Review Article

Comparison of the diagnostic value of 18F-NaF PET/CT and ^{99m}Tc-MDP SPECT for bone metastases: a systematic review and meta-analysis

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Background: Bone scintigraphy, the standard tool for detecting bone metastases has some insufficiencies; thus, supplementary imaging techniques are needed. This study is a comprehensive meta-analysis of studies reporting and comparing the diagnostic efficacy of 18F-sodium fluoride (18F-NaF) positron emission tomography/computed tomography (PET/CT) and ^{99m}Tc-MDP single-photon emission computed tomography (SPECT) for bone metastases.

Methods: Literature related to the diagnosis of bone metastases using 18F-NaF PET/CT and ^{99m}Tc-MDP SPECT was searched on PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang databases, and VIP. Evaluation of study quality was performed according to Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Pooled sensitivity (SEN) and specificity (SPE) were assessed along with heterogeneity. The subject operating characteristic curve was plotted, the area under the curve (AUC) was calculated, and the pre- and post-test probabilities were compared.

Results: Finally, 11 articles, consisting of 1,085 patients and 1,782 lesions, were included. At the patient level (11 articles), the results were pooled SEN =0.92 and SPE =0.96 for PET/CT, SEN =0.80 and SPE =0.90 for SPECT. The AUC of PET/CT [0.98 (0.96–0.99)] was higher than that of SPECT [0.92 (0.89–0.94), P<0.05]. At the lesion level (6 articles), the results were pooled SEN =0.96 and SPE =0.98 for PET/CT, SEN =0.76 and SPE =0.94 for SPECT. The AUC of PET/CT [0.99 (0.98–1.00)] was higher than that of SPECT [0.94 (0.92–0.96); P<0.05]. Statistical heterogeneity existed, and meta-regression showed that, at patient-based level, the study design type, tumor character, and the selection blinding method were the main sources of heterogeneity. Furthermore, both PET/CT and SPECT had superior SEN for osteogenic metastases than non-osteogenic metastases (P=0.01). At the lesion level, tumor character was a source of heterogeneity accompanied by an increased SEN for osteogenic metastases, and the SEN for SPECT combined with CT was improved [SEN =0.87 (0.68–1.00), P=0.03].

Conclusions: 18F-NaF PET/CT has a higher SEN and SPE than ^{99m}Tc-MDP SPECT in diagnosing bone metastases, nevertheless, it is necessary to fully understand the primary tumor and the characteristics of the imaging protocol to choose suitable modality for individuals. Combining SPECT with CT improves the diagnostic efficacy than having SPECT alone and can be a powerful supplement to PET/CT for suspected osteogenic bone metastases.

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Keywords: 18F-sodium fluoride (18F-NaF); positron emission tomography/computed tomography (PET/CT); ^{99m}Tc; single-photon emission computed tomography (SPECT); neoplasm metastasis

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Introduction

Although metastasis of advanced malignant tumors to the skeletal system is one of the most common metastatic pathways, the probability of bone metastasis differs between tumor types (1). Breast and prostate cancer are among the tumor types that exhibit a high propensity for bone metastasis (2). Bone metastasis can be divided into osteolytic, osteogenic or mixed, and is related to a relatively high incidence rate, including pain, pathological fracture, spinal cord infiltration, impaired mobility, and hypercalcemia, which affect subsequent treatment and prognosis (3,4). Therefore, the early identification and diagnosis of bone metastases has an important impact on tumor staging and therapeutic interventions, as well as the quality of life.

Currently, ^{99m}Tc-MDP bone scintigraphy (BS) is a routine tool used for detecting bone metastases. However, as it is a planar scan, its lesion localization and detection abilities are insufficient and can result in both false positives and false negatives due to interference from degenerative changes, fractures, benign bone lesions, and early osteolytic lesions (5). A research by Cristo Santos *et al.* (6) showed that positron emission tomography/computed tomography (PET/CT) outperformed BS with higher accuracy and sensitivity (SEN) scores of 98.0% and 93.83% in detecting bone metastases of breast cancers. In addition, ^{99m}Tc-MDP has been shown to have poorer image quality and lower diagnostic accuracy in patients with obesity and chronic kidney disease, 18F-sodium fluoride (18F-NaF) PET-CT is particularly favorable in these special populations due to its pharmacokinetic superiority over conventional planar imaging (7,8). ^{99m}Tc-MDP SPECT or SPECT/CT can be used to complement BS, but no guidelines currently recommend either option as a routine procedure (9). 18F-NaF PET/CT has a higher SEN and specificity (SPE) than SPECT due to its stereoscopic imaging and high resolution; thus, it can more accurately judge the nature of the lesions. Metastasis to bone may lead to osteolysis, osteogenesis, or both. Radiopharmaceuticals such as 18F-NaF and 18F-fluorodeoxyglucose (FDG) in PET/CT have different propensities in osteogenesis and osteogenesis, which may lead to deviation in results.

^{99m}Tc-MDP and 18F-NaF have unique advantages in the application of bone metastases, both are bone-seeking agents whose uptake is dependent on local blood flow and osteoclast activity. PET has improved spatial resolution and 18F-fluoride has favorable pharmacokinetic characteristics, making it more sensitive for the detection of lysogenic and cytogenic lesions (10), but published results are inconclusive. This meta-analysis aims to comprehensively evaluate and compare the diagnostic value of 18F-NaF PET/CT and ^{99m}Tc-MDP SPECT and provide guidance for selecting suitable imaging modality during clinical examinations. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://tcr.

