Diagnostic performance of ^{18}F-FDG PET/CT vs. ^{18}F-NaF PET/CT in breast cancer with bone metastases: An indirect comparative meta-analysis

HONGYU HU[1*], XIANWEN HU[1*], ZHIGANG LIANG[1], WENBI YANG[1], SONG LI[1], DANDAN LI[2] and JIONG CAI[1]

[1]Department of Nuclear Medicine, The Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China; [2]Department of Gynecology, Zunyi Hospital of Traditional Chinese Medicine, Zunyi, Guizhou 563000, P.R. China

Received March 26, 2024; Accepted August 20, 2024

DOI: 10.3892/ol.2024.14679

Abstract. Breast cancer remains the leading cause of cancer-related death in women, with 5-year survival rates of as high as 90% for patients with early-stage breast cancer without metastasis, falling to 10% once bone metastases (BM) occur. Currently, there is no cure for breast cancer with BM. However, appropriate treatment can extend survival and improve patients' quality of life. Therefore, it is important to accurately evaluate the presence of BM in patients with breast cancer. The present meta-analysis evaluated the diagnostic performance of ^{18}F-FDG and ^{18}F-NaF as PET/CT tracers for breast cancer-associated BM. The present study aimed to compare the diagnostic performance of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomographs (PET/CT) and ^{18}F-sodium fluoride (^{18}F-NaF) PET/CT in patients with breast cancer and BM. The PubMed and Embase databases were searched for English literature on the diagnostic performance of ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT for breast cancer BM, and two authors independently extracted data. All included studies presented data that could be used to construct a 2x2 contingency table. The methodological quality of the selected studies was assessed using QUADAS-2, and forest plots were generated based on the sensitivity and specificity of ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT in the diagnosis of BM associated with breast cancer. A total of 14 articles were identified, including eight on the analysis of ^{18}F-FDG PET/CT, five on ^{18}F-NaF PET/CT and one on both. The studies on ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT included 530 and 270 patients, respectively. The pooled sensitivities were 0.88 [95% confidence interval (95% CI), 0.76-0.94] for ^{18}F-FDG PET/CT and 0.98 (95% CI, 0.92-1.00) for ^{18}F-NaF PET/CT, and the pooled specificities were 0.99 (95% CI, 0.97-1.00) and 0.91 (95% CI: 0.76-0.97), respectively. The area under the summary receiver operating characteristic curve for both ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT was 0.99 (95% CI, 0.98-1.00). Lesion-based analysis using ^{18}F-FDG PET/CT was performed for 909 lesions, with a sensitivity of 0.84 (95% CI, 0.67-1.00) and specificity of 1.00 (95% CI, 0.98-1.00). Compared with ^{18}F-FDG PET/CT, ^{18}F-NaF PET/CT showed higher sensitivity (98 vs. 88%) but lower specificity (91 vs. 99%), although the difference between methods was not statistically significant. In conclusion, the results of the present study indicated that ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT are both accurate methods for the detection of BM in patients with breast cancer, and have comparable diagnostic accuracy.

Correspondence to: Dr Jiong Cai, Department of Nuclear Medicine, The Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Huichuan, Zunyi, Guizhou 563003, P.R. China
E-mail: jiong_cai@163.com

*Contributed equally

Abbreviations: ^{18}F, fluorine-18; BM, bone metastasis; FDG, fluorodeoxyglucose; NaF, sodium fluoride; PET/CT, positron emission tomography/computed tomography; TP, true positive; FP, false positive; FN, false negative; TN, true negative; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; SROC, summary receiver operating characteristic; AUC, area under the curve; CI, confidence interval

Key words: breast cancer, bone metastasis, ^{18}F-FDG PET/CT, ^{18}F-fluoride PET/CT, meta-analysis

Introduction

According to the latest global cancer data, there are expected to be 2.3 million new cases of breast cancer worldwide by 2022, accounting for 11.6% of all cancer cases. In 157 countries, breast cancer is the most common cancer among women (1). The incidence of bone metastasis (BM) in patients with breast cancer is ~8%, but can reach 30-85% in cases of advanced breast cancer (2). Breast cancer remains the leading cause of cancer-associated deaths among women. It is estimated that 666,000 women succumbed to breast cancer in 2022 worldwide, with metastatic disease being the main cause of death rather than the primary cancer (1,3). BM can disrupt bone metabolism, leading to bone-related events such as bone pain, pathological fractures, spinal cord compression, and hypercalcemia, which markedly affect the quality of life of patients and can even be life-threatening (4). A previous study showed

that BM is a crucial factor affecting the prognosis of patients with breast cancer. The 5-year survival rate for patients with early-stage breast cancer without metastasis is as high as 90%, but once BM occurs, the 5-year survival rate drops to 10% (5). There is currently no cure for patients with breast cancer and BM; however, appropriate treatment can prolong survival and improve the quality of life of the patient. Therefore, it is important to accurately assess whether patients with breast cancer have BM (6).

X-ray imaging is routinely used to screen for bone disease, but is not effective for early BM detection because it only identifies lesions after a 30-50% loss of calcium (7). Bone scans are imaging techniques with high sensitivity but low specificity for the detection of bone lesions (8). Therefore, more sensitive and accurate methods are necessary to detect the BM associated with breast cancer earlier so that intervention can be initiated sooner, and thereby improve the survival time of the patient. Positron emission tomography/computed tomography (PET/CT) is an advanced diagnostic imaging technology that provides both metabolic information and precise anatomical localization. It has broad applications in the diagnosis, staging, location and treatment evaluation of various malignant tumors (9,10). Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is a PET/CT tracer that is widely used for the diagnosis, staging and follow-up of patients with breast cancer due to its high diagnostic performance for lesions (11). A bone-specific radiotracer, ^{18}F-sodium fluoride (^{18}F-NaF), is effective in revealing changes in bone activity and has been widely used for the clinical detection of bone lesions (12,13). In patients with breast cancer and BM, metastases are predominantly osteolytic, but are osteogenic in 15-20% of cases (14-16). It has been shown that ^{18}F-FDG is most sensitive in the detection of osteolytic metastases (17). Therefore, the present meta-analysis reviewed studies on the detection of BM in patients with breast cancer using PET/CT. The aim was to quantitatively evaluate and compare the diagnostic performance of ^{18}F-FDG and ^{18}F-NaF as PET/CT tracers in the detection of BM associated with breast cancer.

Patients and methods

Literature search to identify relevant studies. The present study was conducted in accordance with the Cochrane Collaboration's Systematic Review guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses requirements (18). The English literature on ^{18}F-FDG PET/CT or ^{18}F-NaF PET/CT in the detection of BM in breast cancer was retrieved from the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Embase (https://www.embase.com/) databases. A systematic search was performed used multiple keywords: ('PET/CT' OR 'PET-CT' OR 'positron emission tomography/computed tomography' OR 'positron emission tomography-computed tomography') AND ('breast cancer' OR 'breast carcinoma' OR 'mammary cancer' OR 'breast tumor;) AND ('bone metastasis' OR 'skeletal metastases' OR 'osseous metastasis') AND ('^{18}F-fluorodeoxyglucose' OR '^{18}F-FDG' OR '^{18}F-NaF' OR '^{18}F-fluoride'). The publication period was limited from January 1, 2000 to January 31, 2022. The final list of articles was supplemented by cross-checking the reference lists of all retrieved articles.

