Is Technetium-99m Sestamibi Imaging Able to Predict Pathologic Nonresponse to Neoadjuvant Chemotherapy in Breast Cancer? A Meta-analysis Evaluating Current Use and Shortcomings

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Abstract

In breast cancer, interest in technetium-99m (^{99m}Tc) sestamibi-based therapy monitoring is increasing owing to the growing use of ^{99m}Tc-sestamibi-based molecular breast imaging. In the present meta-analysis of 529 patients, ^{99m}Tc-sestamibi planar imaging showed low sensitivity for predicting a pathologic nonresponse to neoadjuvant chemotherapy. In contrast, ^{99m}Tc-sestamibi imaging performed during treatment seemed highly sensitive for the prediction of nonresponse. New tools incorporating quantitative single photon emission computed tomography/computed tomography need to be explored.

Background: Interest in technetium-99m (^{99m}Tc)-sestamibi imaging for neoadjuvant chemotherapy (NAC) response monitoring in locally advanced breast cancer (LABC) is increasing but remains matter of discussion. The present study conducted a meta-analysis of the diagnostic performance of ^{99m}Tc-sestamibi to predict pathologic nonresponse to NAC for primary LABC. **Materials and Methods:** A systematic data search was performed. Studies with a minimum of 10 LABC patients that had evaluated ^{99m}Tc-sestamibi imaging for NAC nonresponse using conventional planar scintimammography, breast-specific γ-imaging, and/or single photon emission computed tomography/computed tomography (SPECT/CT) were included. The histopathologic findings were the reference standard. The meta-analysis was performed using a mixed logistic regression model. **Results:** The search revealed 14 eligible studies with 529 patients. Of the 14 studies, 11 had evaluated scintimammography and 3 breast-specific γ-imaging. No studies examining SPECT or SPECT/CT were found. The overall estimated pooled sensitivity, specificity, and positive and negative likelihood ratios of ^{99m}Tc-sestamibi imaging to predict nonresponsiveness to NAC were 70.3% (95% confidence interval [CI], 56.5%-81.3%%), 90.1% (95% CI, 77.5%-96.0%), 7.13 (95% CI, 3.08-16.53), and 0.33 (95% CI, 0.22-0.49), respectively. Only 3 studies (107 patients) evaluated ^{99m}Tc-sestamibi imaging during NAC, reported an estimated pooled sensitivity of 87% (95% CI, 72%-100%) and specificity of 93% (95% CI, 85%-100%). **Conclusion:** Only planar ^{99m}Tc-sestamibi imaging has been investigated for NAC nonresponse in LABC but showed low sensitivity to predict pathologic nonresponse. However, most studies focused on the prediction of pathologic complete response after NAC. Although experience is limited, ^{99m}Tc-sestamibi uptake during NAC seems highly sensitivity for the prediction of nonresponsiveness. Features such as SPECT/CT imaging, standardized quantification, relation to tumor subtypes, and proper timing have been insufficiently evaluated and require further investigation.

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Introduction

Breast cancer (BC) is the most frequent malignancy in women worldwide. In the Unites States, 246,660 new cases and 40,450 deaths were estimated to have occurred in 2016.[1] Locally advanced BC (LABC) encompasses stage IIb-III invasive BC and presents with ≥ 1 of the following features: a primary tumor > 5 cm (T3), a tumor of any size with direct skin- or chest wall invasion (T4), lymph node metastases (N2-N3), or inflammatory BC.[2] Neoadjuvant chemotherapy (NAC), also known as preoperative chemotherapy, is the first-line treatment for LABC. NAC enables breast-conserving surgery by reducing the tumor size. It also eradicates micrometastatic disease and allows for assessment of tumor chemosensitivity in vivo.[3,4] Tumor resistance to chemotherapy is the major cause of therapy failure in LABC. The early prediction of the response to NAC might allow for a timely switch to alternative drugs in those without a response, avoiding ineffective chemotherapy, and offering more personalized therapy. In recent years, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) with or without computed tomography (CT) has been evaluated for the early prediction of the NAC response after the first or second cycle of therapy, showing a pooled sensitivity of 88% (95% confidence interval [CI], 80%-94%) and specificity of 70% (95% CI, 63%-77%).[5] Therefore, the role of early ^{18}F-FDG PET/CT to monitor the metabolic response remains unclear, most probably owing to the low number of included studies (7 studies).[5] Moreover, ^{18}F-FDG uptake is strongly influenced by the breast tumor subtype (eg, estrogen receptor-negative tumors, triple-negative tumors, and tumors with high expression of proliferation marker Ki-67 have high tumor ^{18}F-FDG uptake).[6] To date, technetium-99m (^{99m}Tc)-methoxyisobutylisonitrile (^{99m}Tc-sestamibi) is the most widely used non-PET radiotracer in oncology. Although originally introduced as a perfusion agent for nuclear cardiology studies,[7] it has been applied as a tumor-seeking agent since 1994 for breast malignancies.[8,9] ^{99m}Tc-sestamibi accumulates principally within the mitochondria, and its diagnostic value is based on the increased vascularity and greater cytoplasmic mitochondrial density in breast cancer cells.[10,11] However, cellular accumulation of ^{99m}Tc-sestamibi is reduced in cases of overexpression of multidrug resistance-associated plasma membrane proteins such as P-glycoprotein (Pgp) and multidrug resistance-associated protein, and the anti-apoptotic Bcl-2 protein on the outer mitochondrial membrane.[12] ^{99m}Tc-sestamibi was originally validated as a transport substrate for Pgp,[13] which is encoded by the multidrug resistance (MDR) gene and functions as an energy-dependent efflux pump for many drugs.[14,15] At present, ^{99m}Tc-sestamibi allows for in vivo assessment of tumor chemoresistance and could potentially identify nonresponding patients early during NAC. For breast functional imaging using ^{99m}Tc-sestamibi, several modalities, such as scintimammography (SMG), breast-specific γ-imaging (BSGI), and single photon emission computed tomography (SPECT)/computed tomography (CT) have been validated. However, only a few of the studies reported on LABC and the chemotherapy response. Therefore, the aim of the present meta-analysis was to evaluate the diagnostic value of ^{99m}Tc-sestamibi imaging to predict pathologic nonresponse to NAC in primary LABC and to establish which modalities were involved.