Highlight box

Key findings

- 18F-sodium fluoride (18F-NaF) positron emission tomography/computed tomography (PET/CT) has better diagnostic efficacy than ^{99m}Tc-MDP single-photon emission computed tomography (SPECT) in the diagnosis of bone metastases, and combining SPECT with CT can be a powerful supplement to PET/CT for suspected osteogenic bone metastases

What is known and what is new?

- ^{99m}Tc-MDP SPECT and 18F-NaF PET/CT have more advantages than bone scintigraphy in the application of bone metastases, but no guidelines currently recommend either option as a routine procedure.
- ^{99m}Tc-MDP SPECT/CT outperforms SPECT in the detection of osteogenic metastases.

What is the implication, and what should change now?

- It is necessary to fully understand the primary tumor and the characteristics of the imaging protocol to choose the appropriate modality for individuals, and ^{99m}Tc-MDP SPECT /CT has the potential to be a routine procedure for detecting osteogenic metastases.

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Methods

Search strategy

Literature related to PET/CT and SPECT used in the diagnosis of bone metastases was searched. The search terms used were "Tomography, Emission-Computed, Single-photon, SPECT, ^{99m}Tc, PET/CT, Positron emission tomography-computed tomography, 18F, Bone, Neoplasm Metastasis, Sensitivity, and Specificity" and literature published before January 2023 was retrieved from PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP. The search strategy was adjusted according to the individual database and a combination of subject terms and free words was used to further obtain literature. This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) in September 2022 (registration number INPLASY2022100036).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) 18F-NaF PET/CT and ^{99m}Tc-MDP/HDP SPECT used in the diagnosis of bone metastases confirmed in the same population; (II) outcome indicators included true positives, false positives, false negatives, and true negatives, and the indicators were extractable as four-grid data.

The exclusion criteria were as follows: (I) effective data extraction was not possible; (II) duplicate publications; (III) no full-text available; (IV) animal experiments, reviews, lectures, and case reports; and (V) sample size <10 cases.

Literature extraction and quality evaluation

Two reviewers independently screened the literature and extracted the data, including the author names, publication year, sample size, study design, whether blinding was applied, imaging agent, and primary tumor type. Disagreements between the reviewers were resolved by discussion or by the addition of one senior researcher. All enrolled studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (11). This tool comprises four key domains: patient selection, index test, reference standard, and flow and timing, which require a "risk of bias" judgement. Signaling questions from each of the 12 entries that were evaluated using a yes, no, or unclear response supported the "risk of bias", rated as low, high, or uncertain.

Statistical analysis

Stata (version 17.0, StataCorp LLC, TX, USA) and Review Manager (version 5.2, The Cochrane Collaboration, Denmark) were used to calculate the pooled SEN and SPE, positive and negative likelihood ratios (+LR, –LR), and diagnostic ratio of PET/CT and SPECT, respectively, based on a bivariate mixed-effects model. The subject operating characteristic curve was plotted, the area under the curve (AUC) was calculated, and the diagnostic accuracy of the two imaging techniques was compared using Z tests. Heterogeneity between studies was assessed using the I^2 and Q tests. If the heterogeneity was large ($I^2 \geq 50\%$ or $P<0.1$), subgroup analysis and meta-regression were performed. A Deeks funnel plot was used for publication bias, and Fagan plots were drawn to compare pre- and post-test probabilities.

Results

The systemic search strategy preliminarily retrieved 67 articles, but only 11 met the inclusion criteria (10,12-21) (*Figure 1*). The main characteristics of these articles are detailed in *Table 1*. Of the included articles, 6 were based on both patient and lesion level, whereas 5 were only based on patient level. In total, 1,085 patients and 1,782 lesions were included in the analysis.

Study quality was evaluated according to QUADAS-2, and the results (*Figure 2*) showed that the compliance rate of the trials with a "yes" rating for patient selection and index test was >75%. This value indicates that >75% of the literature included suspected cases consecutively or randomly, clearly defined the inclusion and exclusion criteria, and the description of the target experiment was sufficiently clear and reproducible. Nevertheless, four of the eleven studies did not clearly define whether the gold standards were independent of the trials to be evaluated (*Figure 2*).

There was statistical heterogeneity caused by threshold effects in the 11 articles, thus, a bivariate mixed-effects model was used with logit transformation of the SEN and SPE of each study. At the patient-based level, the pooled SEN of PET/CT was 0.92 (0.86–0.95) and the SPE was