Study selection and quality assessment. Two reviewers independently screened all titles and read abstracts. The full text of the selected articles was reviewed to determine eligibility. Data extraction and evaluation were performed independently by two authors, with disputes resolved by a third reviewer. Studies included in the meta-analysis met all of the following criteria: i) Patients of any age with breast cancer at any stage of disease, regardless of treatment status; ii) ^{18}F-FDG PET/CT or ^{18}F-NaF PET/CT used in the imaging and characterization of BM in patients with breast cancer; iii) histopathological findings or CT, magnetic resonance imaging (MRI) or clinical follow-up over 6 months included as reference standards; iv) a 2x2 contingency table could be constructed using directly extracted data or by the calculation of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) values based on the sensitivity, specificity, and positive and negative prediction values provided in the article. Exclusion criteria were: i) Studies with <10 patients with breast cancer; ii) studies where the PET/CT tracer was not ^{18}F-FDG or ^{18}F-NaF; iii) studies with multiple published data or subsets of data; iv) case reports, letters, editorials, reviews, animal studies, *in vitro* studies and studies without original data; v) studies presenting results from different imaging modalities jointly, or those in which it was not possible to distinguish between the test performance assessments of individual imaging modalities.

The QUADAS-2 tool was used for the quality assessment of diagnostic accuracy, covering four key areas: Patient selection, index tests, reference standards and the flow and timing of patients through the study (19).

Data extraction. Data extraction was performed independently by two investigators. For each relevant study, the following data were collected: i) Basic information such as the first author, publication year, country and sample size; ii) patient age, patient selection (continuous or non-continuous) and clinical background; iii) study design information; iv) examination results, including the numbers of TP, FP, TN and FN cases; v) parameters of the CT techniques used for ^{18}F-FDG PET or ^{18}F-NaF PET/CT. If there was a dispute between the reviewers, a third researcher evaluated all discordant items until a consensus was reached.

Statistical analysis. Stata software version 14.0 (StataCorp LP) was used to perform the statistical analysis. The diagnostic performance of ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT in the detection of BM in breast cancer was evaluated using specificity, sensitivity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and summary receiver operating characteristic (SROC) curves based on TP, FP, FN, and TN values extracted from the included studies. The area under the curve (AUC) and 95% confidence intervals (CIs) were calculated. Analyses were performed using the DerSimonan-Laird method, a random-effects model, to calculate weighted mean pooled sensitivity, specificity, PLR, NLR and DOR and their corresponding 95% CIs. Variability was assessed graphically by plotting metrics with 95% CIs for each study separately in a forest plot. Values of pooled PLR >10 and DOR >100 indicate that a positive test result helps to confirm the presence of BM, while pooled NLR

values <0.1 indicate that a negative test result helps to exclude BM (20). Hierarchical logistic regression models were used to estimate the sensitivity and specificity of the included studies. For each study included in a forest plot, the corresponding 95% CIs were shown to graphically represent the index being measured. Heterogeneity among the studies was assessed using Cochran's Q test and Higgins I^2 test (20). In Cochran's Q test, P<0.05 indicated the presence of heterogeneity. The degree of heterogeneity was assessed using the following criteria: An inconsistency index (I^2) <50% indicated low heterogeneity; an I^2 of 50-80% indicated moderate heterogeneity; and an I^2 >80% indicated high heterogeneity. Subgroup analyses for ^{18}F-FDG PET/CT were performed based on study sample size, mean patient age, study design type, attenuation correction, minimum scan slice thickness, imaging system supplier and whether the study was patient- or lesion-based. Publication bias was assessed using a funnel plot and Deek's asymmetry test for both ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT (21). The potential publication bias was estimated using Egger's quantitative test. A two-sample Z-test was used to evaluate the difference in diagnostic performance between the two methods for the detection of BM in breast cancer, with P<0.05 considered to indicate a statistically significant result.

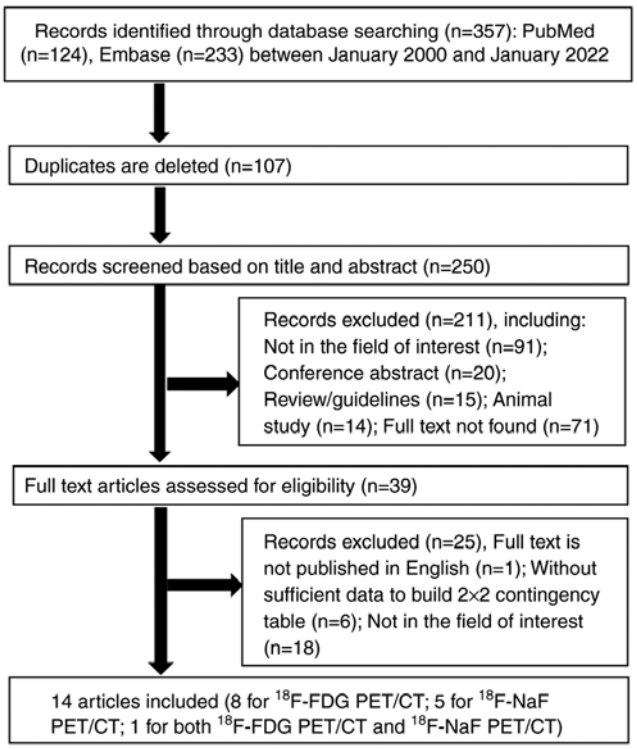

Figure 1. Flow chart of the study selection process. ^{18}F, fluorine-18; FDG, fluorodeoxyglucose; NaF, sodium fluoride; PET/CT, positron emission tomography/computed tomography.

Results

Eligible studies and quality assessment. A literature search identified357 potentially relevant articles. After the exclusion of 107 duplicates, the screening of titles and abstracts led to the exclusion of a further 211 articles for being reviews or guidelines (n=15), conference papers (n=20), animal studies (n=14) or on irrelevant topics (n=91), or due to the full text not being available (n=71). After reading the full texts of the remaining 39 articles, 25 articles were excluded due to not being published in English (n=1), lacking the data to construct a 2x2 contingency table (n=6), or not being relevant to the area of interest (n=18). Finally, 14 articles on the diagnostic performance of ^{18}F-FDG or ^{18}F-NaF PET/CT in breast cancer BM met the criteria for inclusion in the present meta-analysis. The identification and selection process for the studies is shown in Fig. 1.

A total of 14 articles (15,22-34) were included in the study. These comprised 8 studies on ^{18}F-FDG PET/CT, 5 studies on ^{18}F-NaF PET/CT, and 1 study on both, including a total of 919 patients and 2,054 lesions. The sample sizes in the studies ranged from 20 to 150 patients, with mean ages ranging from 43.8 to 64 years. All 14 articles were published between 2010 and 2019, and comprised 8 prospective studies and 6 retrospective studies. Among these, 3 studies included patients with breast cancer who had previously received treatment, 3 studies included patients newly diagnosed with breast cancer who were clinically suspected of having BM, and 8 studies included both treated and newly diagnosed patients. The baseline characteristics of each study are presented in Table I, and the PET/CT parameters used in each study are presented in Table SI. The quality of each study was assessed using the QUADAS-2 tool. This assessment revealed that all studies met at least 5 of the 7 reference criteria, which included 4 items associated with the risk of bias, namely patient selection, index test, reference standard, and flow and timing, and 3 items associated with application concerns, namely patient selection, index test and reference standard; therefore, they were considered satisfactory (35). With regard to patient selection, 5 studies (22,24,25,29,32) were considered high-risk for reference standards, as only imaging and follow-up results were used as the reference standards. Additionally, one study had only a 2-month follow-up period (24), which was also considered high-risk. The risk of bias for flow and timing was unclear in all studies because the time interval between the index test and the reference standard was not reported. The results of the QUADAS-2 assessment are shown in Table SII.