Materials and Methods

Search Strategy

We performed a systematic data search of the PubMed/MEDLINE and Embase databases using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[16] The following keywords were used: "sestamibi" AND "breast cancer" AND "neoadjuvant chemotherapy." Multiple synonyms were included, such as "MIBI," "mamma," and "preoperative" (Supplemental Appendix A; available in the online version). No start date limit was applied, and the search was continued until September 5, 2016. The language was restricted to English. The references of the retrieved reports were screened to identify additional studies.

Study Selection

Two of us (A.C., L.M.P.A.-B.) independently screened the title and abstracts of the retrieved studies. Original articles investigating the value of ^{99m}Tc-sestamibi imaging to predict a pathologic nonresponse to NAC in primary LABC patients were eligible for inclusion. Review articles, letters to the editor, editorials, and case reports were excluded. Also excluded were articles that had included < 10 patients, had overlapping patient data, or that had been written in a language other than English. Two of us (A.C., L.M.P.A.-B.) then independently reviewed the full-text version of the remaining reports to confirm their eligibility for inclusion.

Quality Assessment

Subsequently, 2 of us (A.C., E.J.d.K.) independently evaluated the methodologic quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies tool, version 2 (QUADAS-2).[17] The QUADAS-2 tool grades the risk of bias and applicability on 4 key domains (ie, patient selection, index test, reference standard, and flow and timing), supported by a limited number of signaling questions. The results of the quality appraisals from both authors were compared, and any disagreements were resolved by consensus after re-evaluation and discussion of the respective references. The QUADAS-2 scores for all included studies were tabulated, and a summary report was constructed.

Data Extraction

For each approved study, information was extracted concerning the study data (authors, year of publication, country of origin), study design (prospective or retrospective), number of evaluated patients with LABC, and method (type of imaging, time of acquisition, type of analysis, definition of response on ^{99m}Tc-sestamibi imaging, and method of pathologic assessment). Individual study data were extracted to retrieve the number of true-positive (TP), true-negative (TN), false-positive, and false-negative ^{99m}Tc-sestamibi scans. The TP scan results were defined as showing no response to NAC on ^{99m}Tc-sestamibi imaging with confirmed tumor presence at pathologic examination. The TN scan results were those showing a response to NAC on ^{99m}Tc-sestamibi imaging with subsequent confirmed significant tumor reduction or complete tumor absence at pathologic examination. The extracted data were ordered into 2 × 2 contingency tables, from which

estimations for the pooled diagnostic performance parameters could be calculated using the classic equations.

Statistical Analysis

Statistical analyses were performed using Stata/MP, version 14.2 (StataCorp LP, College Station, TX).[18] The pooled sensitivity, specificity, and positive and negative likelihood ratios (LRs) and their corresponding 95% CIs were estimated using the metandi and midas commands in Stata/MP.[19,20] The metandi command applies a 2-level mixed logistic regression model with independent binomial distributions for the TP and TN results dependent on the sensitivity and specificity in each study, and a bivariate normal model for the logit transforms of between study sensitivity and specificity.[20] The user-written midas command uses a bivariate mixed-effects binary regression model to estimate pooled test performance parameters.[19] Pooled results are presented in forest plots and summary receiver operating characteristic (ROC) plots, including the area under the summary ROC curve (AUC).

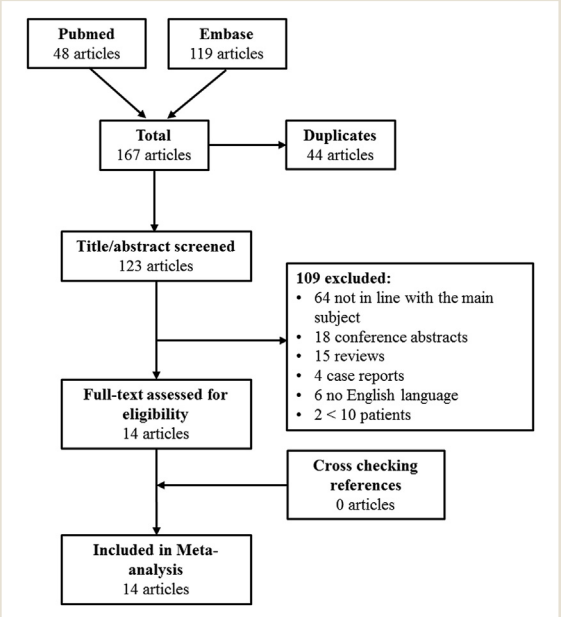
Heterogeneity between studies was assessed by visual inspection of the forest plots and estimated using the inconsistency index I^2. Because sensitivity and specificity are often inversely related, the threshold effect was assessed. The metandi and midas commands can only be applied to data from a minimum of 4 studies. For meta-analysis of fewer studies, we used the Stata/MP metaprop command and random effects modeling to estimate the pooled sensitivity, specificity, and positive and negative LRs.