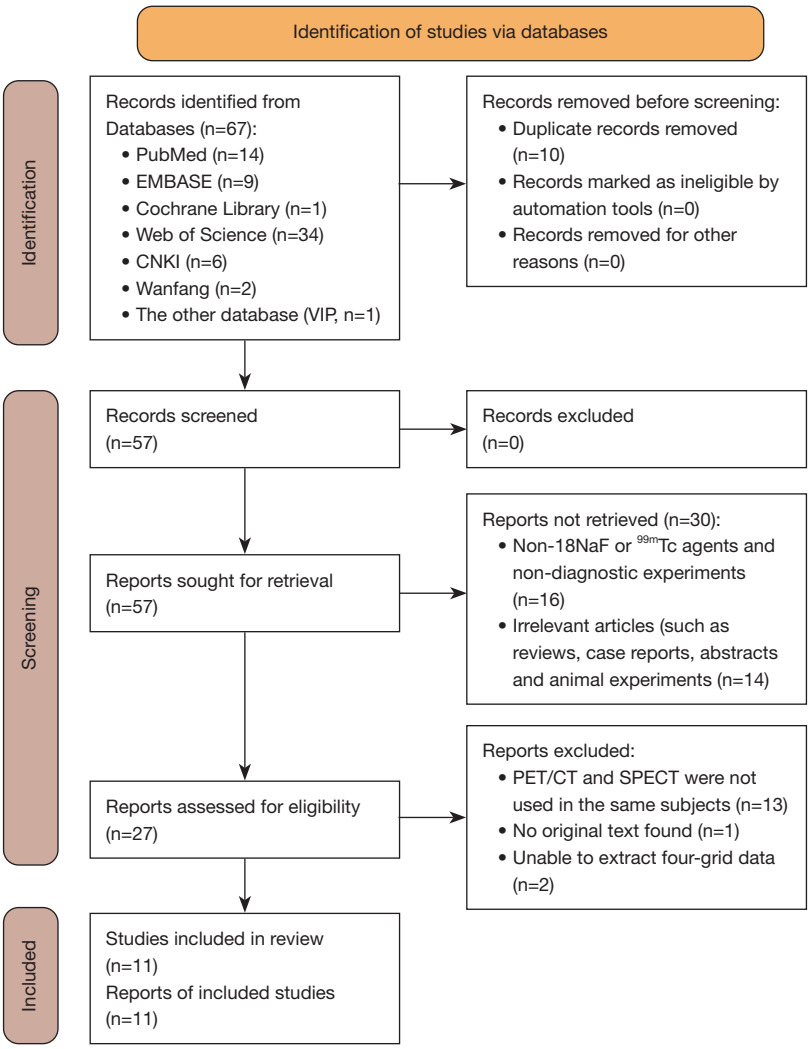

Figure 1 Flow chart of the literature search and inclusion. CNKI, China National Knowledge Infrastructure; SPECT, single-photon emission computed tomography; 18F-NaF, 18F-sodium fluoride; PET/CT, positron emission tomography/computed tomography; CT, computed tomography.

0.96 (0.91–0.98), while the pooled SEN of SPECT was 0.80 (0.71–0.86) and SPE was 0.90 (0.84–0.94). The AUC of PET/CT [0.98 (0.96–0.99)] was significantly higher than that of SPECT [0.92 (0.89–0.94); P<0.05]. At the lesion-based level, the pooled SEN of PET/CT was 0.96 (0.89–0.99) and SPE was 0.98 (0.92–1.00), while the pooled SEN of SPECT was 0.76 (0.55–0.89) and SPE was 0.94 (0.87–0.97). The AUC of PET/CT was significantly higher than that of SPECT (P<0.05) (*Table 2*, *Figures 3*,*4*).

Subgroup analyses were performed according to the study design, tumor character, combined CT, and blinding method. At the patient-based level (*Table 3*), the results revealed that the difference of study design, blinding method, and tumor character were the sources of heterogeneity. Comparing retrospective to prospective studies, the SEN (0.82 *vs.* 0.76, P=0.04) and SPE (0.91 *vs.* 0.88, P=0.02) were increased in retrospective studies in the SPECT group. Similarly, the SEN (0.96 *vs.* 0.84, P<0.001) and SPE (0.95 *vs.* 0.91, P=0.02) were also increased in the PET/CT group. Comparing osteogenic to non-osteogenic metastasis, the SEN (0.86 *vs.* 0.73, P=0.01) in the SPECT group was increased, as was the SEN (0.95 *vs.* 0.89, P=0.01) in the PET/CT group. The SEN (0.75 *vs.* 0.85, 0.87 *vs.* 0.98, P<0.001) were decreased in blinded studies in the

Table 1 Main characteristics of the included studies

First author	Year	Country	Age (years)*	Research target	Number	Study design	Blind	Imaging agent (PET/SPECT)	Primary tumor
Bénard (12)	2022	Canada	68.8 [63.0–74.4]	Patient	261	Prospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Breast, prostate cancer
Mao (13)	2020	China	61.4 [49–81]	Patient	205	Prospectively	Unclear	18F-NaF, ^{99m}Tc-MDP	Prostate cancer
Löfgren (14)	2017	Denmark	62.3±10.7	Patient	117	Prospectively	Yes	18F-NaF, ^{99m}Tc-HDP	Breast, prostate, renal, combined
Fonager (15)	2017	Denmark	71 [46–87]	Patient	37	Prospectively	Yes	18F-fluoride, ^{99m}Tc-HDP	Prostate cancer
Rao (16)	2016	China	56 [29–88]	Patient	181 PET/CT	Retrospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Lung cancer
			58.8 [24–90]	Lesion	157 SPECT				
Abikhzer (17)	2016	Israel	58 [30–75]	Patient	41	Prospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Breast cancer
				Lesion	284				
Jambor (18)	2016	Finland	NA	Patient	53	Prospectively	Yes	18F-NaF, ^{99m}Tc-HDP	Breast, prostate cancer
				Lesion	234				
Ota (19)	2014	Japan	61.9 [47–75]	Patient	11	Retrospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Thyroid carcinoma
				Lesion	176				
Chakraborty (10)	2013	India	60 [35–80]	Patient	48	Prospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Urinary bladder carcinoma
				Lesion	41				
Rao (20)	2012	China	56±11.7	Patient	107 PET/CT	Retrospectively	Unclear	18F-NaF, ^{99m}Tc-MDP	Lung cancer
					167 SPECT/CT				
Even-Sapir (21)	2006	Israel	71.6±8.8	Patient	24	Prospectively	Yes	18F-NaF, ^{99m}Tc-MDP	Prostate cancer
				Lesion	112				

*, data are presented as median [interquartile range] or mean ± standard deviation. PET, positron emission tomography; SPECT, single-photon emission computed tomography; 18F-NaF, 18F-sodium fluoride; CT, computed tomography; NA, not available.

