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Diagnostic Efficacy of Technetium-99m-Sestamibi Scintimammography in Comparison with Mammography to Detect Breast Lesions: A Systematic Review

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ABSTRACT

Background: To systematically review the performance of scintimammography compared with mammography in detecting breast lesions.

Methods: A literature search was performed in PubMed and ScienceDirect databases with "scintimammography AND breast lesions," "mammography AND breast lesions," "diagnostic value," and "accuracy" as keywords to identify all related studies published in English from January 1, 2000, to August 1, 2017. Twenty-five studies, with a total of 4094 patients with clinically suspicious breast lesions, were included in the final analysis to assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of scintimammography vs. mammography in detecting breast lesions.

Results: The sensitivity and specificity of mammography were 75.82 ± 10.53 (95% confidence interval [CI], 50-84) and 59.58 ± 22.79 (95% CI, 20-91.4), respectively. The PPV and NPV of mammography were 75.60 ± 2.21 (95% CI, 42-93) and 61.62 ± 1.67 (95% CI, 39.1-86), respectively. The sensitivity of scintimammography was 86.64 ± 8.84 (95% CI, 58.3-100), and the specificity was 83.42 ± 10.74 (95% CI, 60-100). The PPV and NPV of scintimammography were 82.10 ± 11.65 (95% CI, 58-98.30) and 81.02 ± 17.00 (95% CI, 45-100), respectively.

Conclusions: Although mammography has a high sensitivity in the examination of older patients with fatty breast tissue, it is less reliable in detecting breast lesions in young and premenopausal patients with dense breasts. Diagnostic accuracy of scintimammography, as a functional imaging modality, is not affected by breast density, contrary to mammography. Therefore, scintimammography can improve the specificity of mammography.

Introduction

Breast cancer is the most frequent malignancy in women, affecting 1 in 13 women in their lifetime.[1-4] Patients with breast cancer who have it detected at an early stage will have a better survival rate.[5] The most widely used tool for detection of breast cancer, besides the physical examination, is mammography, which has a high accuracy in detecting breast lesions.[6] The sensitivity of mammography in patients with dense breasts may be low;[7] and, in patients with fibrocystic changes of the breast, mammographic detection of breast carcinoma may be difficult. Mammography has low specificity in distinguishing