Results

Data Search and Study Selection

The systematic study selection is shown in a flowchart in Figure 1. The initial data search identified 167 citations, including 48 citations from PubMed/MEDLINE and 119 from Embase. Forty-four duplicate studies were excluded. Screening of titles and abstracts excluded 109 articles according to the inclusion and exclusion criteria previously described. Specifically, the excluded articles were 64 off-topic studies, 18 conference abstracts, 15 review articles, 4 case reports, 6 articles written in a language other than English, and 2 studies with < 10 patients. The full text of the 14 remaining articles was retrieved. These articles had no data overlap. No additional studies were found by screening the references of the selected articles. Finally, the 14 eligible articles (529 patients) were included in the present meta-analysis (Figure 1).[21-34]

Figure 1 Flow Chart Showing Search Strategy



Quality Appraisal

The results of the QUADAS-2 assessment are shown in Figure 2. The risk of bias was mostly scored as low. However, the risk of bias for the domain "patient selection" often remained unclear owing to absent reports on patient inclusion criteria and consecutiveness of inclusion. No real concerns on the applicability of the studies for this meta-analysis were present. All the studies were deemed of sufficient methodologic quality, and no articles were excluded from further analysis.

Study Characteristics

The results for 529 patients from 14 studies were included in the present meta-analysis. The characteristics of the selected studies are outlined in Table 1. Most of the included reports concerned prospective trials. The sample size of the included studies varied from 17 to 122 patients, SMG was used as the imaging modality in 11 studies[21-27,31-34] and BSGI in 3 studies.[28-30] No studies using SPECT or SPECT/CT were found. Only 3 studies evaluated the role of ^{99m}Tc-sestamibi to predict nonresponsiveness during NAC.[23,29,34]

Figure 2 Summary of Methodologic Quality Scored According to Quality Assessment of Diagnostic Accuracy Studies Tool, Version 2 (QUADAS-2)

