

Molecular imaging approaches in the diagnosis of breast cancer: A systematic review and meta-analysis

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ABSTRACT

Introduction: The accuracy of positron emission tomography with computed tomography (PET/CT), positron emission mammography (PEM), and breast specific-gamma imaging (BSGI) in diagnosing breast cancer has never been systematically assessed, the present systematic review was aimed to address this issue.

Methods: PubMed, Scopus and EMBASE were searched for studies dealt with the detection of breast cancer by PET/CT, PEM or BSGI. Histopathologic examination and/or at least six months imaging follow-up were used as a golden reference. To calculate diagnostic test parameters: sensitivity, specificity, summary receiver operating characteristic curves (SROC) and to test for heterogeneity, true positive (TP), true negative (TN), false positive (FP) and false negative (FN) were extracted.

Results: Thirty one studies were included in the analysis. On per-patient basis, the pooled sensitivities after corrected for threshold effect for ¹⁸F-FDG PET/CT, PEM, and ^{99m}Tc-MIBI BSGI were 0.89 (95% CI: 0.78- 0.95), 0.73 (95% CI: 0.41 - 0.92), and 0.80 (95% CI: 0.72 - 0.86) respectively. The pooled specificities for detection of breast cancer using FDG PET/CT, PEM, and ^{99m}Tc-MIBI BSGI were 0.93 (95 % CI, 0.86 - 0.96), 0.91 (95 % CI, 0.77- 96), and 0.78 (95 % CI, 0.64 - 0.88), respectively. AUC of FDG PET/CT, PEM, and BSGI were 0.9549, 0.8852 and 0.8573, respectively.

Conclusion: This meta-analysis indicated that PET/CT showed better diagnostic accuracy than PEM, and BSGI on per-patient basis. On per-lesion analysis, PEM with the highest AUC, DOR and Q* was better than PET/CT, and BSGI for detecting breast cancer.

Key words: Breast cancer; PET/CT; Positron emission mammography; Breast specific-gamma imaging; Meta-analysis

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INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer death among females [1]. The early diagnosis of BC has a paramount importance to reduce the number of people with breast cancer. Thus, researchers have been engaged in the discovery of modern diagnostic tools that would progress to early diagnosis and decrease in breast cancer fatalities [2]. An accurate at the same time cost effective diagnostic approach remains of interest.

Conventional x-ray mammography (MMG) and ultrasound (US) have been playing great roll in the detection of breast cancer because of their easy availability, sensitivity, and affordability in most organizations. For the detection of breast cancer, physical examination and mammography were recommended to be used routinely while additional anatomical and molecular imaging methods were not recommended [3]. Nevertheless, physical examination and MMG have their drawbacks to detect lesions located at depth [4]. The sensitivity of MMG is inversely proportional to breast tissue density. Rosenberg et al. [5] found that the sensitivity in non-dense breasts to be 85%, and only 68% in dense breasts. Breast density is strongly associated with the risk of developing breast cancer [6]. Furthermore, young patients often have dense breasts, and in this patient group breast cancers tend to be aggressive. In that case, the trustworthiness of the diagnosis could be accompanied by the use of molecular imaging modalities such as breast specific-gamma imaging (BSGI), positron emission mammography (PEM), or whole-body Positron emission tomography with computed tomography (PET/CT), which provides pinpoint the abnormal metabolic activity within breast tissue.

Although extensive researches have been performed with regard to PET/CT, PEM, and BSGI for the detection of breast cancer, no comprehensive comparison has yet been conducted concerning all the non-invasive diagnostic tools. Thus, the target of this meta-analysis is to obtain the overall diagnostic performance of PET/CT, PEM, and BSGI for the detection of breast cancer on per-patient and a per-lesion basis, which, to our knowledge, had not previously been investigated.

METHODS

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7] was our baseline for review. According to the PICO approach [7] the 'PICOS' questions pertinent to this review were: patients (P): over the age of 18 years undergoing PEM, BSGI and PET/CT; intervention (I): diagnostic tests: PEM, BSGI and PET/CT; comparison (C): histopathologic

results or six months follow up; outcome (O): accuracy of imaging modalities to detect breast cancer.

Search strategy

The comprehensive computer literature search of the PubMed, Scopus, and EMBASE for studies about the diagnostic value of PEM, PET/CT, and BSGI for detecting BC was done. A core strategy was developed in PubMed and then translated for each database. The published year was limited between 2008 and 2018. The steps employed to select eligible studies for this systematic review and meta-analysis is depicted in Figure 1. The following key-words were used: ("Breast cancer" OR "breast neoplasm" OR "breast tumor" OR "breast carcinoma") AND ("positron emission tomography with computed tomography" OR "PET/CT" OR "positron emission mammography" OR "PEM" OR "breast-specific gamma imaging" OR "BSGI") AND ("sensitivity" OR "specificity" OR "false negative" OR "false positive" OR "diagnosis" OR "detection"). Besides, reference lists from all relevant articles were searched to identify additional studies. The search was performed in December 2018 to ensure inclusion of all recent publications in the analysis. Then the studies were exported to Endnote to maintain and manage citation and facilitate the review process. All citations were imported into a reference management system, and duplicates were removed.