Diagnostic accuracy. The 9 studies using the ^{18}F-FDG PET/CT method had sensitivities ranging from 0.47 (95% CI, 0.37-0.58) to 1.0 (95% CI, 0.59-1.00) for the identification of breast cancer BM, and specificities ranging from 0.91 (95% CI, 0.82-0.96) to 1.0 (95% CI, 0.98-1.00). The pooled sensitivity and specificity of ^{18}F-FDG PET/CT for the identification of BM derived from breast cancer were 0.88 (95% CI, 0.76-0.94) and 0.99 (95% CI, 0.97-1.00), respectively, as shown in Fig. 2. In addition, Cochran's Q test and Higgins I^2 test indicated high heterogeneity in sensitivity (Q, 168.81, P≤0.01; I^2, 93.48) and moderate heterogeneity in specificity (Q, 44.38, P≤0.01; I^2, 75.21). The 6 studies describing the use of ^{18}F-NaF PET/CT in the detection of breast cancer BM had sensitivities ranging from 0.91 (95% CI, 0.83-0.96) to 1.00 (95% CI, 0.84-1.00) and specificities ranging from 0.46 (95% CI, 0.34-0.59) to 1.00 (95% CI, 0.74-1.00). The pooled sensitivity and specificity were 0.98 (95% CI, 0.92-1.00) and 0.91 [95% CI, 0.76-0.97), respectively, as shown in Fig. 3. Cochran's Q test and Higgins I^2 test also showed high heterogeneity in sensitivity (Q, 70.87,

TTable I. Clinical characteristics and diagnostic results of the detection of bone metastases reported in each eligible study.

A, ^{18}F-FDG PET/CT

First author, year	Country	No. of patients	No. of lesions	Study design			Clinical setting	Mean age (range), years	Patient-based analysis				Lesion-based analysis				Reference standard	(Refs.)
				Prospective	Multicenter	Consecutive			TP	FP	FN	TN	TP	FP	FN	TN		
Koizumi *et al*, 2019	Japan	120	-	No	No	Yes	New + treated	-	34	8	1	77	-	-	-	-	HP follow-up >6 months	(30)
Caglar *et al*, 2016	Turkey	150	-	No	No	Yes	New + treated	52 (27-85)	84	1	1	64	-	-	-	-	HP; follow-up >10 months	(26)
Hahn *et al*, 2011	Germany	28	129	No	No	Yes	New + treated	57.5 (35-78)	7	0	1	20	67	5	3	54	MRI follow-up	(22)
Damle *et al*, 2013	India	72	-	Yes	No	Yes	Treated	52 (30-77)	25	1	9	37	-	-	-	-	HP; consensus from MRI/ thin-slice CECT/skeletal radiograph findings	(15)
Al-Muqbel, 2017	Jordan	35	-	No	No	Yes	Treated	48.1	25	0	9	1	-	-	-	-	Staging or follow-up ^{18}F-FDG-PET/CT.	(25)
Botsikas *et al*, 2019	Switzerland	80	175	Yes	No	Yes	New + treated	48	6	0	3	71	18	0	8	149	HP; follow-up >12 months	(34)
Rager *et al*, 2018	Switzerland	25	109	No	Yes	Yes	New	55 (38-82)	10	0	2	13	43	0	48	18	Follow-up >21 months	(24)
Heusner *et al*, 2010	Germany	20	-	Yes	No	Yes	New + treated	54.5 (25.4-78.2)	7	0	0	13	-	-	-	-	Consensus from MRI and bone scan	(28)
Teke *et al*, 2015	Turkey	-	496	No	No	-	New	44.5 (28-81)	-	-	-	-	141	2	10	343	Follow-up >6 months	(32)

Table I. Continued.

B, ^{18}F-NaF PET/CT

First author, year	Country	No. of patients	No. of lesions	Study design			Clinical setting	Mean age (range), years	Patient-based analysis				Lesion-based analysis				Reference standard	(Refs.)
				Prospective	Multicenter	Consecutive			TP	FP	FN	TN	TP	FP	FN	TN		
Yoon *et al*, 2013	Korea	-	119	Yes	No	-	New + treated	55.6	-	-	-	-	49	36	3	31	HP; follow-up >12 months	(33)
Broos *et al*, 2018	Netherlands	118	-	Yes	No	-	New + treated	64	50	6	2	60	-	-	-	-	Follow-up >6 months	(23)
Damle *et al*, 2013	India	72	-	Yes	No	Yes	Treated	52 (30-77)	34	11	0	27	-	-	-	-	HP; consensus from MRI/ thin-slice CECT/ skeletal radiograph findings	(15)
Passah *et al*, 2017	India	-	199	Yes	No	-	New	43.8	-	-	-	-	178	0	0	21	^{99m}Tc-MDP skeletal scintigraphy	(29)
Abikhzer *et al*, 2016	UK	41	284	Yes	No	-	New + treated	58 (30-75)	21	3	0	17	73	6	7	198	HP; follow-up >33 months	(31)
Piccardo *et al*, 2012	Italy	39	662	Yes	-	-	Treated	60	27	0	0	12	491	11	51	109	Follow-up >12 months	(27)

^{18}F, fluorine-18; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; TP, true positive; FP, false positive; FM, false negative; TN, true negative; HP, histopathological; MRI, magnetic resonance imaging; CECT, contrast-enhanced CT; ^{99m}Tc-MDP, technetium-99m methylene diphosphonate; NaF, sodium fluoride.