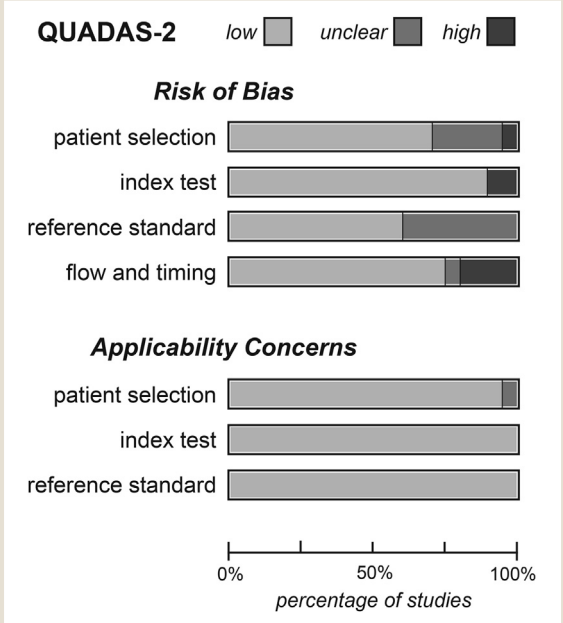


Table 1 Characteristics of Included Studies

Investigator	Year	Country	Study Type	Patients (Lesions)	Imaging in Relation to NAC	Imaging Modality	Acquisition Point and Analysis Type	Definition of Response on MIBI Imaging	Response Definition	Pathologic Criteria for Response	Pathologic Criteria for Nonresponse
Maini et al[21]	1997	Italy	NA	29	After	SMG	Early (10 min); delayed (90 min); visual analysis	No uptake	pCR	Fibrosis or isolated tumor cells	Invasive carcinoma >25%
Ciarmiello et al[22]	1998	Italy	Prospective	39	Before	SMG	Dynamic planar, 5 min, 1 h, 2 h, 4 h; T(1/2) (cutoff, 204 min)	T(1/2) >204 min	pCR	No tumor cells or scattered tumor cells	Macroscopic residual tumor
Mankoff et al[23]	1999	USA	NA	29	During	SMG	Early (10 min); visual analysis	Decreased uptake	pR	Tumor size reduced >50% or complete eradication	Tumor size reduced <50% or increased
Cayre et al[24]	2002	France	Prospective	45	Before	SMG	Early (10 min); visual analysis	Medium or high uptake	pCR	Sataloff criteria	Sataloff criteria
Sciuto et al[25]	2002	Italy	Prospective	30	Before	SMG	Early (10 min); delayed (4 h); WOR (cutoff, 45%)	WOR, ≤45%	pR	Tumor size reduced >75%	Tumor size reduced <75% or increased
Mezi et al[26]	2003	Italy	Prospective	24	After	SMG	Early (10 min); delayed (4 h); WOR (cutoff, 56%)	WOR, ≤56%	pCR	No tumor cells found	Tumor cells found
Marshall et al[27]	2005	UK	Prospective	26	After	SMG	Early (10 min); T/B ratio	T/B ratio, 10	pCR	NA	NA
Wahner-Roedler et al[28]	2012	USA	Prospective	17[a] (18)	After	BSGI	Early (5 min); T/B ratio	T/B ratio, ≤1.0	pCR	Complete eradication	No complete eradication
Mitchell et al[29]	2013	USA	Prospective	19	During	BSGI	Early (5 min); T/B ratio	T/B ratio reduction, ≥50%	pCR	No invasive disease and DCIS	Invasive disease and DCIS
Lee et al[30]	2014	Korea	Retrospective	122	After	BSGI	Early (10 min); visual analysis	No uptake	pCR	No invasive disease and DCIS	Invasive disease and DCIS
Trehan et al[31]	2014	India	Prospective	20	Before	SMG	Early (10 min); delayed (2 h); WOR (cutoff, 45%)	WOR ≤45%	pR	Tumor size reduced >50% or complete eradication	Tumor size reduced <50% or increased
Evangelista et al[32]	2014	Italy	Prospective	18	After	SMG	Early (5 min); delayed (3 h); WOR (cutoff, 45%)	WOR ≤45%	pCR	NA	NA
Evangelista et al[33]	2014	Italy	NA	51	Before	SMG	Early (5 min); delayed (3 h); WOR (cutoff, 45%)	WOR ≤45%	pCR	Sataloff criteria	Sataloff criteria
Novikov et al[34]	2015	Russia	Prospective	59	During	SMG	Early (10 min) T/B ratio	T/B ratio reduction >70%	pCR	No tumor cells found	Tumor cells found

Abbreviations: BSGI = breast- specific gamma imaging; DCIS = ductal carcinoma in situ; MIBI = technetium-99m sestamibi; NA = not available; pCR = pathologic complete response; pR = pathologic response; SMG = scintimammography; T(1/2) = time to half clearance; T/B = tumor-to-background; WOR = washout rate.

[a]One of 17 patients underwent neoadjuvant hormonal therapy.

Meta-analysis Results

The results of the meta-analysis are outlined in Table 2, and forest plots of the accuracy parameters of the 14 included studies are presented in Figure 3. The estimated pooled sensitivity, specificity, positive LR, and negative LR of ^{99m}Tc-sestamibi imaging to predict a nonresponse to NAC (presence of residual tumor) was 70.3% (95% CI, 56.5%-81.3%), 90.1% (95% CI, 77.5%-96.0%), 7.13 (95% CI, 3.08-16.53), and 0.33 (95% CI, 0.22-0.49), respectively. The ROC curve showed an AUC of 0.88 (95% CI, 0.85-0.91; Figure 4). Significant heterogeneity was found among the studies. The I^2 was 79.1% for sensitivity and 79.6% for specificity. The proportion of heterogeneity that was likely due to by the threshold effect was 0.30.

Of the 14 studies, 11 used a strict criterion for the TN definition based on a pathologic complete response (pCR; complete tumor absence). This resulted in an estimated pooled sensitivity, specificity, positive LR, and negative LR of ^{99m}Tc-sestamibi imaging to predict a nonresponse to NAC (presence of microscopic residual tumor) was 69% (95% CI, 54%-80.3%), 91% (95% CI, 72%-97.3%), 7.41 (95% CI, 2.3-24), and 0.35 (95% CI, 0.23-0.52), respectively. The ROC curve showed an AUC of 0.86 (95% CI, 0.83-0.89). Significant heterogeneity was seen among the studies, with an I^2 of 81% for both sensitivity and specificity.

In contrast, using significant tumor reduction (pR) for the definition of TN as applied in 3 studies, the estimated pooled sensitivity and specificity of ^{99m}Tc-sestamibi imaging for predicting a nonresponse to NAC were 74% (95% CI, 39%-100%) and 92% (95% CI, 85%-100%). The I^2 was 82.5% for sensitivity and 0% for specificity.

A subgroup analysis of ^{99m}Tc-sestamibi imaging used during NAC treatment was performed on 3 eligible studies with 107 patients. The diagnostic performance of ^{99m}Tc-sestamibi imaging during NAC in the 3 included studies is listed in Table 3. The estimated pooled sensitivity and specificity of ^{99m}Tc-sestamibi to predict a nonresponse during NAC were 87% (95% CI, 72%-100%) and 93% (95% CI, 85%-100%), respectively. The I^2 was 67% for sensitivity and 0% for specificity.