SPECT and PET/CT groups.

At the lesion-based level (*Table 4*), study design, tumor character, and combined CT were the sources of heterogeneity. Comparing osteogenic to non-osteogenic metastasis, the SEN (0.83 *vs.* 0.64, P<0.001) in the SPECT group and the SEN (0.98 *vs.* 0.89, P=0.04) in the PET/CT group were increased. Comparing SPECT alone or combined with CT, the SEN (0.87 *vs.* 0.69, P=0.03) was increased. Deeks funnel plots showed no significant publication bias for SPECT or PET/CT (P>0.05; *Figure 5*).

Discussion

Lung, breast, and prostate cancers are highly prevalent in the population, and bone metastases often manifest as the disease worsens. Early diagnosis of bone metastasis is of great significance to the patient's treatment and prognosis. As systemic examinations, SPECT and PET/CT are important screening modalities for bone metastases. Our meta-analysis revealed that both ^{99m}Tc-MDP and 18F-NaF had high SEN and SPE for bone metastases in patient-based and lesion-based studies, with 18F-NaF being more favorable. Additionally, the combination of SPECT and CT improved the diagnostic efficiency over SPECT alone and could be a powerful complement to PET/CT for suspected osteogenic bone metastases.

Nevertheless, there was high heterogeneity among these results (I^2≥50%). Further subgroup analysis revealed that the difference of study design was a source of heterogeneity at the patient-based level, with P values <0.05 for SEN and

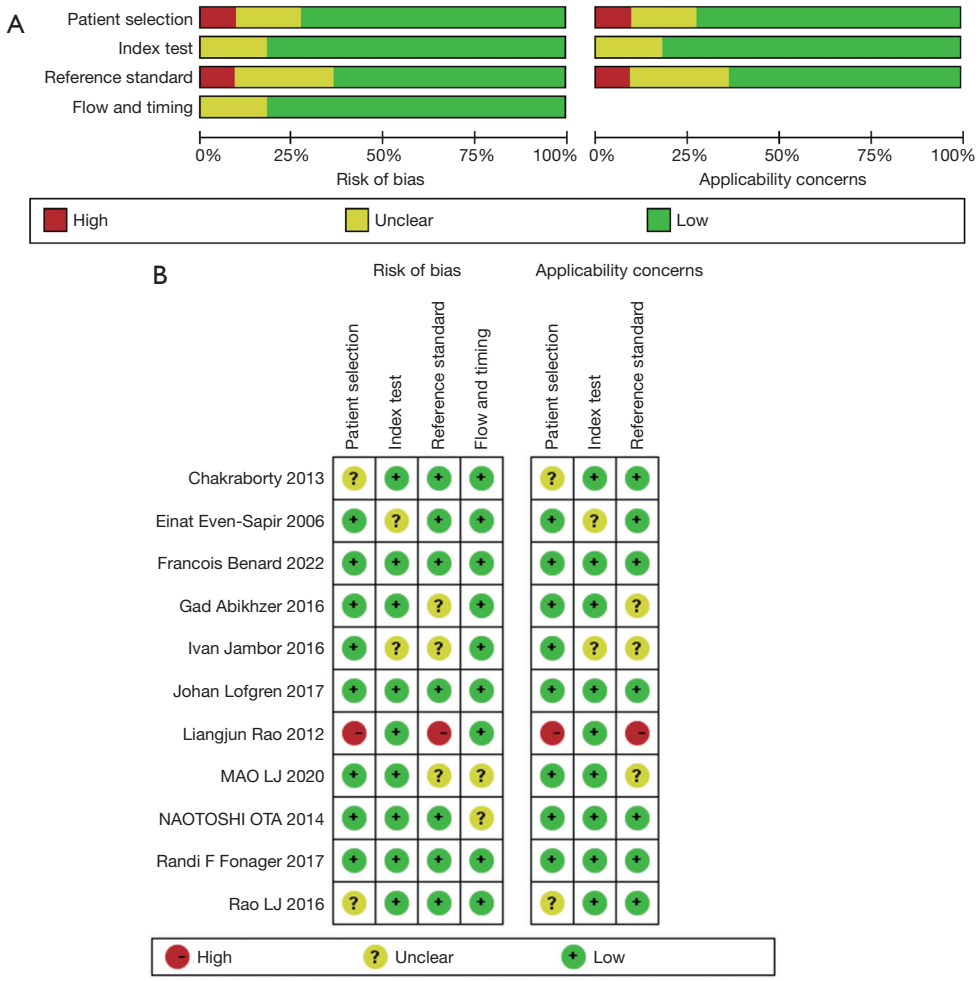

Figure 2 Quality evaluation for enrolled studies. (A) Risk of bias and applicability concerns graph: judgements regarding each domain presented as percentages across included studies. (B) Risk of bias and applicability concerns summary: judgements regarding each domain for each included study.