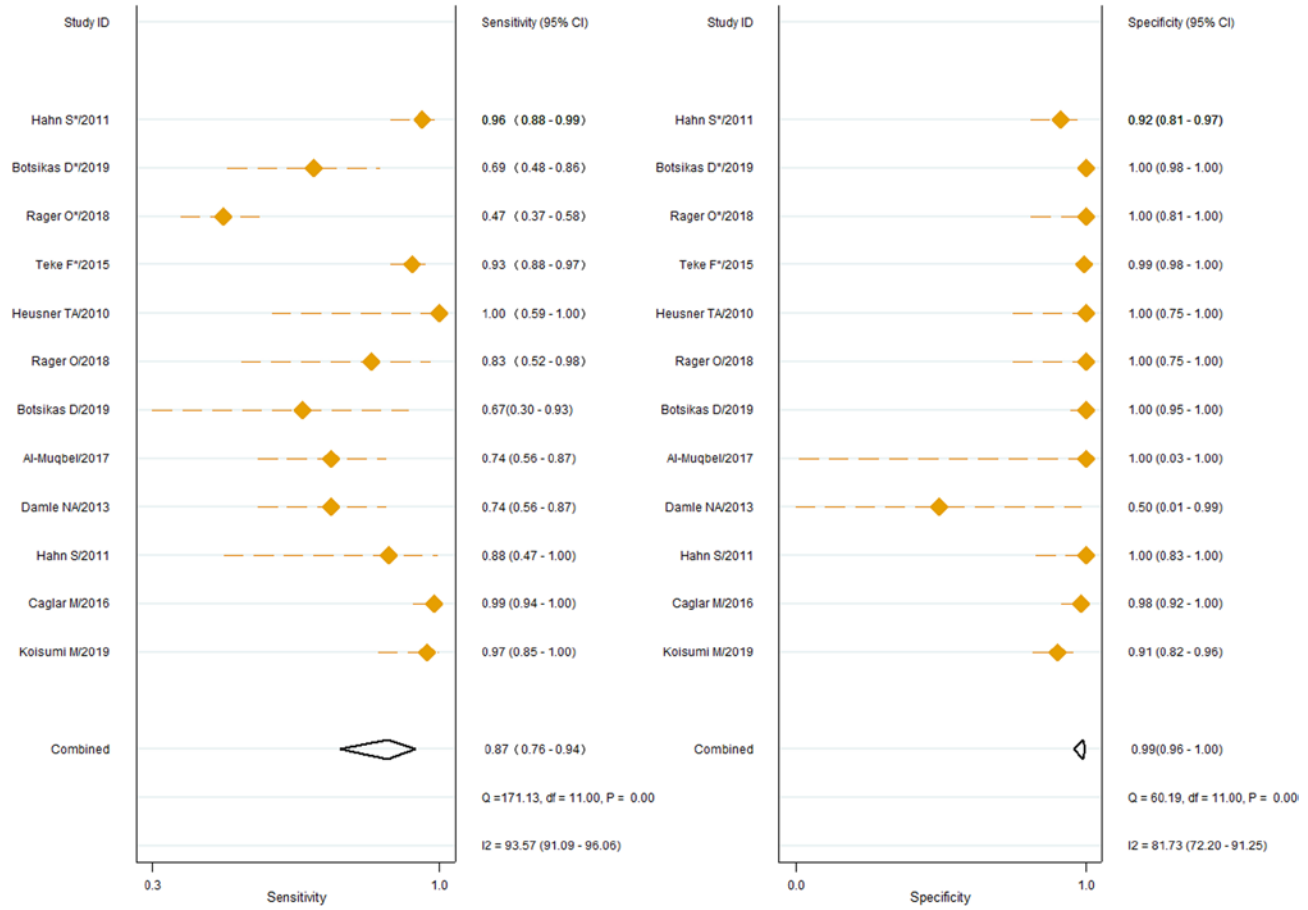

Figure 2. Pooled sensitivity and specificity for fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography. Patient- and lesion-based analyses were separately included in the pooled analysis; *indicates lesion-based analysis. CI, confidence interval; df, degrees of freedom.

P≤0.01; I^2, 90.12) and specificity (Q, 228.86, P≤0.01; I^2, 96.94) among the studies. The pooled PLR and NLR for ^{18}F-FDG PET/CT were 129.2 (95% CI, 27.1-616.4) and 0.13 (95% CI, 0.06-0.25), respectively. For ^{18}F-NaF PET/CT, the pooled PLR and NLR were 10.9 (95% CI, 3.8-31.5) and 0.02 (95% CI, 0.01-0.1), respectively. The pooled DOR for ^{18}F-FDG PET/CT in the diagnosis of breast cancer BM was 1,028 (95% CI, 244-4,330), while for ^{18}F-NaF PET/CT, the pooled DOR was 489 (95% CI, 65-3,654), as shown in Table II. These data suggest that a positive result from FDG testing helps confirm the presence of BM, while a negative result from NaF testing helps to rule out BM. No significant difference in the DOR between ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT was detected. The area under the SROC curves for ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT were both 0.99 (95% CI, 0.98-1.00), as shown in Fig. 4.

Publication bias. Deek's funnel plots for publication bias in the studies on ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT are shown in Fig. 5. The statistical significance of the slope coefficient for ^{18}F-FDG PET/CT (P=0.02) is suggestive of publication bias. However, the slope coefficient for ^{18}F-NaF PET/CT lacked significance (P=0.37), indicating a low possibility of publication bias. When analyzed using Egger's test, both ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT exhibited no evidence of publication bias (P=0.187 and P=0.123, respectively; Fig. 6).

Exploration of heterogeneity. The results of the meta-regression analysis are shown in Table III. Eight studies reported patient-based results for the performance of ^{18}F-FDG PET/CT in the diagnosis of breast cancer BM, with a sensitivity of 0.89 (95% CI, 0.80-0.99) and a specificity of 0.99 (95% CI, 0.98-1.00). Four studies, including 909 lesions, were lesion-based, with a sensitivity of 0.84 (95% CI, 0.67-1.00) and a specificity of 1.00 (95% CI, 0.98-1.00). The 7 studies in which the mean age of the patients was ≥50 years had a sensitivity of 0.88 (95% CI, 0.78-0.99) and specificity of 0.98 (95% CI, 0.96-1.00), while the 4 studies in which the mean age of the patients was <50 years had a sensitivity of 0.80 (95% CI, 0.60-0.99) and specificity of 1.00 (95% CI, 0.99-1.00). Patient-based analysis, mean patient age, slice thickness and imaging system supplier were not found to be responsible for the between-study heterogeneity (P>0.05). However, study design, sample size, attenuation correction value and the different imaging system supplier were identified as sources of heterogeneity in the diagnostic performance of ^{18}F-FDG PET/CT in breast cancer BM (P<0.05). Due to the small number of studies on ^{18}F-NaF PET/CT, it was not possible to perform a further subgroup analysis to identify the causes of heterogeneity.

Discussion

In the present meta-analysis, covering 919 patients and 2,054 lesions from 14 studies, the diagnostic performance of ^{18}F-NaF