Selection criteria

The inclusion criteria were as follows: (a) evaluating the diagnostic value of PEM or PET/CT or BSGI in detecting breast cancer; (b) Breast cancer has to be confirmed by histopathological analysis, or imaging follow-up for at least 6 months; (c) Absolute number of data were provided for patient-based analysis compared with standard to calculate the true positive, true negative, false negative and false positive results ; (d) the study should include ten or more patients; (e) Only woman breast diagnosis is included; (f) radiopharmaceuticals used in the study for PET/CT was ^{18}F -FDG and for BSGI was $^{99\text{m}}\text{Tc}$ -MIBI.

Exclusion criteria

The exclusion criteria of the studies were as follows: (a) case reports, letters, comments, animal experiments, review studies, and original studies with incomplete data; (b) repeatedly published literature or similar literature.

Selection of studies and data extraction

Two investigators (GFT and EMT) independently assessed and included the potentially eligible studies according to the inclusion and exclusion criteria mentioned above after reading the title and abstract.

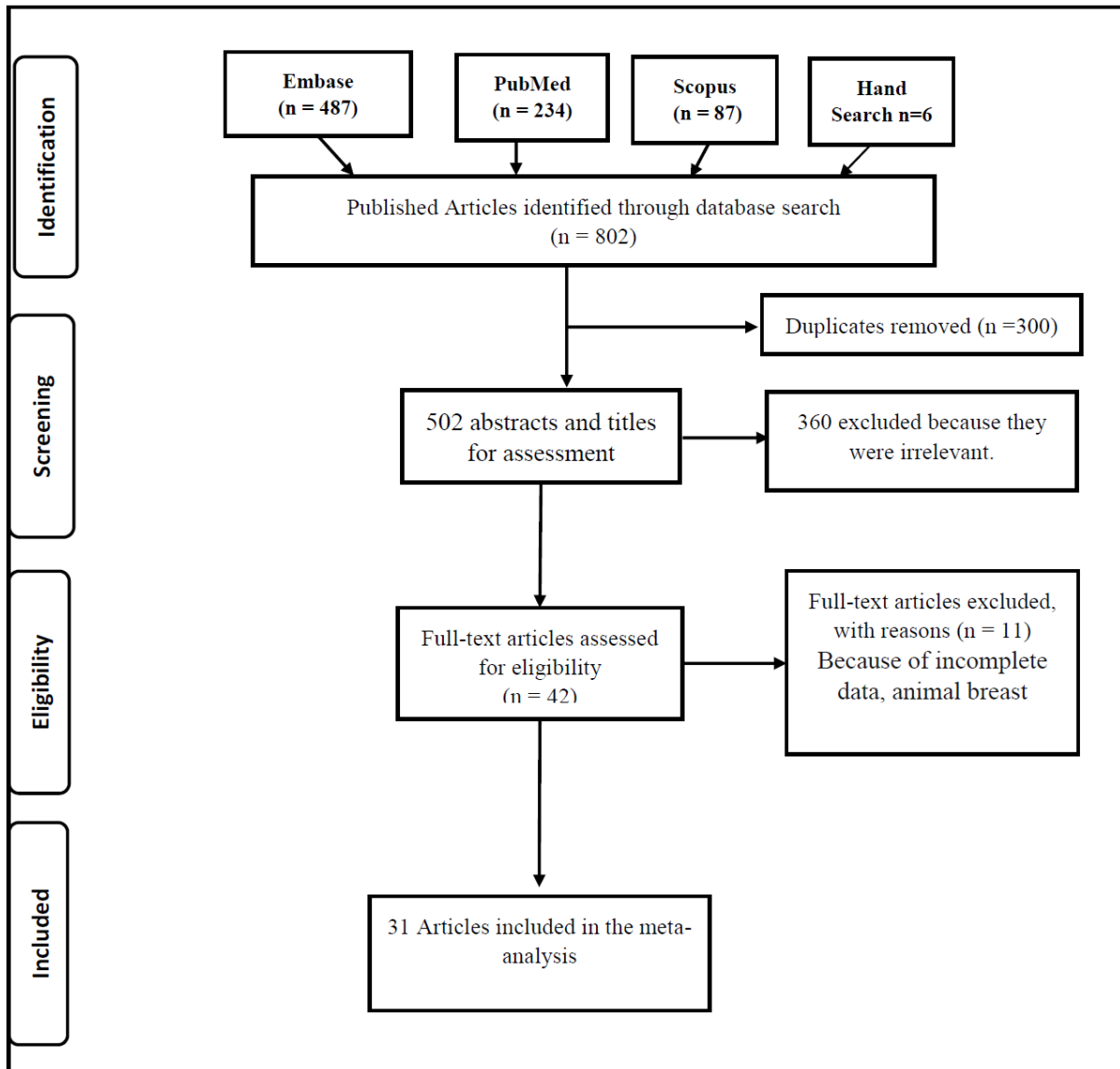


Fig 1. PRISMA flow diagram for the meta-analysis.