Discussion

Although consensus exists about ^{18}F-FDG PET/CT as a useful tool for the staging of LABC,[35] its role in therapy monitoring remains a matter of discussion. The use of ^{18}F-FDG PET/CT for this purpose likely depends on the breast cancer subtype and combined application of magnetic resonance imaging (MRI).[6,36] As an alternative to ^{18}F-FDG PET/CT, ^{99m}Tc-sestamibi allows the in vivo assessment of tumor chemoresistance and could potentially identify nonresponding patients early during NAC. The results from our meta-analysis of 14 studies showed that ^{99m}Tc-sestamibi imaging based on planar imaging has a relatively low sensitivity (70.3%) and high specificity (90.1%) to correctly predict nonresponse in LABC patients undergoing NAC.

However, the number of available studies using ^{99m}Tc-sestamibi was rather limited, and an adequate comparison of the results was quite difficult owing to the substantial heterogeneity among the studies. Because of the findings from the present meta-analysis, we would like to discuss the heterogeneity among the studies from a clinical viewpoint and make suggestions for improvement of the technique and future research.

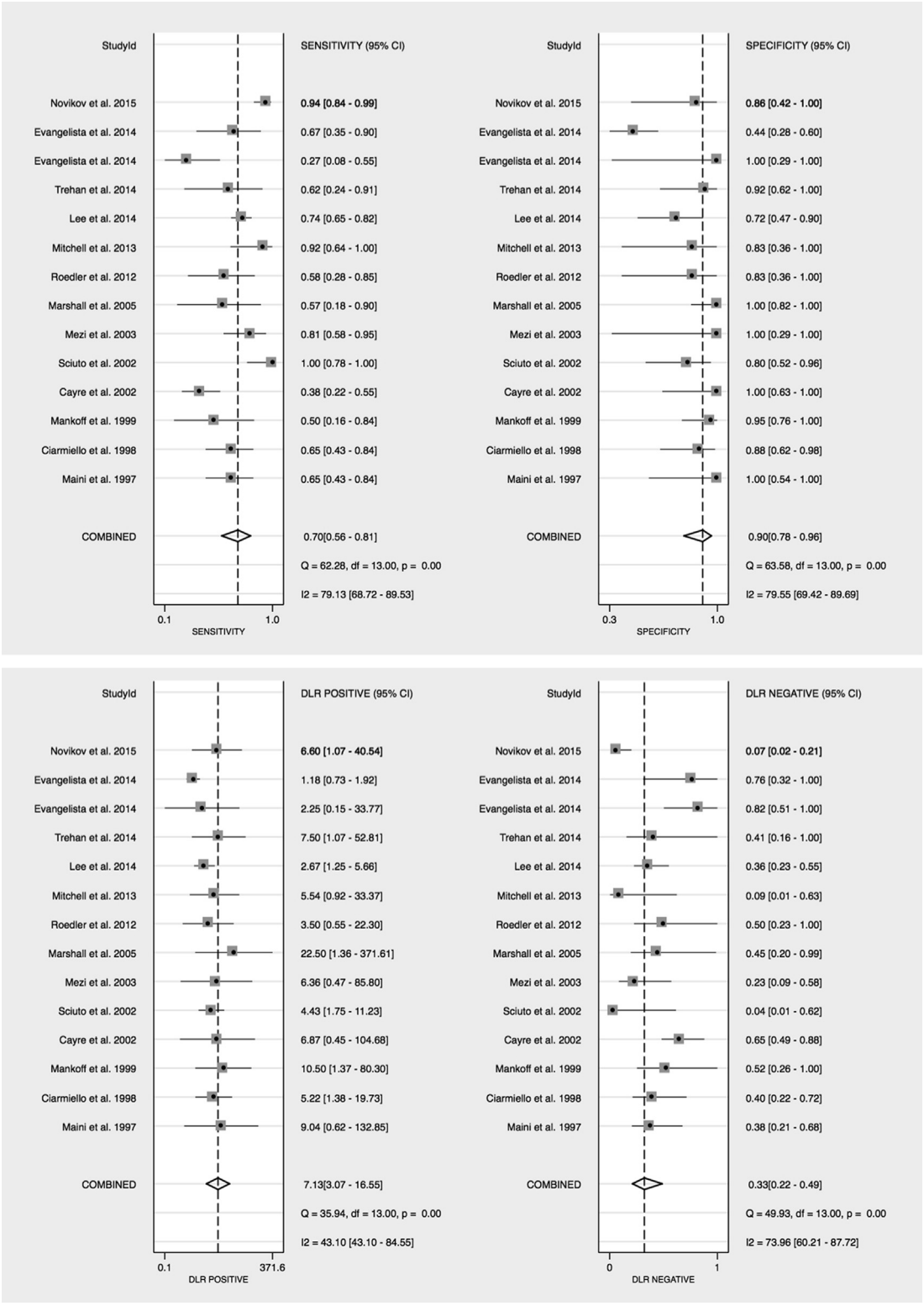
The most remarkable heterogeneity was that the studies focused on different tasks for ^{99m}Tc-sestamibi imaging. The studies included in our meta-analysis used different definitions to describe NAC response and nonresponse. Most studies used a strict

Table 2 Pooled Diagnostic Performance Estimates for Prediction of NAC Nonresponse Using Technitium-99m Sestamibi Imaging