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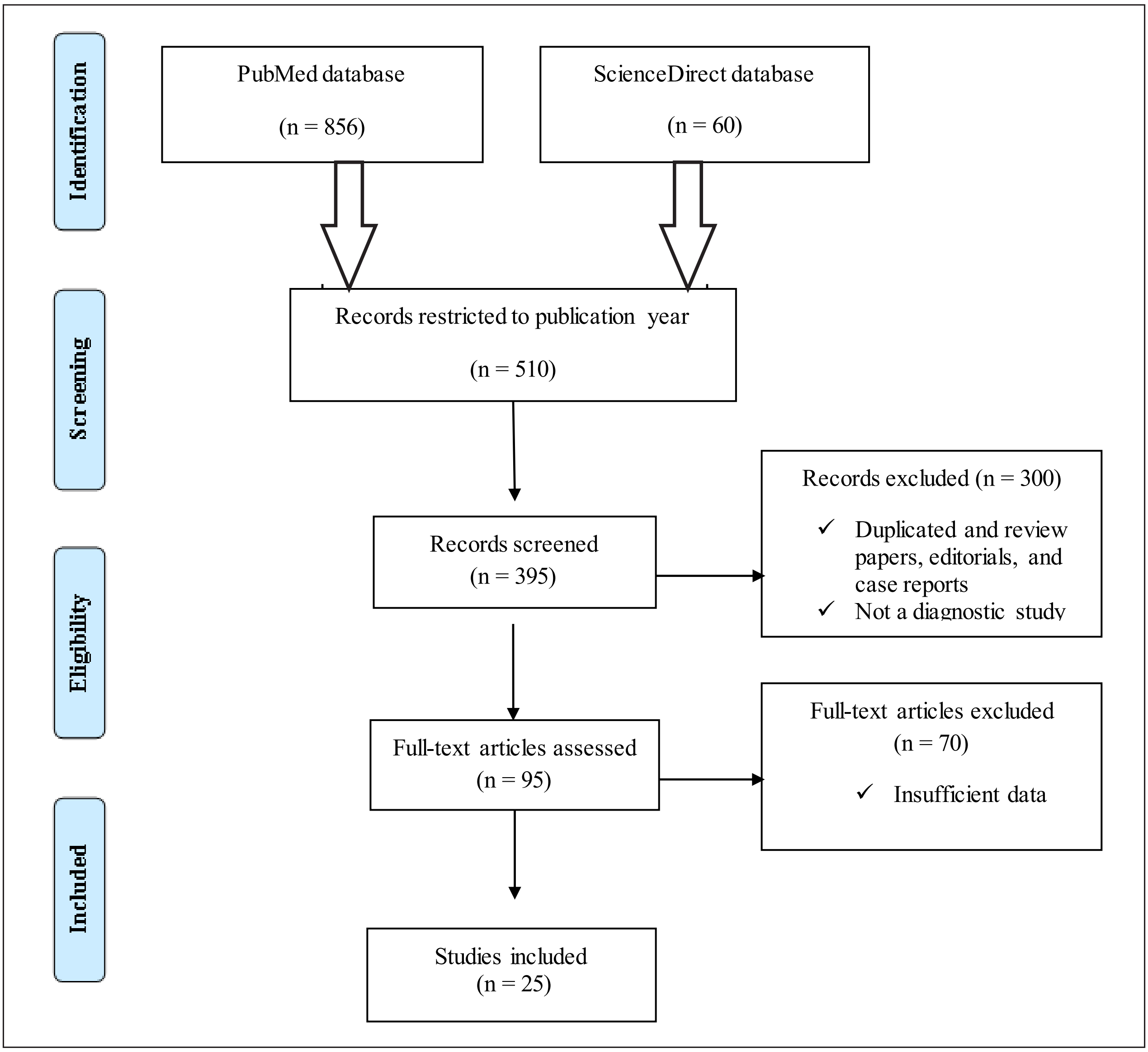

Figure 1. Flowchart Summarizing Search Strategy and Study Selection

between malignant and benign processes. Therefore, it is impossible to detect breast lesions using mammography alone in some cases.[8,9]

The high rate of breast biopsies in patients with benign lesions has encouraged the use of non-invasive imaging modalities with greater accuracy such as magnetic resonance imaging (MRI), ultrasound (US), positron emission tomography (PET), and scintigraphy.[10] Recently, it was demonstrated that technetium-^{99m}-sestamibi (^{99m}Tc-MIBI) accumulates in different types of tumors. For suspected breast lesions, some studies demonstrated that scintigraphy with ^{99m}Tc-MIBI differentiated benign from malignant lesions.[11] ^{99m}Tc-MIBI scintigraphy is a noninvasive diagnostic modality in evaluating breast carcinoma in the field of nuclear medicine.

The aim of the present systematic review was to compare the performance of scintimammography with mammography in the detection of breast lesions.

Methods

Search strategy

A literature search was performed in PubMed and ScienceDirect databases using the following keywords: "scintimammography (mammoscintigraphy) AND breast lesions," "mammography AND breast lesions," "diagnostic value," and "accuracy." Articles that cited related studies were also searched to find any related publication (using PubMed, Europe PubMed Central, and Google Scholar citation tracking tools). An updated search strategy was developed in order to identify all related papers published in English from January 1, 2000, to August 1, 2017. The full search strategy is presented in Figure 1.