For the equivocal studies, we read the full text to make a decision. If there was still a disagreement, a third investigator evaluated the results and reached a consensus.

The same investigators independently extracted relevant data from the included studies based on a piloted form, with disagreement resolved through discussion and consultation.

The authors extracted the following data from each included data: (a) First author last name, publication year, country, study design, sample size, mean age of study participants, (b) unit of analysis (patients or lesions), (c) diagnostic value of PEM, PET/CT and BSGI in terms of true positive, true negative, false negative and false positive for detection of breast cancer.

Quality assessment of each study and statistical analysis

To assess the quality of each study, Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria were used. QUADAS criteria is a systematic, comprehensive quality assessment tool for diagnostic accuracy of a study [8]. There are 14 items in QUADAS criteria, and for each question, there are three answers: "yes," "no," and "unclear" with scores of 1 for "yes" and 0 for "unclear" or "no." When there was disagreement in the scoring of quality the third author acted as a referee.

Statistical analysis

A conventional random effects model was used to obtain a pooled sensitivity and specificity with 95%

confidence intervals (CI) of each non-invasive technique [9] and to account a variance between studies and within the study. Bivariate meta-analysis method also used to evaluate the effect of threshold using the correlation between sensitivity and specificity [10]. The sensitivity and specificity of each study were used to plot a summary receiver operating characteristic (SROC) curve [11, 12]. Q^* indexes (the point on the SROC curve where sensitivity and specificity are equal) were calculated. The higher the Q^* value, the better the diagnostic test performance [12]. We used chi-squared (χ^2) test to assess statistical heterogeneity of included studies at P -value < 0.1 . We also calculated the I-square (I^2) statistic to reflect the percentage of total variation across the studies [13]. We set the acceptability of heterogeneity at I-square 50%. Since data on PET/CT, PEM and BSGI imaging were limited, we did not perform subgroup analyses. The possibility of publication bias in the study was examined by visually inspecting off funnel plots and by using Egger's test [14]. Obtaining a P value of less than 0.05 indicates the existence of publication bias.

The DOR is one of the parameters used to measure the effectiveness of diagnostic test that associates sensitivity and specificity [15]. DOR is the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease and has a value that ranges from 0 to infinity, with higher values indicating higher accuracy. All statistical analyses were performed using Meta-Disc1.4, OpenMeta analyst current version and STATA version 13.

RESULTS

Literature search

After the first computer search, there were a total of 802 including six studies identified by hand search. After reading the title and abstract of each article, according to the inclusion and exclusion criteria, 760 studies were excluded including duplicates. Eleven of the remaining 42 studies didn't fulfill the inclusion criteria after the full texts were assessed. Reasons for the exclusion of the other eight studies were as follows: incomplete data sensitivity, specificity of the modality ($n=7$); molecular imaging using other radiopharmaceuticals such as ^{18}F -NaF PET/CT ($n=1$), case report ($n=1$) and animal breast ($n=1$). Finally, a total of 31 studies [16-46] were included, 13 studies for FDG PET/CT, ten studies for PEM and ten studies for BSGI (Figure 1). However, two studies have reported two imaging modalities.

Study characteristics

There were 19 retrospective studies and 12 prospective studies in all included studies. A total of 9 research were performed in Europe, 15 in Asia, 6 in the USA

and 1 in South America. In total, there were 5,166 patients in the included studies, with the publication year ranging from 2008 to the end year of 2018. The features of the included studies are presented in Table 1.

Publication bias

To assess possible publication bias, scatter plots were designed using the log diagnostic odds ratios (DORs) of individual studies against their sample size. The funnel plot of PET/CT, PEM and BSGI were given in Figures 2, 3 and 4, respectively. There was significant publication bias for PET/CT. However, there was no significant publication bias for PEM and BSGI.

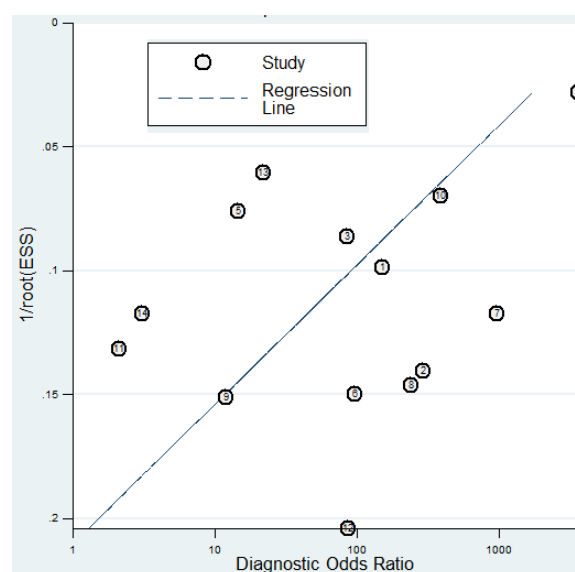


Fig 2. Funnel plot for PET/CT (p value=0.01).