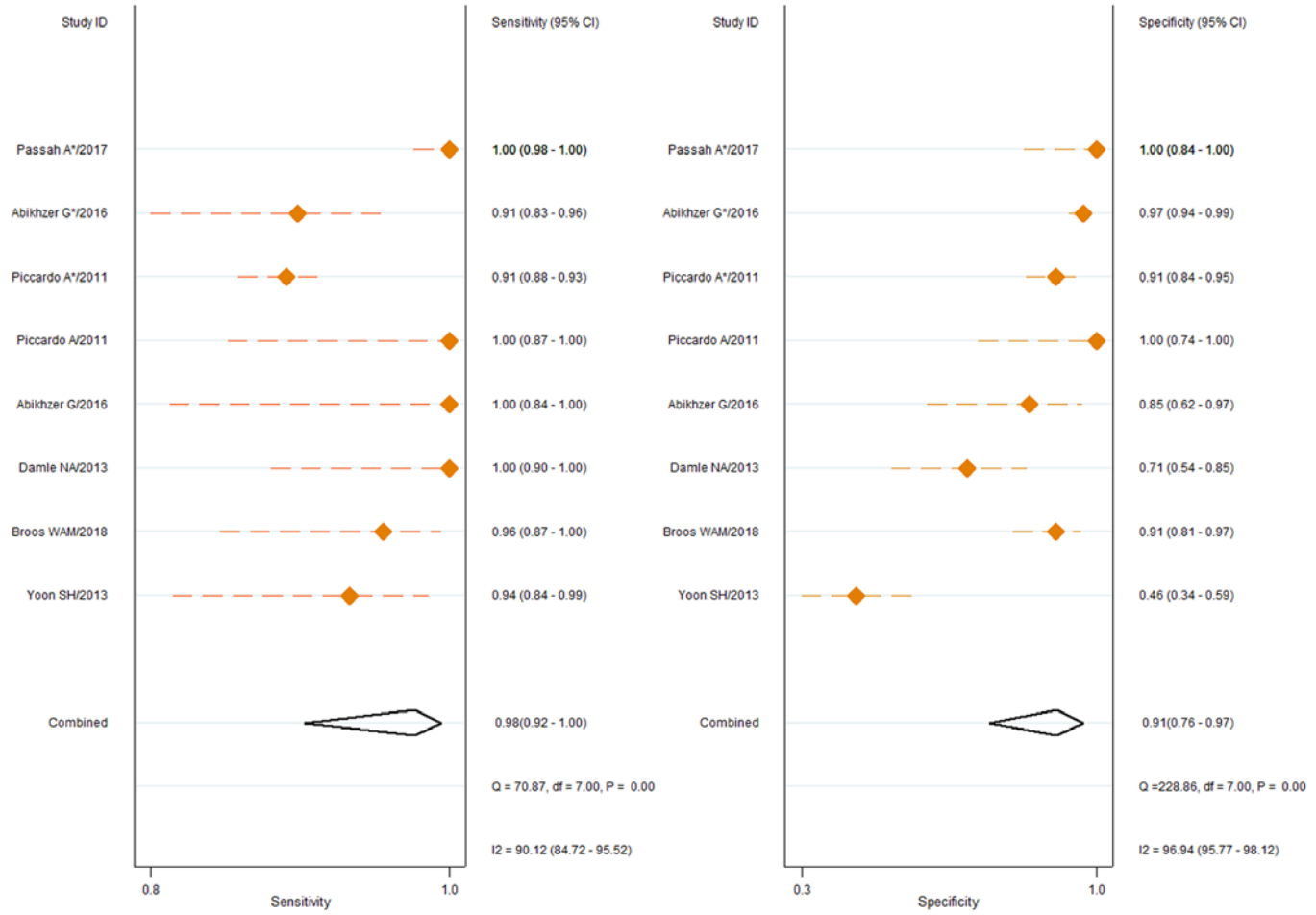

Figure 3. Pooled sensitivity and specificity for fluorine-18 positron emission tomography/computed tomography. Patient- and lesion-based analyses were separately included in the pooled analysis; *indicates lesion-based analysis. CI, confidence interval; df, degrees of freedom.

PET/CT and ^{18}F-FDG PET/CT was compared in the detection of breast cancer BM. The results indicate that ^{18}F-NaF PET/CT is more sensitive than ^{18}F-FDG PET/CT for the detection of BM in patients with breast cancer (98 vs. 88%), while ^{18}F-FDG PET/CT is more specific than ^{18}F-NaF PET/CT for this purpose (99 vs. 91%). However, these differences are not statistically significant, suggesting that both tracers have a good diagnostic performance, with both having an AUC of 0.99 (95% CI, 0.98-1.00) when used in PET/CT imaging for the detection of BM associated with breast cancer.

^{18}F-FDG PET/CT is a sensitive molecular imaging method that is able to diagnose BM by detecting the increased uptake of FDG in metastatic cancer cells (36). Previous meta-analyses have shown that ^{18}F-FDG PET/CT has high diagnostic performance in the identification of lymph node metastasis, staging, evaluation of treatment efficacy and assessment of the prognosis of patients with breast cancer after chemotherapy (37-41). The present meta-analysis, which included 9 studies on ^{18}F-FDG PET/CT with 530 patients and 909 lesions, showed that ^{18}F-FDG PET/CT has a good diagnostic performance. As an osteophytic tracer, ^{18}F-NaF offers the advantageous features of high and rapid bone uptake accompanied by very rapid blood clearance. This results in a high bone-to-background ratio in a short time and allows areas of altered skeletal activity to be displayed, which makes it an increasingly favored agent for use in the detection of bone lesions (42). Previous studies have shown that ^{18}F-NaF PET/CT can accurately detect BM in malignant tumors such as non-small cell lung cancer, breast cancer and prostate cancer. In particular, it is useful for assessing the extent of BM and aiding in treatment decisions, making it a good tool for the early and accurate detection of BM (15,43). The present meta-analysis, which included 6 studies on ^{18}F-NaF PET/CT, showed that ^{18}F-NaF PET/CT is more sensitive but less specific than ^{18}F-FDG PET/CT in the detection of breast cancer BM. This lower specificity may be due to benign diseases also being able to cause new bone formation and increase NaF uptake, which can create false positives (26). Moreover, it is notable that in addition to showing high accuracy in the detection of BM, ^{18}F-FDG is also highly accurate in the identification of distant organ tissue metastasis and lymph node metastasis (38,39). The results of the present meta-analysis indicate that ^{18}F-FDG and ^{18}F-NaF have comparable accuracy in the detection of BM in patients with breast cancer. Therefore, it is suggested that ^{18}F-FDG should be considered first in clinical practice, and additional ^{18}F-NaF examinations may not be necessary. Previous studies revealed that ^{18}F-FDG PET/CT is more useful than bone imaging for the detection of osteolytic BM, and that it more accurately detects pure bone marrow metastases, particularly fast-growing lesions (41,44), while it is not recommended for detecting blastic BM (45). For BM with low ^{18}F-FDG intake, ^{18}F-NaF PET/CT has been shown to be a better choice due to

Table II. Summary of the diagnostic performance characteristics of ^{18}F-FDG and ^{18}F-NaF PET/CT in breast cancer bone metastases.

	^{18}F-FDG PET/CT		^{18}F-NaF PET/CT	
Parameter	Estimate	95% CI	Estimate	95% CI
Sensitivity	0.88	0.76, 0.94	0.98	0.92, 1.00
Specificity	0.99	0.97, 1.00	0.91	0.76, 0.97
Positive likelihood ratio	129.2	27.1, 616.4	10.9	3.8, 31.5
Negative likelihood ratio	0.13	0.06, 0.25	0.02	0.01, 0.1
Diagnostic odds ratio	1,028	244, 4,330	489	65, 3,654
AUC	0.99	0.98, 1.00	0.99	0.98, 1.00

^{18}F, fluorine-18; FDG, fluorodeoxyglucose; NaF, sodium fluoride; PET/CT, positron emission tomography/computed tomography; CI, confidence interval; AUC, area under the curve.