Investigator	Patients (n)	TP (n)	FP (n)	FN (n)	TN (n)	NAC Response (%)	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
Maini et al[21]	29	15	0	8	6	21	65 (43-84)	100 (54-100)	9.04 (0.62-132.85)	0.38 (0.21-0.68)
Ciarmiello et al[22]	39	15	2	8	14	41	65 (43-84)	88 (62-98)	5.22 (1.38-19.73)	0.40 (0.22-0.72)
Mankoff et al[23]	29	4	1	4	20	72	50 (16-85)	95 (76-100)	10.50 (1.37-80.30)	0.52 (0.26-1.06)
Cayre et al[24]	45	14	0	23	8	18	38 (22-55)	100 (63-100)	6.87 (0.45-104.68)	0.65 (0.49-0.88)
Sciuto et al[25]	30	15	3	0	12	50	100 (78-100)	80 (52-96)	4.43 (1.75-11.23)	0.04 (0.00-0.62)
Mezi et al[26]	24	17	0	4	3	13	81 (58-95)	100 (29-100)	6.36 (0.47-85.80)	0.23 (0.09-0.58)
Marshall et al[27]	26	4	0	3	19	73	57 (18-90)	100 (82-100)	22.50 (1.36-371.61)	0.45 (0.20-0.99)
Wahner-Roedler et al[28]	18	7	1	5	5	33	58 (28-85)	83 (36-100)	3.50 (0.55-22.30)	0.50 (0.23-1.07)
Mitchell et al[29]	19	12	1	1	5	32	92 (64-100)	83 (36-100)	5.54 (0.92-33.37)	0.09 (0.01-0.63)
Lee et al[30]	122	77	5	27	13	15	74 (65-82)	72 (47-90)	2.67 (1.25-5.66)	0.36 (0.23-0.55)
Trehan et al[31]	20	5	1	3	11	60	63 (24-91)	92 (62-100)	7.50 (1.07-52.81)	0.41 (0.16-1.02)
Evangelista et al[32]	18	4	0	11	3	17	27 (8-55)	100 (29-100)	2.25 (0.15-33.77)	0.82 (0.51-1.33)
Evangelista et al[33]	51	8	22	4	17	76	67 (35-90)	44 (28-60)	1.18 (0.73-1.92)	0.76 (0.32-1.84)
Novikov et al[34]	59	49	1	3	6	12	94 (84-99)	86 (42-100)	6.60 (1.07-40.54)	0.07 (0.02-0.21)
Pooled results	529	246	37	104	142	33.8	70.3 (56.5-81.3)	90.1 (77.5-96.0)	7.13 (3.08-16.53)	0.33 (0.22-0.49)

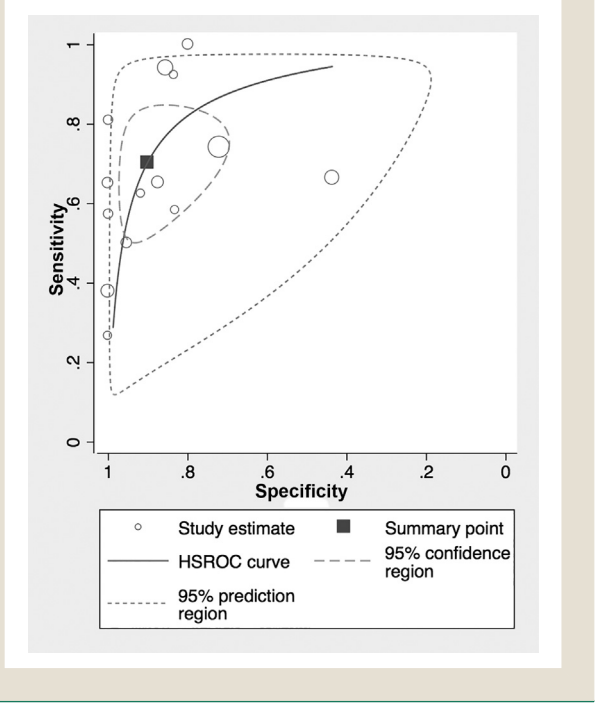
Data in parentheses are 95% confidence intervals.
Abbreviations: FN = false-negative; FP = false positive; LR = likelihood ratio; NAC = neoadjuvant chemotherapy; TN = true negative; TP = true positive.

Figure 3 Forest Plots of Overall Sensitivity, Specificity, and Positive and Negative Likelihood Ratios for the Prediction of Neoadjuvant Chemotherapy Nonresponse in Locally Advanced Breast Cancer Using Technetium-99m Sestamibi Imaging



Abbreviations: CI = confidence interval; Studyld = study identification.

Figure 4 Hierarchical Summary Receiver Operating Characteristic Curve (HSROC) for Prediction of Neoadjuvant Chemotherapy Nonresponse in Locally Advance Breast Cancer Using Technetium-99m Sestamibi Imaging



definition of TN (response), defined as the absence of tumor cells in the surgical specimen after NAC (pCR). Using this definition, we found that ^{99m}Tc-sestamibi imaging had a relatively low sensitivity (69%) and high specificity (91%) for the prediction of microscopic residual disease after NAC. This suggests that ^{99m}Tc-sestamibi imaging is not clinically useful to rule out the presence of residual tumor. However, these results are comparable to the performance of ^{18}F-FDG PET/CT for this indication. Recent meta-analyses have shown that MRI and ^{18}F-FDG PET/CT might play a complementary role for this purpose,[37,38] albeit it is unlikely that any imaging modality will be able to rule out microscopic foci of viable tumor cells.