Table 2 Combined effect results of 18F-NaF PET/CT and ^{99m}Tc-MDP/HDP SPECT compared with the gold standard (95% CI)

Method	Research target	SEN (95% CI)	SPE (95% CI)	+LR (95% CI)	−LR (95% CI)	DOR (95% CI)	AUC (95% CI)	Pre-test probability (%)	Post-test probability (%)	
									+LR	−LR
18F-NaF PET/CT	Patient	0.92 (0.86–0.95)	0.96 (0.91–0.98)	23.2 (10.1–53.1)	0.09 (0.05–0.15)	270 (86–848)	0.98 (0.96–0.99)	20	85	2
	Lesion	0.96 (0.89–0.99)	0.98 (0.92–1.00)	59.0 (11.9–291.7)	0.04 (0.01–0.12)	1,627 (212–8,184)	0.99 (0.98–1.00)	20	94	1
^{99m}Tc-MDP/ HDP SPECT	Patient	0.80 (0.71–0.86)	0.90 (0.84–0.94)	8.2 (5.1–13.2)	0.23 (0.16–0.33)	36 (20–65)	0.92 (0.89–0.94)	20	67	5
	Lesion	0.76 (0.55–0.89)	0.94 (0.87–0.97)	12.2 (6.0–24.5)	0.26 (0.12–0.53)	48 (17–134)	0.94 (0.92–0.96)	20	75	6

18F-NaF, 18F-sodium fluoride; PET/CT, positron emission tomography/computed tomography; SPECT, single-photon emission computed tomography; CI, confidence interval; SEN, sensitivity; SPE, specificity; +LR, positive likelihood ratio; −LR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve.

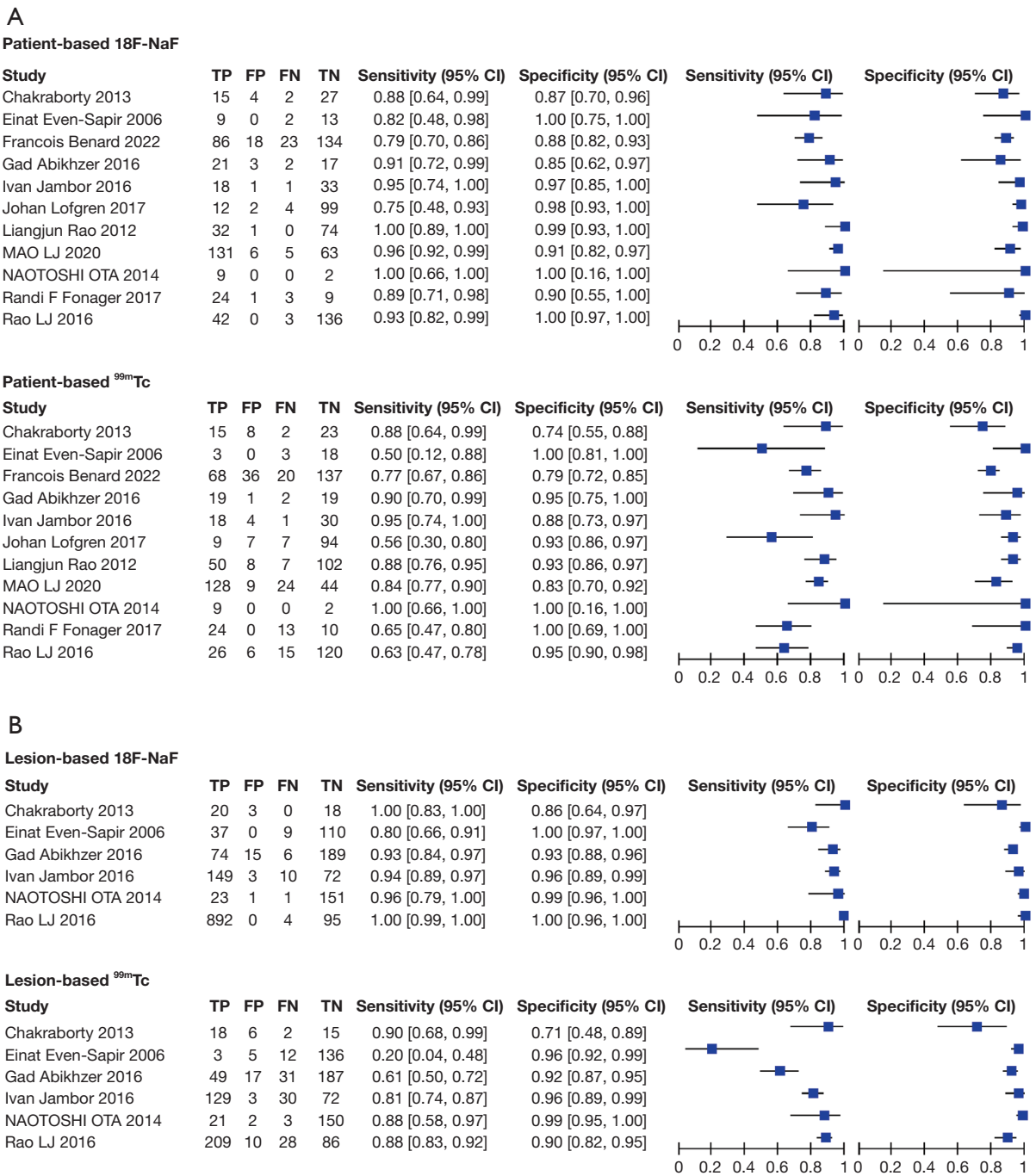

Figure 3 Sensitivity and specificity forest maps of enrolled studies. (A) Patient-based level (11 articles), and (B) lesion-based level (6 articles). 18F-NaF, 18F-sodium fluoride; TP, true positive; FP, false positive; FN, false negative; TN, true negative; CI, confidence interval.

