹⁸ F]FDG PET/MRI	Sen	N/A	88%	81.8%	N/A	N/A
		Spe	N/A	93%	97.6%	N/A	N/A
		Acc	N/A	91%	94.2%	57%	N/A
		PPV	N/A	88%	N/A	N/A	N/A
		NPV	N/A	93%	N/A	N/A	N/A
The SUVmax of NSCLC	[¹⁸ F]FDG PET/CT	11.7 ± 8.3		10.5 + 5.3	N/A	N/A	
	[¹⁸ F]FDG PET/MRI	12.7 ± 8.7		12.0 + 5.7	N/A	N/A	
Measured size	[¹⁸ F]FDG PET/CT	N/A	4.2 ± 2.7 cm	N/A	N/A	N/A	
	[¹⁸ F]FDG PET/MRI	N/A	4.2 ± 2.6 cm	N/A	N/A	N/A	

Sen — sensitivity; Spe — specificity; Acc — accuracy; PPV — positive predictive value; NPV — negative predictive value

of a lesion. Other limitations were related to the design of studies, such as sampling and publication bias, and limited information in reports. Explanations of the properties of metastatic lesions were not accessible in most studies, as well.

Conclusions

The present meta-analysis showed that [¹⁸F]FDG PET/CT and [¹⁸F]FDG PET/MRI exhibit relatively the same performance in detecting N and T stages in patients with NSCLC. Thus, [¹⁸F]FDG

PET/MRI can be a worthy alternative for [¹⁸F]FDG PET/CT in the diagnosis of advanced of NSCLC in the chest area, more specifically in N-staging, since it provides higher soft-tissue contrast. There is a need for more reliable research for comparing the diagnostic performance of these imaging techniques and various optimized [¹⁸F]FDG PET/MRI protocols.

Conflict of interest

All the authors declare that they have no conflict of interest.

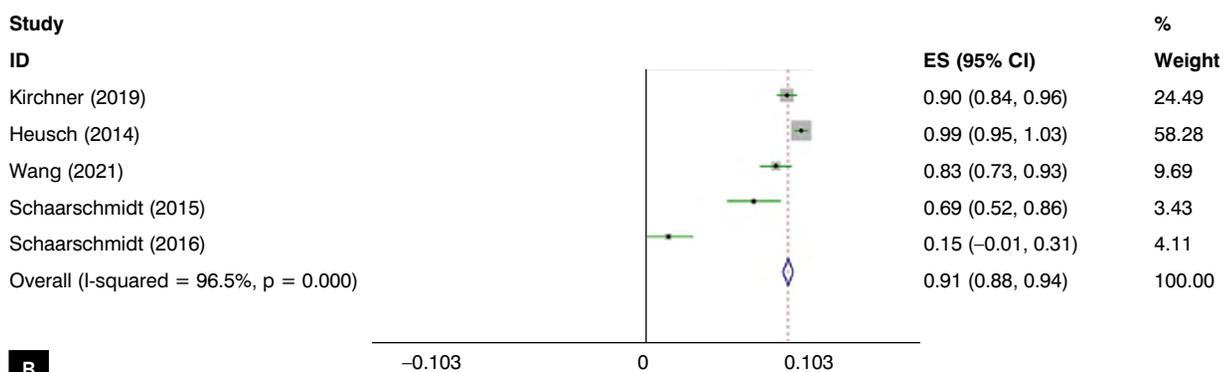
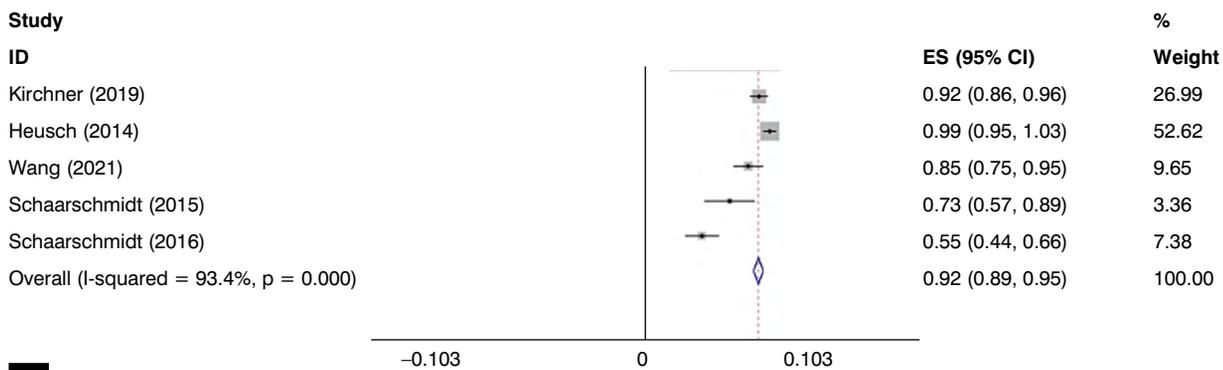