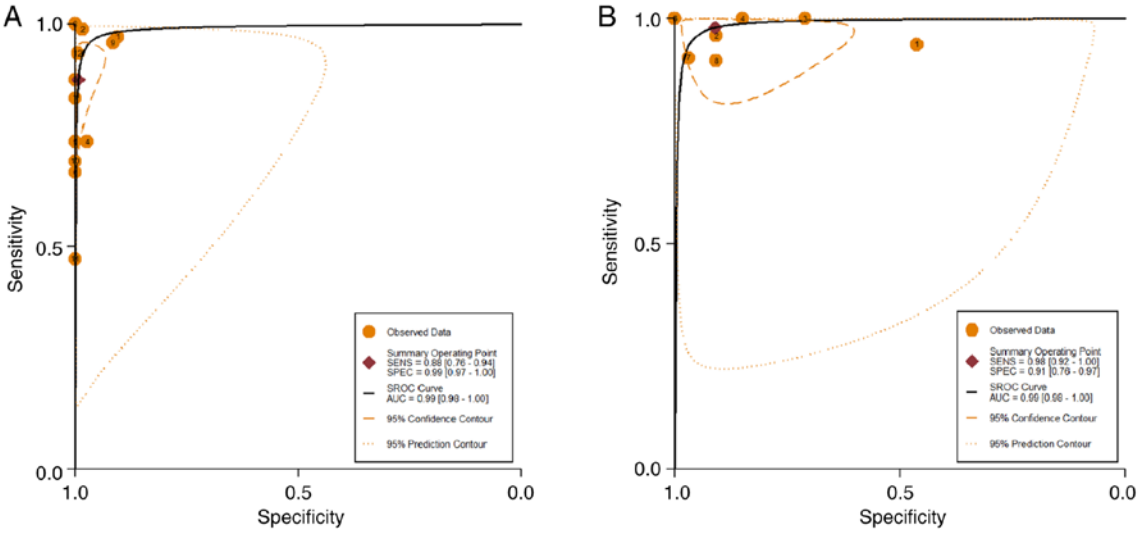

Figure 4. SROC curves of the diagnostic performance of different PET/CT imaging agents. SROC curves for (A) ^{18}F-fluorodeoxyglucose PET/CT and (B) ^{18}F-sodium fluoride PET/CT in the diagnosis of breast cancer bone metastases. SROC, summary receiver operating characteristic; PET/CT, positron emission tomography/computed tomography; ^{18}F, fluorine-18; AUC, area under the curve; Sens, sensitivity; Spec, specificity.

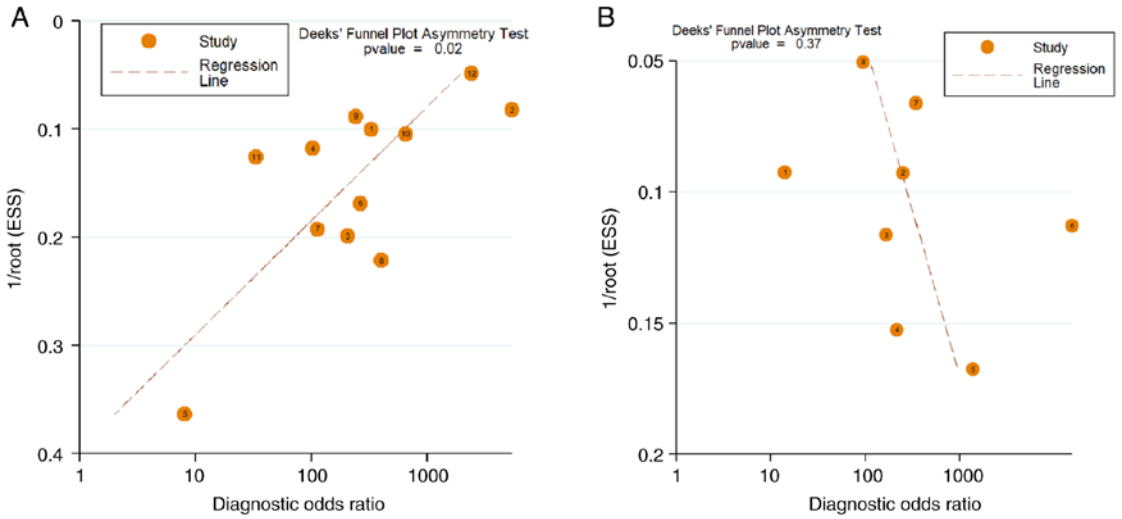

Figure 5. Deeks' funnel plots for publication bias in the studies of different PET/CT imaging agents. Deeks' funnel plots for (A) ^{18}F-fluorodeoxyglucose PET/CT and (B) ^{18}F-sodium fluoride PET/CT with P-values for funnel plot asymmetry. PET/CT, positron emission tomography/computed tomography; ^{18}F, fluorine-18; ESS, effective sample size.

Table III. Meta-regression analysis results for fluorine-18 fluorodeoxyglucose positon emission tomography/computed tomography in the detection of bone metastases in patients with breast cancer.

Parameter	No. of studies	Sensitivity (95% CI)	P-value	Specificity	P-value
Basis			0.88		0.21
Patient	8	0.89 (0.80-0.99)		0.99 (0.98-1.00)	
Lesion	4	0.84 (0.67-1.00)		1.00 (0.98-1.00)	
Design			0.13		<0.01
Prospective	4	0.78 (0.55-1.00)		1.00 (0.99-1.00)	
Retrospective	8	0.91 (0.83-0.98)		0.99 (0.97-1.00)	
Mean age, years			0.73		0.38
≥50	7	0.88 (0.78-0.99)		0.98 (0.96-1.00)	
<50	4	0.80 (0.60-0.99)		1.00 (0.99-1.00)	
Sample no.			0.65		<0.01
>50	4	0.91 (0.81-1.00)		0.98 (0.95-1.00)	
≤50	4	0.87 (0.71-1.00)		1.00 (1.00-1.00)	
Vendor			0.82		0.07
GE Healthcare	4	0.92 (0.81-1.00)		1.00 (0.99-1.00)	
Siemens Healthineers	6	0.89 (0.77-1.00)		1.00 (0.99-1.00)	
AC			0.85		0.02
Yes	7	0.89 (0.78-1.00)		1.00 (0.98-1.00)	
No	5	0.86 (0.72-1.00)		0.99 (0.98-1.00)	
Slice thickness, mm			0.55		0.08
≥4	4	0.90 (0.76-1.00)		0.99 (0.95-1.00)	
<4	4	0.83 (0.64-1.00)		0.99 (0.95-1.00)	

CI, confidence interval; AC, attenuation correction.

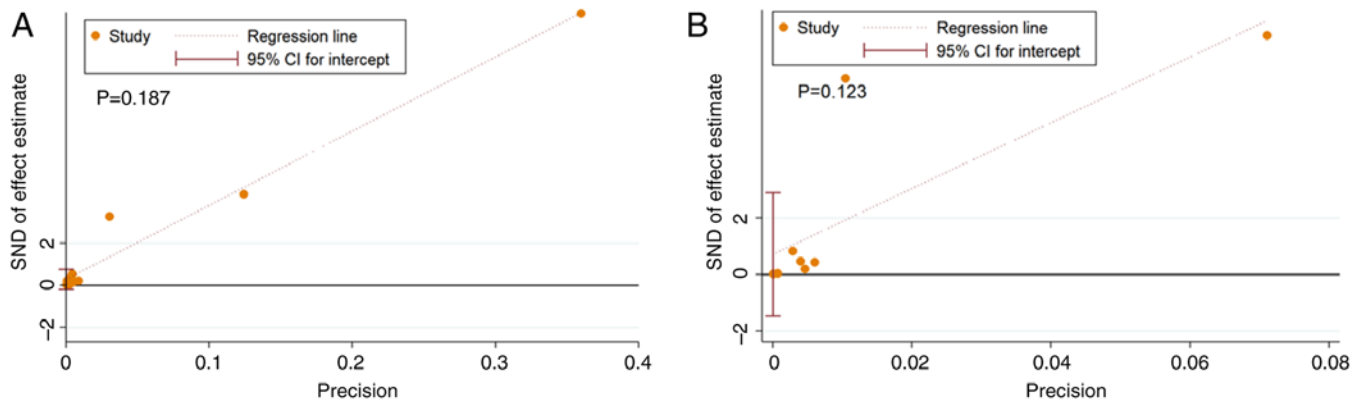

Figure 6. Egger's publication bias plots for the studies of different PET/CT imaging agents. Egger's plots for (A) ^{18}F-fluorodeoxyglucose PET/CT and (B) ^{18}F-sodium fluoride PET/CT. PET/CT, positron emission tomography/computed tomography; ^{18}F, fluorine-18; CI, confidence interval; SND, standard normal deviate.

greater sensitivity (46). Although the current study indicates that ^{18}F-FDG and ^{18}F-NaF have similar diagnostic value, the choice of imaging agent may differ according to the clinical situation.