Quality assessment

QUADAS criteria were used to assess the quality of articles [8] (Figures 5, 6 and 7). The results for the included studies were indicative of generally good quality. Only 2 of the QUADAS items (uninterpretable result or indeterminate results, and reporting of withdrawals) were met less than 40% of the studies. About 70% of the studies fulfilled 9 or more of the 14 items. Due to the results of question 1, 2, and 3, patients in selected studies were included following strict criteria, which minimized the spectrum bias. There was also low risk of bias in other aspects such as disease progression (item 4), partial verification bias (item 5), reference standard independence bias (item 7), test details (item 8), test review bias (item 10), diagnostic review bias (item 11), clinical data analysis (item 12), differential verification bias (item 6), reference standard details (item 9). If there were more than four answers "No" or "Unclear", articles were excluded.

Table 1: Main Characteristics of included studies.

Author	Year of publication	Country	Patients/lesions (n)	Mean age (range)	Imaging modalities	Study design
Yano, F	2018	Japan	100	57 ± 11.8(28-81)	FDG -PET/CT	Retrospective
Aukema, TS	2010	Netherlands	53	48 (27-74)	FDG -PET/CT	Retrospective
Champion, L	2011	France	228	NA	FDG -PET/CT	Retrospective
Jung, NY	2016	Korea	1161/1819	52 (22-88)	FDG-PET/CT	Retrospective
Kim, YH	2015	Korea	206	52.6 (30–84)	FDG-PET/CT	Retrospective
Koolen, BB	2014	Netherland	44	66.8 (60.1-74.8)	FDG-PET/CT	Prospective
Koolen, BB	2012	Netherland	154	49.1 ± 11.0	FDG-PET/CT	Prospective
Murakami, R	2012	Japan	47	50 (35–79)	FDG-PET/CT	Retrospective
Nakajo, M	2010	Japan	44	NA	FDG-PET/CT	Retrospective
Niikura, N	2011	Japan	225	53.4 (23–84)	FDG-PET/CT	Retrospective
Vassiou, K	2009	Greece	69/78	39-78	FDG-PET/CT	Prospectively
Magometschnigg, HF	2015	Austria	23	57 (18-87)	FDG-PET/CT	Prospective
Kalinyak, JE	2013	USA	178/109	59±12	FDG-PET/CT	Prospective
Schilling, K	2011	USA	64/67	59.7±14.1	PEM	Prospective
Müller, FHH	2015	Germany	108/166	NA	PEM	Prospective
Müller, FHH	2014	Germany	102/163	NA	PEM	Prospective
Berg, WA	2011	USA	388	58(26-93)	PEM	Prospective
Bitencourt, AG	2017	Brazil	40	56.4±11.3 (28-81)	PEM	Prospective
Berg, WA	2012	USA	367	58(26-93)	PEM	Retrospective
Dai, D	2017	China	253	50.1 ± 9.3	PEM	Prospective
Yamamoto, Y	2015	Japan	54/108	<50	PEM	Retrospective
Meissnitzer, T	2015	Austria	90/92	>50	BSGI	Prospective
Kim, BS	2011	Korea	66/97	44.1 ± 8.2	BSGI	Retrospective
Lee, HS	2014	Korea	122	45.9 ± 9.5	BSGI	Retrospective
Brem, RF	2016	USA	23/33	53 ± 10 (33-70)	BSGI	Retrospective
Cho, M.J	2016	Korea	162	NA	BSGI	Retrospective
Kim, S	2018	USA	114	52.4 ± 10.2	BSGI	Retrospective
Lee, A	2012	Korea	107/474	49.6 ± 10.4	BSGI	Retrospective
Park, JS	2013	Korea	76	49.3 (33–61)	BSGI	Retrospective
Park, KS	2014	Korea	114/118	49.6 ±9.8	BSGI	Retrospective
Yu, X	2016	China	287	48.2(32-75)	BSGI	Retrospective

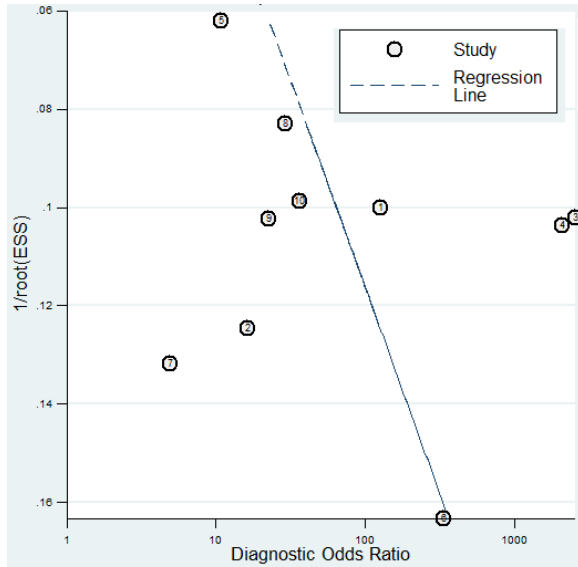


Fig 3. Funnel plot for PEM (p value=0.34).