Selection of studies

Titles and abstracts obtained from the literature search were examined for eligibility. Information given in the titles and abstracts had to suggest that the study (1) included patients with suspected breast lesions, (2) conducted scintimammography or mammography in those patients, and (3) evaluated diagnostic values of the tests (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). Full-text articles were retrieved for further assessment.

Inclusion/exclusion criteria

Studies were included if they assessed sensitivity, specificity, PPV, or NPV of scintimammography or mammography in the diagnosis of breast lesions. We included studies with or without comparator groups. Editorials, case reports, and review articles were excluded. All eligible papers were compared independently assessed by two authors for predefined inclusion criteria.

Data extraction

Two authors independently extracted the following data from each included study: the first author's name, publication year, journal, country, details of study design, number of patients and their characteristics, index test or tests, reference standard, sensitivity, specificity, PPV, and NPV. The diagnostic performance of scintimammography and mammography in the detection of breast lesions was assessed by comparing index test results with the reference standards. Any discrepancies between the two researchers were resolved through consensus.

The patients were classified as true positive (TP) when both the index test (i.e., scintimammography or mammography) and the reference standard (pathological assessment) detected breast lesion, true negative (TN) when neither test detected breast lesion, false negative (FN) when the index test failed to detect a breast lesion identified by the reference standard, and false positive (FP) when the index test incorrectly suggested a breast lesion not detected by the reference standard. Sensitivity was defined as TP/(TP+FN) and specificity as TN/(TN+FP).

Quality assessment

We used the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to evaluate the quality of the included studies. Assessment of the risk of bias and applicability concerns were performed in 4 domains including patient selection, index test, reference standard, and flow and timing. Applicability concern and risk of bias were judged as low, high, or unclear for the various QUADAS domains.[12]

Statistical analysis

SPSS 16 was used for data analysis using descriptive statistics. Sensitivity, specificity, PPV, and NPV, along with 95% confidence intervals (CIs), were calculated for each study.

Table 1. Main Characteristics of the Studies Evaluating the Diagnostic Value of Scintimammography

First author (Year)	Number of patients	Mean age (Year)	Index test	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)
Chen (2000)[13]	35	—	Scintimammography (Planar)	77.8	88.2	—	—
Prats (2001)[14]	253	53.5	Scintimammography (Planar)	91	71	81	85
			Palpable lesions	97	57	82	86
			Nonpalpable lesions	77	83	78	82
Yildizi (2001)[15]	63	55	Scintimammography (Planar)	100	96	88	100
Koukouraki (2001)[16]	116	—	Scintimammography (Planar)	95	80	92	86
Aguilar (2001)[17]	36	57	Scintimammography (Planar)	78.9	72.2	75	76.5
Horne (2001)[18]	35	53.5	Scintimammography (Planar)	89.4	80	85	85.7
Bagni (2003)[19]	45	51	Scintimammography (Planar)	84	71	94	45
Sampalis (2003)[20]	1243	56	Scintimammography (Planar)	93	87	58	98
Myslivecek (2004)[21]	303	—	Scintimammography (Planar)	82	91	—	—
			Scintimammography (SPECT)	92	91		
Fondrinier (2004)[22]	41	—	Scintimammography (Planar)	58.3	81	78	63
Cicco (2004)[23]	40	52	Scintimammography (Planar)	87.5	60.0	72.4	80
Kim (2005)[24]	520	≤45	Scintimammography (Planar)	79.6	78.6	—	—
		>45		85.7	77.5		
Prats (2007)[25]	308	54	Scintimammography (Planar)	85	95	80	96
			Palpable lesions	97	94	91	98
			Nonpalpable lesions	68	96	68	96
Usmani (2008)[26]	36	47.13	Scintimammography (Planar)	86	88	96	64
Habib (2009)[27]	28	—	Scintimammography (Planar)	93.3	71.4	87.5	83.3
Cesare (2011)[28]	172	—	Scintimammography (SPECT)	100	93.5	92.5	100

**PPV: Positive predictive value; **NPV: Negative predictive value*

Results

Twenty-five studies assessing the sensitivity, specificity and/or PPV and NPV of scintimammography or mammography in the detection of breast lesions were included in the analysis. The studies included a total of 4094 patients (age: 51.68 ± 4.07 y) with clinically suspicious breast lesions. Table 1 shows the main characteristics of the 16 studies evaluating the diagnostic value of scintimammography, and Table 2 shows the main characteristics of the 3 studies assessing the diagnostic value of mammography. Six studies compared the diagnostic value of scintimammography with mammography (Table 3).