Figure 4. PET /CT (A) and PET/MRI (B) accuracies in T staging

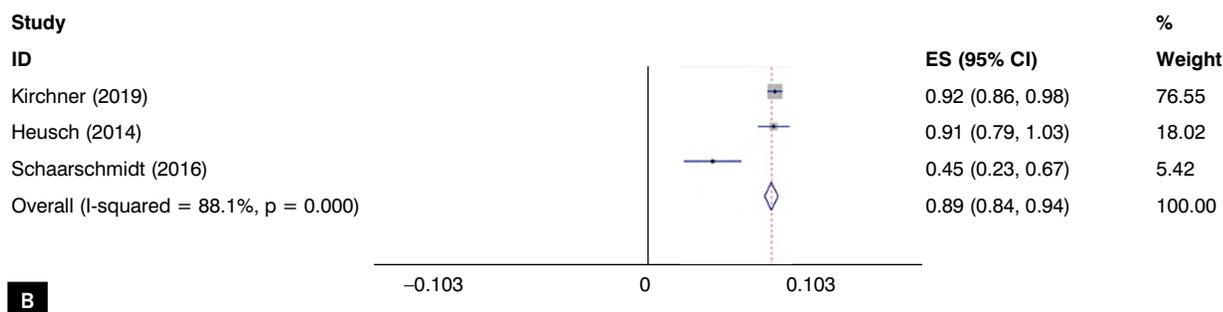
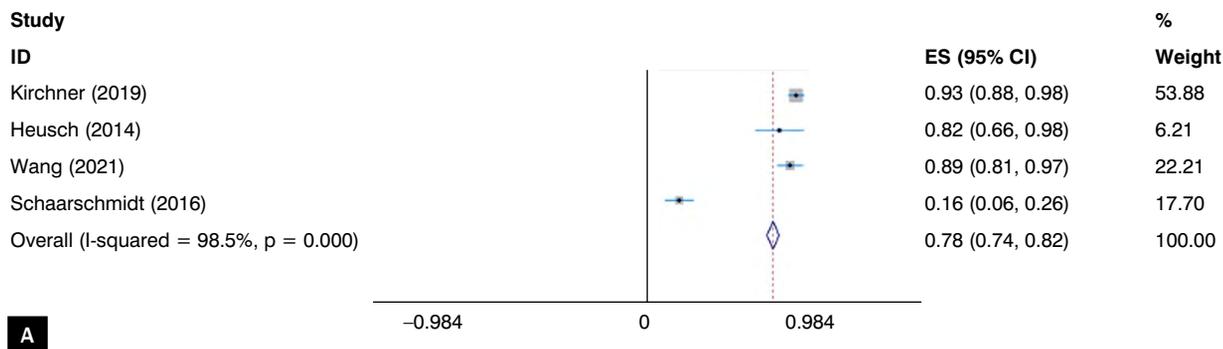


Figure 5. PET/CT (A) and PET-MRI (B) accuracies in N-staging

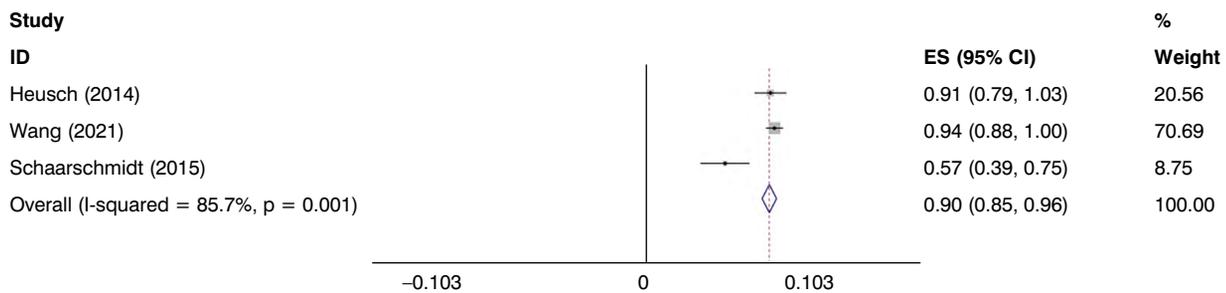


Figure 6. PET/MRI accuracy in detecting mediastinal lymph-node metastasis

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