SPE in the SPECT and PET/CT groups. In terms of the design types, prospective studies were preferable as they reduced bias and were able to obtain more comprehensive clinical data. In contrast, retrospective studies could yield incomplete clinical data and subjective selectivity of the study objects, resulting in bias. Furthermore, tumor character was also a source of heterogeneity, with P values <0.05 for SPE and SEN in the SPECT group and SEN

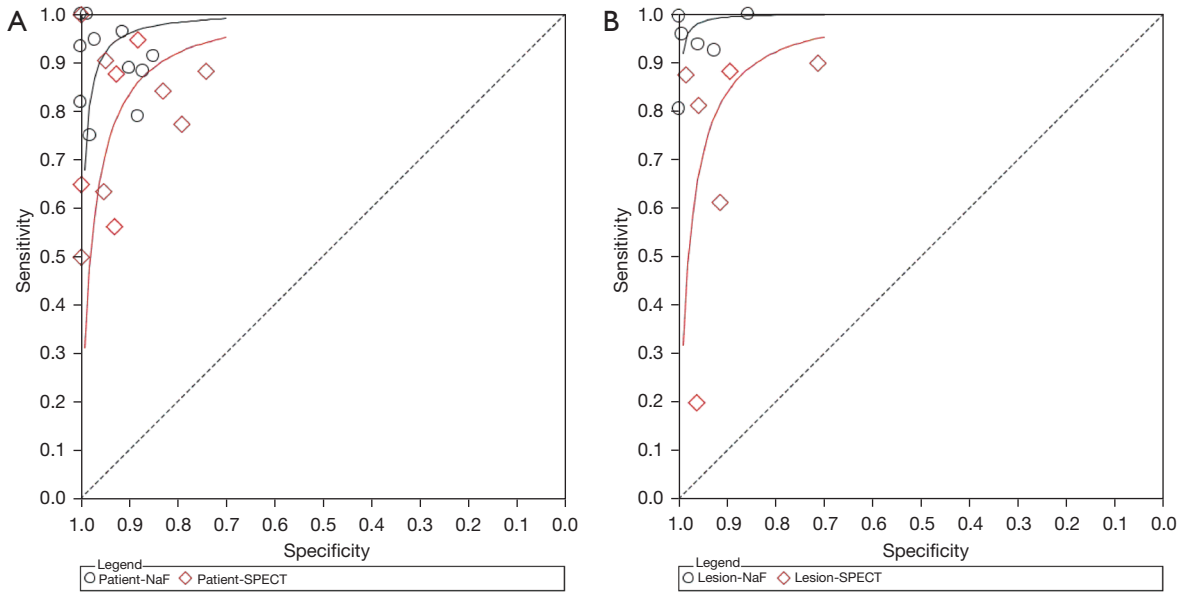

Figure 4 Summary receiver operating characteristic curve. (A) 18F-NaF PET/CT *vs.* ^{99m}Tc SPECT patient-based. (B) 18F-NaF PET/CT *vs.* ^{99m}Tc SPECT lesion-based. 18F-NaF, 18F-sodium fluoride; PET/CT, positron emission tomography/computed tomography; SPECT, single-photon emission computed tomography.

Table 3 Subgroup analysis results on a patient-based level

Sub-groups	Number	SPECT				PET/CT			
		SEN (95% CI)	P value	SPE (95% CI)	P value	SEN (95% CI)	P value	SPE (95% CI)	P value
Study design			0.04		0.02		<0.001		0.02
Prospectively	7	0.76 (0.66–0.87)		0.88 (0.82–0.96)		0.84 (0.78–0.90)		0.91 (0.85–0.98)	
Retrospectively	4	0.82 (0.72–0.93)		0.91 (0.85–0.98)		0.96 (0.93–0.99)		0.95 (0.90–1.00)	
Tumor character			0.01		0.03		0.01		0.29
Osteogenic	6	0.86 (0.77–0.95)		0.89 (0.79–0.99)		0.95 (0.90–1.00)		0.95 (0.90–1.00)	
Non-osteogenic	5	0.73 (0.62–0.85)		0.91 (0.84–0.97)		0.89 (0.82–0.96)		0.97 (0.93–1.00)	
Combine CT			0.13		0.06				
Yes	4	0.80 (0.71–0.89)		0.90 (0.81–0.98)					
No	7	0.77 (0.64–0.92)		0.91 (0.85–0.97)					
Blinded			<0.001		0.28		<0.001		0.94
Yes	9	0.75 (0.66–0.84)		0.90 (0.85–0.96)		0.87 (0.82–0.93)		0.96 (0.93–1.00)	
No	2	0.85 (0.76–0.94)		0.89 (0.79–0.99)		0.98 (0.95–1.00)		0.96 (0.91–1.00)	

SPECT, single-photon emission computed tomography; PET/CT, positron emission tomography/computed tomography; SEN, sensitivity; SPE, specificity; CI, confidence interval.