A more attainable goal for ^{99m}Tc-sestamibi imaging in this respect would to identify treatment failure at an early stage during NAC, which would enable clinicians to adjust the chemotherapy plan. However, only a few of the investigated studies focused on this task. Only 3 studies investigated the ability of ^{99m}Tc-sestamibi to predict nonresponsiveness before or early during NAC, showing a moderate sensitivity (74%) and a high specificity (92%). However, because of the limited number of studies and their methodologic heterogeneity, conclusions could not be drawn. Further studies are needed to assess the role of ^{99m}Tc-sestamibi in predicting nonresponsiveness to NAC at an early stage.

Another source of heterogeneity was the diversity in imaging modalities used in the studies. Most of the included studies used conventional SMG. Compared with breast-dedicated devices such as BSGI and molecular breast imaging (MBI), traditional SMG has the following drawbacks: (1) limited intrinsic resolution for breast lesions < 1 cm; (2) a greater effect of scatter radiation from the heart and liver owing to the large field of view; (3) an inability to apply light breast compression for motion reduction and minimize breast tissue attenuation, and (4) limited possibilities for breast positioning, thus the impossibility of multiple projections comparable to that with mammography.[39] These limitations result in low resolution and contrast of breast lesions and might, in particular, limit the detection of small residual tumors using conventional SMG. In contrast, modern BSGI and dual-head MBI systems achieve a resolution of 2 to 5 mm and provide a lower scatter fraction.[40,41] Furthermore, the solid-state, cadmium-zinc-telluride, dual-head technology of new MBI devices allows for a reduction of the administrated dose of ^{99m}Tc-sestamibi to 150 to 300 MBq.[42]

None of the ^{99m}Tc-sestamibi studies assessing the response to NAC used SPECT or SPECT/CT. SPECT is a tomographic technique with better contrast resolution compared with conventional planar imaging and,[43] combined with CT in a SPECT/CT device, provides fused functional and anatomic images. The new generation of SPECT/CT systems includes, not only a more sensitive SPECT, but also an improved CT component able to display an anatomic environment with specific landmarks to evaluate the functional SPECT findings. Although the spatial resolution of SPECT/CT is lower than that of MBI systems, modern SPECT/CT systems provide the possibility of absolute quantification, enabling measurement of quantitative tumor parameters such as the SPECT standardized uptake value and metabolic tumor volume. This in vivo absolute tumor quantification might improve the performance of ^{99m}Tc-sestamibi imaging as a therapy-monitoring tool in LABC. Moreover, recent improvements in SPECT/CT technology have resulted in the development of a breast-dedicated SPECT/CT system with high intrinsic resolution comparable to that of modern MBI devices. However, although this dedicated SPECT/CT

Table 3 Pooled Diagnostic Performance Estimates for Prediction of NAC Nonresponse Using Technetium-99m Sestamibi Imaging During NAC

Investigator	Patients (n)	TP (n)	FP (n)	FN (n)	TN (n)	NAC Response (%)	Sensitivity (%)	Specificity (%)
Mankoff et al[23]	29	4	1	4	20	72	50 (16-85)	95 (76-100)
Mitchell et al[29]	19	12	1	1	5	32	92 (64-100)	83 (36-100)
Novikov et al[34]	59	49	1	3	6	12	94 (84-99)	86 (42-100)
Pooled results	107	65	3	8	31	31.8	87 (72-100)	93 (85-100)

Data in parentheses are 95% confidence intervals.
Abbreviations: FN = false-negative; FP = false positive; NAC = neoadjuvant chemotherapy; TN = true negative; TP = true positive.

camera, which combines the advantage of high resolution and eligibility for in vivo quantification, has high clinical potential,[44] it requires validation in larger series of patients.

In addition to the variability in imaging techniques, the methods and criteria used for image interpretation were diverse in the currently available data. Some studies used the washout rate (WOR) of the tracer as an evaluation parameter,[25,26,31-33] and others evaluated the tumor-to-background uptake ratios.[27-29,34] We believe that the ^{99m}Tc-sestamibi WOR is the best parameter for predicting tumor nonresponse to NAC because it reflects tumor cell chemoresistance. In particular, the rapid washout of ^{99m}Tc-sestamibi (WOR $\leq$ 45%) was associated with tumor chemoresistance due to the overexpression of Pgp and *MDR1*.[12] In contrast to the PET/CT approach, which applies standardized PET Response Criteria in Solid Tumors to assess ^{18}F-FDG tumor uptake,[45] response evaluation criteria for functional ^{99m}Tc-sestamibi imaging have not yet been established.

Finally, most studies used different timing for ^{99m}Tc-sestamibi monitoring in relation to NAC (before, during, or after treatment). The combined interpretation of the results hints that the timing of ^{99m}Tc-sestamibi imaging is a possible key to accurately delineating a model of prediction for the NAC response. The studies that used ^{99m}Tc-sestamibi imaging during NAC for response evaluation showed relatively high performance for predicting nonresponsiveness (pooled sensitivity and specificity rates of 87% and 93%, respectively). Again, conclusions should not yet be drawn because of the limited number of studies and because different definitions of the pathologic response were applied (pCR vs. significant tumor reduction).