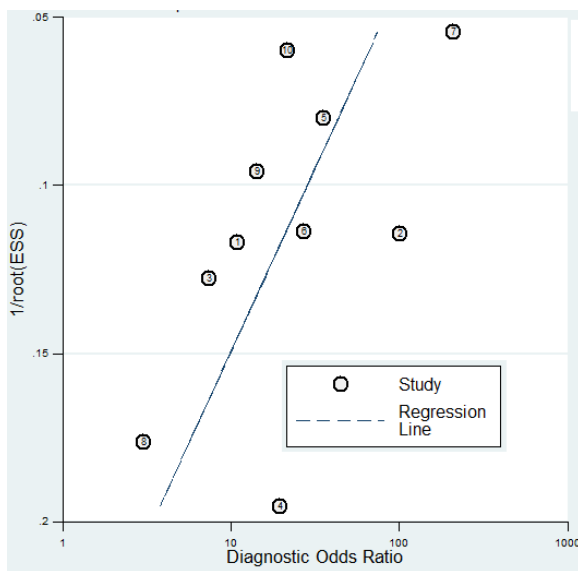


Fig 4. Funnel plot for BSGI (p value=0.07).

In this way, we excluded low-quality articles to make sure the results of this research were credible.

Study heterogeneity assessment

The heterogeneity test indicated statistical heterogeneity for imaging modalities among studies, so we chose a random-effects model to calculate the pooled estimates. The statistical heterogeneity per-patient of PET/CT, PEM, and BSGI are displayed in Table 2 (sensitivity, I² value=86.7%, 96.3%, and 61.1% respectively; specificity, I² value=73.3%, 92%, and 68.8% respectively). Therefore, sensitivity and specificity per-patient of PET/CT, PEM, and BSGI

were heterogeneous. The reason is that maybe there was no accepted gold standard, which may be a universal drawback to all modalities included in this study for detecting breast cancer.

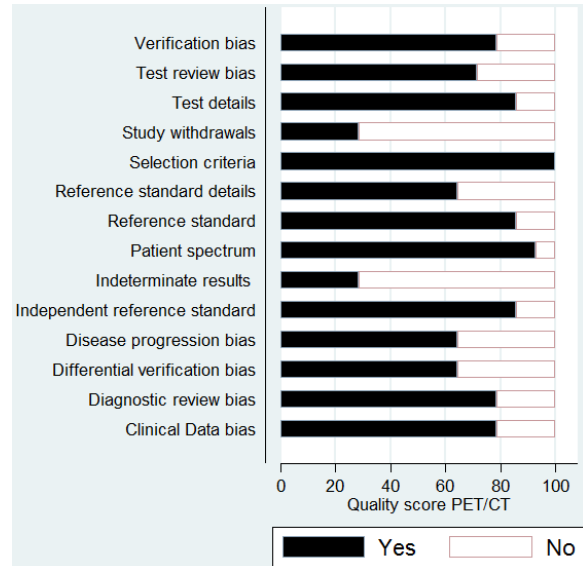


Fig 5. Methodological quality of included studies for PET/CT, according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

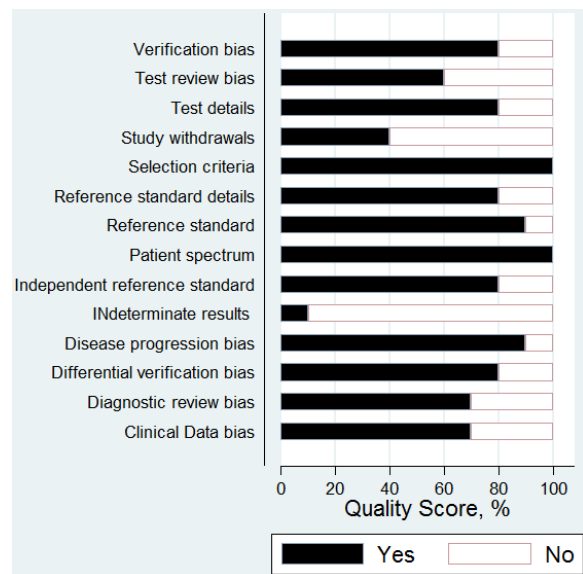


Fig 6. Methodological quality of included studies for PEM according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

Summary of the diagnostic performance

The pooled sensitivity, pooled specificity, pooled DOR, AUC, and Q* of those modalities by per-patient and per-lesion are presented in the Table 3.



Fig 7. Methodological quality of included studies for BSGI according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.

For the per-patient, the pooled sensitivities of PET/CT, PEM, and BSGI were 0.87 (95% CI: 0.85 - 0.90), 0.80 (95% CI: 0.75 - 0.84), and 0.78 (95% CI: 0.74 - 0.81) respectively. The pooled specificities for FDG PET/CT, PEM, and BSGI were 0.90 (95% CI: 0.85 - 0.90), 0.92 (95% CI: 0.90 - 0.94), and 0.79 (95% CI: 0.74 - 0.83) respectively. The pooled DOR estimates for FDG PET/CT, PEM, and BSGI were 93.58, 23.84, and 13.55 respectively.

Table 2: Assessment of heterogeneity and threshold effect of included articles.