Table 4 Subgroup analysis results on a lesion-based level

Sub-group	Number	SPECT				PET/CT			
		SEN (95% CI)	P value	SPE (95% CI)	P value	SEN (95% CI)	P value	SPE (95% CI)	P value
Study design			0.16		0.20		<0.001		0.24
Prospectively	4	0.68 (0.47–0.90)		0.92 (0.86–0.99)		0.90 (0.80–1.00)		0.99 (0.96–1.00)	
Retrospectively	2	0.87 (0.71–1.00)		0.96 (0.90–1.00)		0.96 (0.94–1.00)		0.98 (0.94–1.00)	
Tumor character			<0.001		0.81		0.04		0.02
Osteogenic	2	0.83 (0.70–0.97)		0.97 (0.92–1.00)		0.98 (0.96–1.00)		0.99 (0.96–1.00)	
Non-osteogenic	4	0.64 (0.39–0.89)		0.92 (0.86–0.98)		0.89 (0.76–1.00)		0.98 (0.94–1.00)	
Combine CT			0.03		0.29				
Yes	2	0.87 (0.68–1.00)		0.95 (0.91–0.99)					
No	4	0.69 (0.46–0.92)		0.89 (0.76–1.00)					

SPECT, single-photon emission computed tomography; PET/CT, positron emission tomography/computed tomography; SEN, sensitivity; SPE, specificity; CI, confidence interval.

in the PET/CT group. Due to differences in tracer SEN for osteogenic and osteolytic bone metastases. Finally, blinding methods were also a source of heterogeneity at the patient-based level. As blinding methods could effectively avoid subjectivity and bias. At the lesion-based level, the difference of study design was a source of heterogeneity for SEN in the PET/CT group and tumor character was a source of heterogeneity, with P values <0.05 for SEN in the SPECT and PET/CT groups. In addition, the SPECT combined CT was a source of heterogeneity, with P values <0.05 for SEN. Although SPECT is tomography generating three-dimensional image display, it has limits to accurately reflect complex bone structures such as the vertebrae, ribs, and pelvises. ^{99m}Tc-MDP SPECT is more sensitive to osteoblastic bone metastases, but less sensitive to osteolytic lesions. When combined with CT, anatomical structure information is enhanced, which can facilitate localization of poor radionuclide aggregation and improve diagnostic capabilities (22).

The tracer 18F-FDG routinely used in PET/CT is a glucose analog, which can reflect the degree of active metabolism in tumor cells. Therefore, 18F-FDG has good SEN to osteolytic bone metastases, while it has limited value in diagnosing osteogenic metastatic tumors that exhibit low levels of active metabolism (23,24). In contrast, 18F-NaF is more suitable for identifying bone metastatic tumors with low 18F-FDG uptake. 18F-NaF detects the presence of lesion directly by bonemineral metabolism, fluoride ions is an analog of the hydroxyl group found in the hydroxyapatite bone crystals which exchange with hydroxyl groups in hydroxyapatite bone crystals to form fluoroapatite. ^{99m}Tc-MDP, an analog of pyrophosphate in hydroxyapatite bone crystals, is a common agent for SPECT, and can be chemically absorbed and combine with the surface of hydroxyapatite crystals present in the inorganic components of bones. The action mechanism of 18F-NaF is similar to ^{99m}Tc-MDP. When osteoblasts are active and new bone is formed, both 18F-NaF and ^{99m}Tc-MDP can facilitate imaging, and 18F-NaF has a two-fold higher bone affinity than ^{99m}Tc-MDP (25-27). Depending on the different pharmacokinetics of the tracer, combined with the characteristics of the bone metastases, 18F-FDG can be a powerful complement to 18F-NaF and ^{99m}Tc-MDP. Considering the above tracer characteristics, it is necessary to have a certain understanding of features of the primary tumor to select the appropriate examination method. For instance, osteoblast metastasis is the most common type of prostate cancer, followed by mixed metastasis, and osteolytic metastasis is very rare. Breast cancer is predominantly osteolytic or mixed metastases. The bone metastasis of lung cancer is osteolytic, with a few being osteoblasts and some being mixed. Moreover, in patients who receive chemotherapy and radiotherapy, the metabolism of tumor cells may be weakened, impairing the uptake of 18F-FDG. Thus, individualized imaging agents should be selected based on tumor features.

Our patient-based results revealed that 18F-NaF PET/CT had a greater diagnostic effectiveness than ^{99m}Tc-