Sensitivity and specificity of mammography were 75.82 ± 10.53 (95% CI, 50-84) and 59.58 ± 22.79 (95% CI, 20-91.4), respectively. Also, mammography had a PPV of 75.60 ± 2.21 (95% CI, 42-93) and an NPV of 61.62 ± 1.67 (95% CI, 39.1-86).

The sensitivity of scintimammography was 86.64 ± 8.84 (95% CI, 58.3-100), and its specificity was 83.42 ± 10.74 (95% CI, 60-100). PPV and NPV of scintimammography were 82.10 ± 11.65 (95% CI, 58-98.30) and 81.02 ± 17.00 (95% CI, 45-100), respectively.

Table 2. Main Characteristics of the Studies Evaluating the Diagnostic Value of Mammography

First author (Year)	Number of patients	Mean age (Year)	Index test	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)
Hoi (2000)[29]	60	60	Mammography	84	80	93	63
Chen (2002)[30]	60	60	Mammography	84	80	93	63
Kotsianos-Hermle (2009)[31]	97	97	Mammography	76.5	91.4	—	—

*PPV: Positive predictive value; **NPV: Negative predictive value*

Table 3. Main Characteristics of the Studies Evaluating the Diagnostic Value of Mammography

First author (Year)	Number of patients	Mean age (Year)	Index test	Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)
Mulero (2000)[32]	109	—	MG (dense breasts)	81	28	—	—
	8	under 30	MG (young females)	50	20	—	—
	24	—	MG (previous surgery)	80	42	—	—
			SM (dense breasts)	88	90	—	—
			SM (young females)	100	100	—	—
			SM (previous surgery)	80	100	—	—
Sun (2000)[33]	81	55	MG	83	47	—	—
			SM (Planar)	88	87	—	—
Lumachi (2001)[34]	87	47	MG	80.6	60.0	90.6	39.1
			SM (Planar)	80.6	93.3	98.3	50.0
Cwikła (2003)[35]	154	—	MG	69	72	81	57
			SM (Planar)	87	65	81	75
Krishnaiah (2003)[36]	94	44	MG	65	72	42	86
			SM (Planar)	83	83	59	94
Ozulker (2010)[37]	46	46	MG	81	63	54	86
			SM (Planar)	93	86	78	96

MG: Mammography; SM: Scintimammography; *PPV: Positive predictive value; **NPV: Negative predictive value

Discussion

Although mammography has high sensitivity in the examination of older patients with fatty breast tissue, it is less reliable in detecting breast lesions in patients with dense breasts, breast implants, and architectural distortion after radiation therapy or surgery.[7] In a mammography unit with both a rhodium (Rh) anode and a molybdenum (Mo) anode, filtered with rhodium and molybdenum, respectively, the mammograms obtained by using the Mo/Mo combination were preferred. However, the mammograms obtained with the Rh/Rh combination were better than the Mo/Mo mammograms for young patients with dense breasts.[38]

^{99m}Tc-MIBI scintigraphy plays an important role in localizing the breast tumors when ultrasound or mammography is not contributory. Diagnostic accuracy of scintimammography, as a functional imaging modality, is not affected by breast density, contrary to mammography, because of the advantages of labeling with ^{99m}Tc sestamibi radiopharmaceutical. Its uptake in the lesion involves several causes, including mitochondrial activity, angiogenesis, and presence of malformed vessels, but does not depend on the presence of architectural distortion and localized variation in breast density.[39-45]