		Chi ²	df	p value	I ² index (%)
Per-patient Sensitivity	PET/CT	67.7	9	0.000	86.7
	PEM	106.73	4	0.000	96.3
	BSGI	12.85	5	0.025	61.1
Per-patient Specificity	PET/CT	33.69	9	0.00	73.3
	PEM	49.72	4	0.000	92
	BSGI	16.04	7	0.007	68.8
Per-lesion Sensitivity	PET/CT	124.28	2	0.000	98.4
	PEM	23.71	4	0.000	83.1
	BSGI	11.24	4	0.024	64.4
Per-lesion Specificity	PET/CT	68.08	2	0.000	97.1
	PEM	24.79	4	0.000	83.9
	BSGI	28.57	4	0.000	86

Chi²: Chi-square, df: Degree of freedom, I²: I-square (inconsistency).

The SROC curves, AUC, and Q* index are shown in Figure 8. The AUC for FDG-PET/CT, PEM, and BSGI were 0.96, 0.88, and 0.85, and Q* values were 0.91, 0.82, and 0.78, respectively.

On a per-lesion basis, the pooled sensitivities of PET/CT, PEM, and BSGI 0.91 (95% CI: 0.88 - 0.93), 0.85 (95% CI: 0.79 - 0.90), and 0.90 (95% CI: 0.85 - 0.93) respectively. The pooled specificities were 0.98 (95% CI: 0.97 - 0.99) for PET/CT, 0.94 (95% CI: 0.92 - 0.96) for PEM, and 0.88 (95% CI: 0.85 - 0.90) for BSGI. The pooled DOR estimates for PET/CT, PEM, and BSGI were 29.31, 79.76, and 37.25 respectively. The AUC for PET/CT, PEM, and BSGI were 0.92, 0.97, 0.93, and Q* values were 0.86, 0.92, and 0.87 respectively. All corresponding results were shown in Table 3.

The bivariate meta-analysis also confirmed that a pooled sensitivity and specificity were higher for the per-patient of PET/CT 0.89 (95% CI: 0.78 - 0.95) and 0.93 (95% CI: 0.86 - 0.96) with a correlation of -0.25 respectively after correcting for threshold effect compared with PEM and BSGI. However, on per-lesion basis the sensitivity 0.93 (95% CI: 0.68 - 0.98) and specificity 0.94 (95% CI: 0.85 - 0.97) were higher for PEM with correlation of 0.8962 compared to BSGI. Pooled sensitivity and specificity for PET/CT per-lesion basis was not demonstrated due to a small number of studies (less than five). All corresponding results are shown in Table 3.

DISCUSSION

In this meta-analysis, we found that PET/CT was more accurate than PEM and BSGI for detecting breast cancer. The sensitivity and specificity of PET/CT on per-patient basis were 89 and 93 %, respectively. The AUC estimates for PET/CT (0.96) on per-patient basis were also higher than that of BSGI (0.85), and PEM (0.88). The pooled DOR values for PET-CT for per-patient basis was 93.58, indicating that PET-CT had a higher level of accuracy.

In this study, in addition to conventional random-effect, a bivariate random-effects model was used to consider the relation between sensitivity and specificity observed across studies. Because not all studies use the same cut-off value for a positive result, the threshold effect is the most significant source of heterogeneity in meta-analysis of diagnostic studies. This can be due to an explicit cut-off point value or explicit human or instrumental factors. To measure the threshold effect in diagnostic studies and to be a single measure diagnostic accuracy of the imaging modalities, SROC method and reporting Q^* have been used commonly, but it cannot distinguish between the ability to detect the diseased (sensitivity) and identifying the healthy case (specificity) [12]. Discerning between these abilities is of utmost importance to determine the optimal use of a test in clinical practice.

The bivariate model we used has the distinct advantage of preserving the two-dimensional nature of the underlying data. It can also produce summary estimates of sensitivity and specificity, acknowledging any possible correlation between these two measures and the best way to report the possible effect of threshold [12]. In this study, we found that the threshold effect was prominent over the PEM studies with correlation -0.7272 for per-patient basis and 0.8962 for per-lesion basis.

For the reduction of patient morbidity and mortality, the early diagnosis of breast cancer has important value. PET/CT, PEM and BSGI are widely used for detecting breast cancer while they are rapid technological developments to faster and accurate diagnosis in molecular imaging [47]. PET/CT provides both the anatomical details of CT and the metabolic and quantitative capabilities of PET, which bonds the gap between molecular imaging and systematic diagnosis. Plentiful studies have been conducted to evaluate PET/CT to test its potential role in breast cancer detection, staging, therapy assessment, and follow-up. The sensitivity and specificity of PET-CT were 93 and 99% according to meta-analysis done on bone metastases in breast cancer patients, respectively [48]. This finding is consistent with our findings of pooled sensitivity and specificity of 91 and 98% for a per-lesion basis.