The early prediction of response and nonresponse during NAC might allow switching to alternative chemotherapy schedules for those with no response, thereby tailoring their personal treatment and reducing unnecessary side effects. As previously mentioned, we found that ^{99m}Tc-sestamibi imaging before or during the course of NAC had a moderate pooled sensitivity (74%) and high specificity (92%) to correctly predict treatment failure, although the number of studies investigating this task of ^{99m}Tc-sestamibi imaging was limited. In contrast, PET/CT and MRI assessments during NAC could potentially demonstrate a similar accuracy if the 2 modalities are used together, but the evidence is limited.[36]

The correlation between ^{99m}Tc-sestamibi uptake and tumor subtype (luminal, human epidermal growth factor receptor, triple negative) was evaluated in only 3 studies.[21,30,33] Although few data were included, no strong correlation was found between ^{99m}Tc-sestamibi uptake and tumor subtype. This appears to contrast with the results from PET/CT studies showing ^{18}F-FDG uptake is strongly influenced by breast tumor subtype.[6]

Recently, Guo et al[46] published a meta-analysis of 14 studies that used ^{99m}Tc-sestamibi to predict the NAC response in breast cancer. Of the 14 studies evaluated in their analysis, 13 were also included in our study. Although the method and analysis of Guo et al[46] were well described, some individual patient data were incorrectly cited and concerns exist with respect to their data extraction. Meta-regression was performed but did not include the necessary study-level parameters to determine the factors related to heterogeneity. We deemed the number of available studies too small to perform a strong and accurate meta-regression analysis; therefore, we opted for a qualitative discussion. Finally, Guo et al[46] did not relate their results to the clinical setting nor suggest possible future investigations in this field.

In the future, it will be necessary to determine whether standardization of ^{99m}Tc-sestamibi imaging and quantification might improve the results. Also, a focus on early response monitoring, the incorporation of variables such as tumor subtype, SPECT/CT, and/or MBI, the application of appropriate imaging criteria for determining the response, and the determination of the appropriate timing are needed. In analogy to the PET/CT approach, a semiautomatic segmentation tool allowing measurement of regional concentrations of tumor uptake in MBq/mL should be validated further in future ^{99m}Tc-sestamibi studies that include dedicated SPECT/CT for early NAC response monitoring.

Furthermore, the incorporation of new tracers as possible markers of early tumor response might become relevant when using SPECT/CT for monitoring. In particular, tracers such as ^{99m}Tc-$a_v ß_3$, with high affinity for the $a_v ß_3$ integrin in endothelial cells undergoing angiogenesis,[47,48] ^{99m}Tc-annexin V assessing apoptosis,[49] ^{99m}Tc-DMSA,[50] and ^{99m}Tc bombesin[51,52] might provide new insights.

Finally, it is necessary to highlight some limitations in our meta-analysis. First, the assessed heterogeneity among the studies was not completely eliminated by the subgroup analysis. Second, the research was limited to the English language, which introduced an additional possible selection bias. Third, a limited number of studies were included in the subgroup analysis, highlighting the need for larger series and more multicenter studies.

Conclusion

Only conventional planar ^{99m}Tc-sestamibi SMG and, to a limited extent, dedicated breast planar imaging have been investigated to monitor the NAC nonresponse in LABC patients. Low sensitivity and high specificity were found to predict pathologic nonresponsiveness, albeit most studies focused on the prediction of pCR after NAC and not on the early prediction of treatment failure. ^{99m}Tc-sestamibi imaging during NAC seems highly sensitive for the prediction of nonresponsiveness; however, the experience is limited to a few small and heterogenic studies. Future research should focus on the early prediction of treatment failure using quantitative SPECT/CT and MBI, standardization of the definition of the ^{99m}Tc-sestamibi response and timing, and the possible associations with tumor subtypes.

Clinical Practice Points

- In recent years, ^{18}F-FDG PET/CT has been extensively investigated for therapy monitoring purposes in breast cancer patients receiving NAC; however, its use in early response monitoring should be standardized and appears to be influenced by breast tumor subtype.
- Interest in ^{99m}Tc-sestamibi imaging is increasing owing to the increased use of molecular breast imaging devices in breast cancer clinics; however, its performance for therapy monitoring is not yet clear.
- The purpose of the present study was to conduct a meta-analysis on the diagnostic performance of ^{99m}Tc-sestamibi to predict a pathologic nonresponse to NAC in primary LABC and to establish which imaging protocols were involved.

- The present study revealed that only planar ^{99m}Tc-sestamibi imaging has been evaluated for therapy monitoring and showed relatively low pooled sensitivity and high specificity for the correct prediction of nonresponsiveness in primary LABC, although most studies focused on the prediction of a pCR after NAC and not on the early prediction of treatment failure.
- Major heterogeneity were present among the studies in the definition of the pathologic response, definition of imaging criteria for response, applied imaging technique, and timing of imaging.
- ^{99m}Tc-sestamibi imaging performed during NAC appears to be highly sensitive for the prediction of nonresponsiveness, although experience is limited.
- SPECT/CT imaging, standardized quantification, standardization of the imaging response criteria, and proper timing could optimize performance; the tumor subtype-related response requires further investigation.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figure accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2017.06.008.

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