The intensity of ^{99m}Tc-MIBI uptake varies from mild to high depending on factors such as the type, size, location, and hormonal factors. The size of the lesion affects sensitivity. The sensitivity for palpable lesions is significantly higher than that for nonpalpable ones.[46,47] Another clinical application of ^{99m}Tc-MIBI scintigraphy is the detection of patients with microcalcifications. Scintimammography seems to be helpful in differentiating malignant from benign calcifications and leads to a decrease in the frequency of breast biopsies.[48] Some studies had separated the statistics for palpable and nonpalpable lesions because of the difference in management strategy.[14, 25, 49] Palmedo reported that the total specificity and sensitivity of 99mTc-MIBI scintimammography were 69% and 71%, respectively; for palpable lesions, however, the specificity and sensitivity of scintimammography increased to 91% and 83%, respectively.[49] Palmedo reported similar results in another research and showed that the total sensitivity of scintimammography was 88%, increasing to 100% for palpable lesions.[50] Another study reported that the sensitivity of scintimammography in detecting nonpalpable lesions was 78.3% compared with 89.1% for mammography; but, in palpable lesions, the sensitivity of scintimammography (91.3%) was higher than the sensitivity of mammography (78.2%).[51] Based on the clinical studies, ^{99m}Tc-MIBI scintimammography is more accurate than mammography in differentiating palpable breast lesions. Therefore, the utility of the technique has been emphasized to decrease the frequency of breast biopsies.[1] As mentioned, the sensitivity of scintimammography can be affected by tumor size, and the specificity and sensitivity of ^{99m}Tc-MIBI scintimammography increase for palpable breast lesions.[49, 50] Therefore, attempts have been made to enhance the sensitivity of scintimammography for the detection of cancer, especially for nonpalpable and ≤1-cm lesions.[52, 53] Myslivecek compared the specificity and sensitivity of scintimammography in detecting primary breast lesions with both single-photon emission computed tomography (SPECT) and planar images (Table 1). The results showed that SPECT scintimammography was slightly (10%) more sensitive than planar scintigraphy.[21] Taillefer and Khalkhali reported PPV values of 97.7% and 76.9%, respectively, and NPV values were 81% and 97%, respectively.[54,55] Palmedo reported that in 60% of false-negative (FN) mammograms, scintimammography was able to detect malignant lesions true-positive (TP).[49] It is worth mentioning that scintimammography with ^{99m}Tc-MIBI or ^{99m}Tc-sestamibi scintimammography is a noninvasive imaging modality and highly sensitive test in detecting primary breast lesions.[49,54,55]

The present systematic review demonstrates the high diagnostic value of scintimammography with ^{99m}Tc-MIBI as a complementary method that improves the specificity of mammography and is potentially able to reduce the frequency of breast biopsies. Scintimammography is a noninvasive, low–radiation dose diagnostic method and an easy-to-perform procedure which may offer additional information above that provided by conventional radiology, especially in young, premenopausal patients with dense breasts and in patients who are on hormone replacement therapy, where the sensitivity of mammography is limited by the characteristics of the breast tissue. Technetium-99m-sestamibi scintimammography has the potential to determine the metabolic state of microcalcification, primary breast lesion, axillary lymph node detected by other imaging modalities. Scintimammography may discriminate between benign and malignant breast lesions in patients with a palpable mass or when the lesion size is more than 10 mm.

However, mammography has a high sensitivity in the examination of older patients with fatty breast and is associated with a small amount of radiation exposure. Mammography has a better spatial resolution compared with scintimammography. Nevertheless, the development and general availability of high-resolution cameras dedicated to breast imaging will probably allow scintimammography to become of routine use.

Conflict of Interest

The authors have no potential conflict of interest concerning the content of the present article.

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