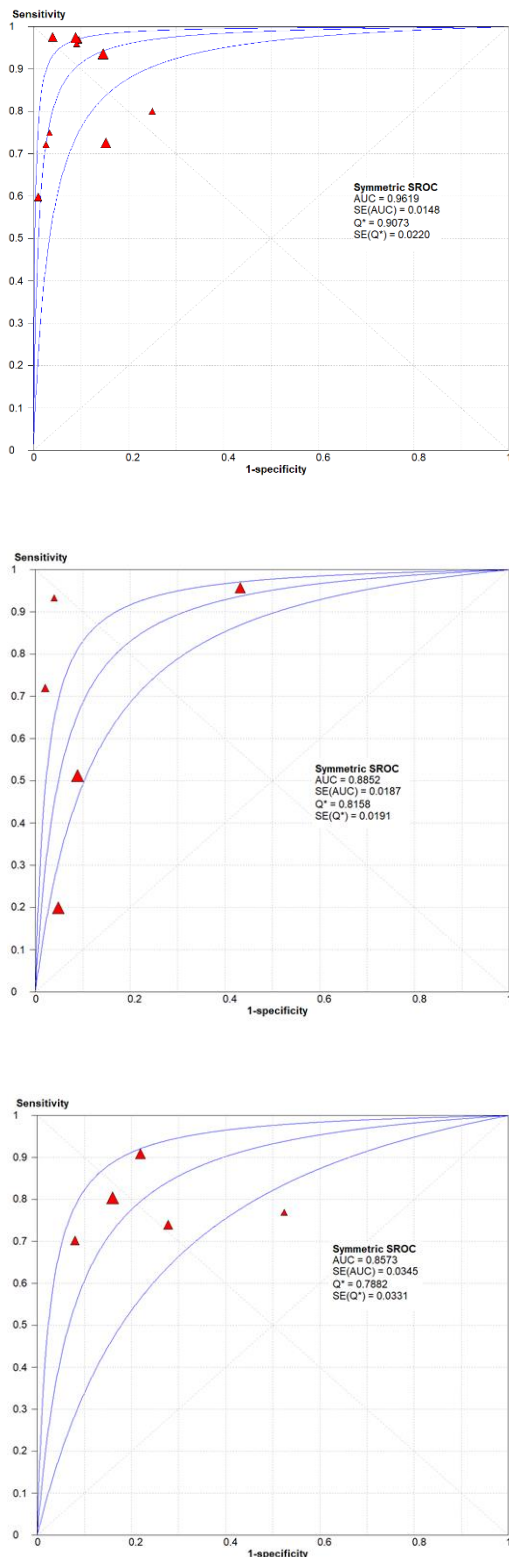


Fig 8. The SROC curves for PET/CT (above), PEM (middle), and BSGI (below) on a per-patient basis. Each solid triangle represents each study in the meta-analysis. The size of the triangle indicates the study size. The AUC and Q^* for PET/CT, PEM, and BSGI were 0.9549, 0.8852, 0.8573 and 0.8972, 0.8158, 0.7882, respectively. PET/CT showed better diagnostic accuracy than others.

Table 3: Diagnostic performance for PET/CT, PEM and BSGI on per-patient and per-lesion basis.

Modality and group	Study numbers	Convectional meta-analysis summery					Bivariate meta-analysis summery		
		Sensitivity (95 % CI)	Specificity (95 % CI)	DOR(95%CI)	AUC	Q*	Sensitivity (95 % CI)	Specificity (95 % CI)	Correlation
		Per-patient					Per-patient		
PET/CT	11	0.87 (0.85 - 0.90)	0.90 (0.85 - 0.90)	93.58 (32.81 - 266.96)	0.9619	0.9073	0.89 (0.78 - 0.95)	0.93 (0.86 - 0.96)	-0.2506
PEM	5	0.80 (0.75 - 0.84)	0.92 (0.90 - 0.94)	23.84 (8.07 - 70.42)	0.8852	0.8158	0.73 (0.41 - 0.92)	0.91 (0.77 - 0.96)	-0.7272
BSGI	5	0.78 (0.74 - 0.81)	0.79 (0.74 - 0.83)	13.55 (6.85 - 26.82)	0.8573	0.7882	0.80 (0.72 - 0.86)	0.78 (0.64 - 0.88)	-0.3804
		Per-lesion					Per-lesion		
PET/CT	3	0.91 (0.88 - 0.93)	0.98 (0.97 - 0.99)	29.31 (0.132 - 6495.9)	0.9269	0.8614			
PEM	5	0.85 (0.79 - 0.90)	0.94 (0.92 - 0.96)	79.76 (18.11 - 351.26)	0.9725	0.9240	0.93 (0.68 - 0.98)	0.94 (0.85 - 0.97)	0.8962
BSGI	5	0.90 (0.85 - 0.93)	0.88 (0.85 - 0.90)	37.25 (9.79 - 141.58)	0.9366	0.8732	0.89 (0.81 - 0.94)	0.83 (0.70 - 0.91)	0.4201

Tatsumi et al. [49] compared the performance of PET and PET/CT with the 75 suspected breast cancer patients. PET/CT showed better diagnostic accuracy compared with PET in 60% of patients and in 55% of regions. In a previous study Xiao et al. [50] have presented the diagnostic efficacy of ^{18}F -FDG-PET/CT in breast cancer with suspected recurrence and reported the sensitivity, specificity, and AUC of 90%, 81% and 0.9358, respectively. This result is in line with our finding of sensitivity and AUC of 91% and 0.9269 respectively for PET/CT per-lesion basis. Moreover, several studies showed that FDG-PET/CT had dynamic importance on the management of 51–69% of patients [51, 52].