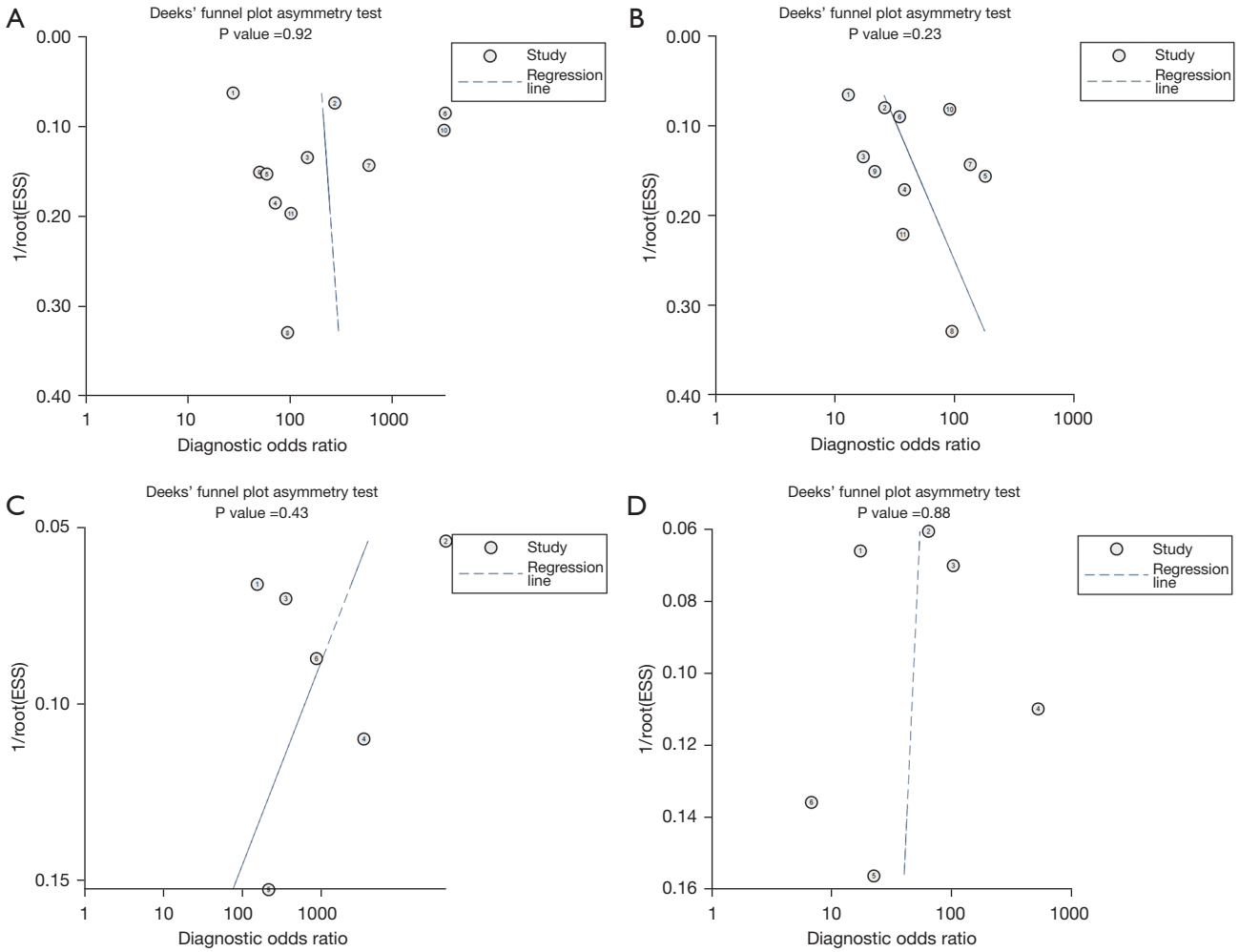

Figure 5 Deeks funnel plot detecting publication bias. (A) 18F-NaF PET/CT patient-based. (B) ^{99m}Tc SPECT patient-based, (C) 18F-NaF PET/CT lesion-based, and (D) ^{99m}Tc SPECT lesion-based. 18F-NaF, 18F-sodium fluoride; PET/CT, positron emission tomography/computed tomography; SPECT, single-photon emission computed tomography; ESS, error sum of squares.

MDP SPECT. The use of 18F-NaF has been proven to be superior to traditional planar imaging due to its good pharmacokinetics, maintaining image quality under acceptable radiation exposure, and providing excellent diagnostic reliability. As previously reported by Usmani *et al.* (28), in a retrospective analysis of morbidly obese patients, the diagnostic accuracy of 18F-NaF in detecting bone metastasis was high, and this technology provided superior diagnostic testing characteristics compared to ^{99m}Tc-MDP. In addition, the SEN and SPE were increased in both 18F-NaF and ^{99m}Tc-MDP when the research subjects were mainly osteogenic. Our lesion-based results also revealed a difference in SEN and SPE between osteogenic and non-osteogenic classifications, providing further confirmation that the diagnosis of osteogenic bone metastasis had higher SEN. Furthermore, SPECT combined with CT had a higher SEN. In general, the spatial resolution of PET/CT is superior to that of SPECT. However, some researchers (22) believe that combining SPECT with CT can compensate for this disadvantage, particularly in the diagnosis of osteoblastic bone metastases. Degeneration, fractures, and cysts may lead to increased ^{99m}Tc-MDP uptake and affect the diagnoses. Therefore, CT can be a complementary technique reflecting the osteogenic or osteolytic changes and improving anatomical localization and detection of morphological information. This meta-analysis showed that, in the lesion-level subgroup, the SEN and SPE of SPECT combined with CT were higher

than those of SPECT alone. Considering the time- and cost-effectiveness, SPECT in combination with CT can be a useful supplementary examination to PET/CT as an initial assessment for suspected osteogenic bone metastasis. Fonager *et al.* (15) also reported similar SPE between 18F-NaF and ^{99m}Tc-MDP, with the possible explanation being that the two hybrid modalities improve their SPE mainly through accurate localization and characterization using CT. Although 18F-NaF PET/CT had advantages in the diagnosis of osteogenic bone metastases in this meta-analysis as well as in previous studies (17,29), it is rarely used clinically due to its high cost and usually not being covered by insurance policy.

The current study had some limitations. First, although a variety of primary tumors were included, the number of cases in each subgroup was relatively small, which limited the impact of our conclusions. Second, the medical equipment and imaging experience of physicians varied among studies, which might have led to bias. Third, a part of this study was not blinded, and the different study designs may have induced bias. Fourth, both ^{99m}Tc-MDP and ^{99m}Tc-HDP belong to technetium methylenediphosphate, with similar effects. Therefore, no further subgroup analysis was conducted. Fifth, further subgroup analyses could be performed in specific primary tumors to provide more accurate references for clinical decision-making.

Conclusions

In conclusion, 18F-NaF PET/CT has a higher SEN and SPE than ^{99m}Tc SPECT in diagnosing bone metastases, nevertheless, it is necessary to fully understand the primary tumor and the characteristics of the imaging protocol to choose the appropriate modality for individuals. Combining SPECT with CT improves the diagnostic efficacy than having SPECT alone and can be a powerful supplement to PET/CT for suspected osteogenic bone metastases.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-817/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-817/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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