The current meta-analysis revealed heterogeneity in pooled sensitivity and specificity for the studies on both ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT. Subgroup analysis showed that study design, sample size and the use of attenuation correction were factors contributing to heterogeneity among the studies. Specifically, the specificity of retrospective studies was lower than that of prospective studies, possibly due to inherent bias in patient selection. In addition, studies with a sample size of <50 patients showed higher specificity, which may be due to the fact that a small sample size means that the diversity of the sample may be reduced. The specificity of studies using attenuation correction was higher than that of those without, likely due to improved image quality and clearer visualization of the lesions after attenuation correction (44). The meta-regression

results indicated that lesion-based analysis was more specific than patient-based analysis, and that the specificity of studies with a mean patient age <50 years was greater than that of studies with a higher mean patient age, but these differences were not statistically significant. Slice thickness was not found to contribute to the heterogeneity between studies observed in the present meta-analysis. Meta-regression analysis of ^{18}F-NaF PET/CT was not possible because only 6 studies met the inclusion criteria, and some data were not available.

The main limitation of the present meta-analysis is the limited number of eligible studies, particularly those on ^{18}F-NaF PET/CT. During data extraction, it was found that two articles had inconsistencies in the reported TP, FP, FN and TN values, and their sensitivity and specificity; therefore, these studies were excluded (45,46). Additionally, heterogeneity in the assessment of diagnostic accuracy among the studies on ^{18}F-FDG PET/CT and ^{18}F-NaF PET/CT limits the quality of the meta-analysis. Histopathological validation was not available for BM in all patients; instead, imaging-based reference standards such as CT and MRI were used, which may increase clinical heterogeneity. However, as it is impractical and unethical to obtain histological evidence for all skeletal lesions, non-invasive imaging results that are not rigorously validated by histological examination are considered acceptable. Although the present study compared the diagnostic performance of ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT in the detection of breast cancer BM, limited data may affect the estimates of diagnostic efficacy. However, the diagnostic performance of these imaging techniques provides a reference for clinical practice and helps to avoid the subjective interpretation of results.

In conclusion, the current study shows that ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT are accurate methods for the detection of BM in patients with breast cancer, and are comparable in diagnostic accuracy. Moreover, it contributes to a more comprehensive understanding of the use of ^{18}F-FDG and ^{18}F-NaF as PET/CT imaging agents for the detection of BM in patients diagnosed with breast cancer, and may serve as a point of reference for patient care.

Acknowledgements

Not applicable.

Funding

This study was funded by the National Natural Science Foundation of the People's Republic of China, NSFC (grant no. 82260353).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JC, XH and HH conceived the study and designed the structure of the manuscript. XH and JC were involved in the methodology, data validation, writing, reviewing and editing the study, and project supervision/CMS validated the data, carried out investigation, wrote, reviewed and edited the manuscript, and completed project supervision. JC, ZL, WY, DL and SL were involved in the conceptualization of the study, data visualization, supervision and project administration. XH and JC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Cook GJ, Houston S, Rubens R, Maisey MN and Fogelman I: Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. J Clin Oncol 16: 3375-3379, 1998.
3. Zengel B, Kilic M, Tasli F, Simsek C, Karatas M, Ozdemir O, Cavdar D, Durusoy R, Bas KK and Uslu A: Breast cancer patients with isolated bone metastases and oligometastatic bone disease show different survival outcomes. Sci Rep 11: 20175, 2021.
4. Pantel K and Hayes DF: Disseminated breast tumour cells: Biological and clinical meaning. Nat Rev Clin Oncol 15: 129-131, 2018.
5. Makhoul I, Montgomery CO, Gaddy D and Suva LJ: The best of both worlds-managing the cancer, saving the bone. Nat Rev Endocrinol 12: 29-42, 2016.
6. Brook N, Brook E, Dharmarajan A, Dass CR and Chan A: Breast cancer bone metastases: Pathogenesis and therapeutic targets. Int J Biochem Cell Biol 96: 63-78, 2018.
7. Weigelt B, Peterse JL and van 't Veer LJ: Breast cancer metastasis: Markers and models. Nat Rev Cancer 5: 591-602, 2005.
8. Liu T, Cheng T, Xu W, Yan WL, Liu J and Yang HL: A meta-analysis of 18FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with breast cancer. Skeletal Radiol 40: 523-531, 2011.
9. Cook GJ, Azad GK and Goh V: Imaging bone metastases in breast cancer: Staging and response assessment. J Nucl Med 57 (Suppl 1): 27S-33S, 2016.
10. Hansen JA, Naghavi-Behzad M, Gerke O, Baun C, Falch K, Duvnjak S, Alavi A, Høilund-Carlsen PF and Hildebrandt MG: Diagnosis of bone metastases in breast cancer: Lesion-based sensitivity of dual-time-point FDG-PET/CT compared to low-dose CT and bone scintigraphy. PLoS One 16: e0260066, 2021.
11. Garami Z, Hascsi Z, Varga J, Dinya T, Tanyi M, Garai I, Damjanovich L and Galuska L: The value of 18-FDG PET/CT in early-stage breast cancer compared to traditional diagnostic modalities with an emphasis on changes in disease stage designation and treatment plan. Eur J Surg Oncol 38: 31-37, 2012.
12. Bastawrous S, Bhargava P, Behnia F, Djang DS and Haseley DR: Newer PET application with an old tracer: Role of 18F-NaF skeletal PET/CT in oncologic practice. Radiographics 34: 1295-1316, 2014.
13. Xiong Z, Deng G, Huang X, Li X, Xie X, Wang J, Shuang Z and Wang X: Bone metastasis pattern in initial metastatic breast cancer: A population-based study. Cancer Manag Res 10: 287-295, 2018.
14. Tsuzuki S, Park SH, Eber MR, Peters CM and Shiozawa Y: Skeletal complications in cancer patients with bone metastases. Int J Urol 23: 825-832, 2016.