PEM has a higher spatial resolution than whole-body PET/CT and more accurate detection of breast lesions, particularly in women with dense breast and small lesions. The previous meta-analysis has demonstrated that PEM using FDG is an accurate technique in the detection of primary breast malignancies in women with suspicious lesions and reported that pooled sensitivity and specificity of 85% (95% CI: 83%-88%) and 79% (95% CI: 74%-83%), respectively. The same meta-analysis reported that the AUC value of PEM is 0.88 [53]. This result is close to our findings of pooled sensitivity 80%, and AUC 0.88 for per-patient basis.

In the routine clinical trials, the sensitivity of PEM reported 80-86% in detecting primary breast cancer in patients with palpable or impalpable highly suspicious mammographic lesions [54, 55]. This meta-analysis has also confirmed this finding comparable to the sensitivity of 80% for per-patient basis and 85% for a per-lesion basis found in our study. Tafra et al. [56] conducted a subsequent study in patients with biopsy-confirmed breast cancer with median size of 22 mm reported 89 % sensitivity of PEM in the detection of malignancy, and additionally the PEM scan also showed mammographically occult, ductal carcinoma in situ (DCIS) lesion measuring 2–3 mm in width [56].

Sensitivity and specificity of PEM were compared with PET and Magnetic resonance imaging (MRI) [39]. Their result showed that PEM had higher sensitivity than PET and higher specificity than MRI. Another finding also indicated that PEM had a higher sensitivity than PET/CT mostly for the detection of small tumors [57]. Our study also revealed that the diagnostic performance of PEM was better for per-lesion than per-patient. Moreover, Berg et al. [58] found that integrating PEM and MRI findings significantly improves the detection of additional lesions and of eventual extensive intraductal involvement.

In recent years, BSGI with intravenous injection of technetium-99m-methoxy isobutyl isonitrile (MIBI) is increasingly used for diagnosis of breast cancer in clinical practice while its sensitivity is not influenced by breast density [59]. It is a breast imaging technique

that uses a high resolution, small field-of-view breast-specific gamma camera [28]. BSGI offers a higher intrinsic spatial resolution than single photon emission tomography (SPET), and it can obtain standard mammographic views (craniocaudal [CC] and mediolateral oblique [MLO]) [60].

A recent meta-analysis conducted on the comparison of BSGI with the MRI in the breast cancer patients revealed that BSGI has a better diagnostic performance with sensitivity of 0.84 (95% CI: 0.79-0.88) vs. 0.89 (95% CI: 0.84-0.92) and specificity 0.82 (95% CI, 0.74-0.88) vs. 0.39 (95% CI, 0.30-0.49), respectively [61]. Our result of meta-analysis is comparable with this study in which we found the sensitivity and specificity of BSGI for per-lesion basis (Table 3). Moreover, our result revealed BSGI offers better diagnostic performance with a per-lesion basis than a per-patient basis.

Tumor diameter is an independent predictive indicator. The wider the diameter of breast cancer, the lower the survival rate [62]. So it is important to find an effective examination technique for detecting small cancer to achieve early detection and early treatment. Sun et al. [63] have revealed that BSGI showed a sensitivity for detecting small breast cancer of 84 %, and the smallest carcinoma identified by BSGI was 1 mm.

BSGI has also shown a particular advantage for detecting invasive lobular carcinoma with higher sensitivity of 93% than mammography 34-81% [59, 64-66]. BSGI was also used to evaluate the therapy response. For the study conducted on the 15 patients with locally advanced breast cancer treated by neoadjuvant chemotherapy or hormone therapy, BSGI had shown the capability to correctly categorize all patients [67]. Moreover, BSGI has also is of great importance to reduce the rate of unnecessary biopsies [68]. In spite of the advantages of BSGI described above, it also has the drawbacks of the increasing dose to the patient compared with screening mammography [69]. Researchers from various institutions are developing numerous method to overcome this limitation [70, 71].

Our study had some limitations. Firstly, the impact of characteristics of the patients could not be tested due to lack of data. Secondly, the same reference standard was not used for all studies. Thirdly, heterogeneity was high among the studies signifying the requirement of high-quality prospective studies and numerous center trials. Unfortunately, with only limited information available, it is difficult for us to find the exact source of heterogeneity Fourthly, significant publication bias for PET/CT. Fifthly, since BSGI and PEM are new imaging modalities for diagnosis of breast cancer, their accuracy can be affected by different factors such as the protocol details, camera specifications, the injected radiation dose, breast

position, and finally the skill of radiologist which might have been the reasons for the heterogeneity observed in our study.

CONCLUSION

In this meta-analysis, PET/CT was found to have better accuracy than PEM and BSGI on per-patient basis in both conventional random effect and bivariate meta-analysis. However, PEM has better diagnostic accuracy than PET/CT and BSGI for detecting breast cancer particularly for small lesions on per-lesion analysis according to the value of DOR, AUC and Q*. A follow-up study with enough information and adequate sample size should be conducted in the future.

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