15. Damle NA, Bal C, Bandopadhyaya GP, Kumar L, Kumar P, Malhotra A and Lata S: The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: A comparison with FDG PET/CT and 99mTc-MDP bone scan. Jpn J Radiol 31: 262-269, 2013.
16. Al-Muqbel KM, Yaghan RJ, Al-Omari MH, Rousan LA, Dagher NM and Al Bashir S: Clinical relevance of 18F-FDG-negative osteoblastic metastatic bone lesions noted on PET/CT in breast cancer patients. Nucl Med Commun 37: 593-601, 2016.
17. Gaeta CM, Vercher-Conejero JL, Sher AC, Kohan A, Rubbert C and Avril N: Recurrent and metastatic breast cancer PET, PET/CT, PET/MRI: FDG and new biomarkers. Q J Nucl Med Mol Imaging 57: 352-366, 2013.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 339: b2700, 2009.
19. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA and Bossuyt PM: QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155: 529-536, 2011.
20. Deeks JJ: Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ 323: 157-162, 2001.
21. Deeks JJ, Macaskill P and 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 58: 882-893, 2005.
22. Hahn S, Heusner T, Kümmel S, Köninger A, Nagarajah J, Müller S, Boy C, Forsting M, Bockisch A, Antoch G and Stahl A: Comparison of FDG-PET/CT and bone scintigraphy for detection of bone metastases in breast cancer. Acta Radiol 52: 1009-1014, 2011.
23. Broos W, van der Zant FM, Wondergem M and Knol R: Accuracy of 18F-NaF PET/CT in bone metastasis detection and its effect on patient management in patients with breast carcinoma. Nucl Med Commun 39: 325-333, 2018.
24. Rager O, Lee-Felker SA, Tabouret-Viaud C, Felker ER, Poncet A, Amzalag G, Garibotto V, Zaidi H and Walter MA: Accuracy of whole-body HDP SPECT/CT, FDG PET/CT, and their combination for detecting bone metastases in breast cancer: An intra-personal comparison. Am J Nucl Med Mol Imaging 8: 159-168, 2018.
25. Al-Muqbel KM: Bone marrow metastasis is an early stage of bone metastasis in breast cancer detected clinically by F18-FDG-PET/CT imaging. Biomed Res Int 2017: 9852632, 2017.
26. Caglar M, Kupik O, Karabulut E and Høilund-Carlsen PF: Detection of bone metastases in breast cancer patients in the PET/CT era: Do we still need the bone scan. Rev Esp Med Nucl Imagen Mol 35: 3-11, 2016.
27. Piccardo A, Altrinetti V, Bacigalupo L, Puntoni M, Biscaldi E, Gozza A, Cabria M, Iacozzi M, Pasa A, Morbelli S, *et al*: Detection of metastatic bone lesions in breast cancer patients: fused (18)F-Fluoride-PET/MDCT has higher accuracy than MDCT. Preliminary experience. Eur J Radiol 81: 2632-2638, 2012.
28. Heusner TA, Kuemmel S, Koeninger A, Hamami ME, Hahn S, Quinsten A, Bockisch A, Forsting M, Lauenstein T, Antoch G and Stahl A: Diagnostic value of diffusion-weighted magnetic resonance imaging (DWI) compared to FDG PET/CT for whole-body breast cancer staging. Eur J Nucl Med Mol Imaging 37: 1077-1086, 2010.
29. Passah A, Tripathi M, Ballal S, Yadav MP, Kumar R, Roesch F, Meckel M, Sarathi Chakraborty P and Bal C: Evaluation of bone-seeking novel radiotracer ^{68}Ga-NO2AP-Bisphosphonate for the detection of skeletal metastases in carcinoma breast. Eur J Nucl Med Mol Imaging 44: 41-49, 2017.
30. Koizumi M, Motegi K and Umeda T: A novel biomarker, active whole skeletal total lesion glycolysis (WS-TLG), as a quantitative method to measure bone metastatic activity in breast cancer patients. Ann Nucl Med 33: 502-511, 2019.
31. Abikhzer G, Srour S, Fried G, Drumea K, Kozlener E, Frenkel A, Israel O, Fogelman I and Kagna O: Prospective comparison of whole-body bone SPECT and sodium 18F-fluoride PET in the detection of bone metastases from breast cancer. Nucl Med Commun 37: 1160-1168, 2016.
32. Teke F, Teke M, Inal A, Kaplan MA, Kucukoner M, Aksu R, Urakci Z, Tasdemir B and Isikdogan A: Significance of hormone receptor status in comparison of 18F-FDG-PET/CT and 99mTc-MDP bone scintigraphy for evaluating bone metastases in patients with breast cancer: Single center experience. Asian Pac J Cancer Prev 16: 387-391, 2015.
33. Yoon SH, Kim KS, Kang SY, Song HS, Jo KS, Choi BH, Lee SJ, Yoon JK and An YS: Usefulness of (18)F-fluoride PET/CT in breast cancer patients with osteosclerotic bone metastases. Nucl Med Mol Imaging 47: 27-35, 2013.
34. Botsikas D, Bagetakos I, Picarra M, Da Cunha Afonso Barisits AC, Boudabbous S, Montet X, Lam GT, Mainta I, Kalovidouri A and Becker M: What is the diagnostic performance of 18-FDG-PET/MR compared to PET/CT for the N- and M-staging of breast cancer. Eur Radiol 29: 1787-1798, 2019.
35. Hu X, Li D, Liang Z, Liao Y, Yang L, Wang R, Wang P and Cai J: Indirect comparison of the diagnostic performance of 18F-FDG PET/CT and MRI in differentiating benign and malignant ovarian or adnexal tumors: A systematic review and meta-analysis. BMC Cancer 21: 1080, 2021.
36. Evangelista L, Panunzio A, Polverosi R, Ferretti A, Chondrogiannis S, Pomerri F, Rubello D and Muzzio PC: Early bone marrow metastasis detection: The additional value of FDG-PET/CT vs. CT imaging. Biomed Pharmacother 66: 448-453, 2012.
37. Han S and Choi JY: Impact of 18F-FDG PET, PET/CT, and PET/MRI on staging and management as an initial staging modality in breast cancer: A systematic review and meta-analysis. Clin Nucl Med 46: 271-282, 2021.
38. Zhang X, Liu Y, Luo H and Zhang J: PET/CT and MRI for identifying axillary lymph node metastases in breast cancer patients: Systematic review and meta-Analysis. J Magn Reson Imaging 52: 1840-1851, 2020.
39. Han S and Choi JY: Prognostic value of 18F-FDG PET and PET/CT for assessment of treatment response to neoadjuvant chemotherapy in breast cancer: A systematic review and meta-analysis. Breast Cancer Res 22: 119, 2020.
40. Diao W, Tian F and Jia Z: The prognostic value of SUVmax measuring on primary lesion and ALN by 18F-FDG PET or PET/CT in patients with breast cancer. Eur J Radiol 105: 1-7, 2018.
41. Krüger S, Buck AK, Mottaghy FM, Hasenkamp E, Pauls S, Schumann C, Wibmer T, Merk T, Hombach V and Reske SN: Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging 36: 1807-1812, 2009.
42. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A and Treves ST: Skeletal PET with 18F-fluoride: Applying new technology to an old tracer. J Nucl Med 49: 68-78, 2008.
43. Schirrmeister H, Guhlmann A, Kotzerke J, Santjohanser C, Kühn T, Kreienberg R, Messer P, Nüssle K, Elsner K, Glatting G, *et al*: Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. J Clin Oncol 17: 2381-2389, 1999.
44. Bebbington NA, Zacho HD and Holdgaard PC: Lesion detection in 18F-sodium fluoride bone imaging: A comparison of attenuation-corrected versus nonattenuation-corrected PET reconstructions from modern PET-CT systems. Nucl Med Commun 43: 78-85, 2022.
45. Capitanio S, Bongioanni F, Piccardo A, Campus C, Gonella R, Tixi L, Naseri M, Pennone M, Altrinetti V, Buschiazzo A, *et al*: Comparisons between glucose analogue 2-deoxy-2-((18)F) fluoro-D-glucose and (18)F-sodium fluoride positron emission tomography/computed tomography in breast cancer patients with bone lesions. World J Radiol 8: 200-209, 2016.
46. Balci TA, Koc ZP and Komek H: Bone scan or (18)f-fluorodeoxyglucose positron emission tomography/computed tomography; which modality better shows bone metastases of breast cancer. Breast Care (Basel) 7: 389-393, 2012.