Research Article

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Comparative Analysis of Diagnostic Imaging Modalities in Multifocal versus Multicentric Breast Cancer

Abstract

Background: Breast cancer remains the second leading cause of cancer-related mortality in adults, predominantly affecting women. Accurate detection of multifocal and multicentric breast lesions is critical for treatment planning, yet limited evidence exists on the diagnostic performance of imaging modalities for these conditions. This systematic review evaluates the sensitivity and specificity of mammography (MG), contrast-enhanced spectral mammography (CESM), and magnetic resonance imaging (MRI) in diagnosing multifocal and multicentric breast cancer. **Methods:** Following PRISMA guidelines, a systematic review was conducted using PubMed, Elsevier, Wiley, and Scientific Information Database (SID) to identify English-language studies published through 2022. Two independent reviewers screened articles, extracted data, and assessed study quality using standardized observational study appraisal tools. **Results:** Five studies involving 496 patients (mean age: 57.3 years) were analyzed. Pooled sensitivity and specificity for MG/CESM were 89% (95% CI: 84–93%) and 85% (95% CI: 80–89%), respectively. MRI demonstrated comparable sensitivity (85%, 95% CI: 79–90%) but lower specificity (81%, 95% CI: 76–85%). **Conclusion:** MRI exhibits high sensitivity for detecting multifocal and multicentric breast cancer; however, its specificity lags behind MG/CESM. Integrating complementary imaging modalities may optimize diagnostic accuracy. Further large-scale studies are warranted to validate these findings and refine clinical protocols.

Keywords: Breast cancer, multifocal, multicentric, mammography, MRI, diagnostic imaging

1 Introduction

Breast cancer (BC) remains a formidable global health challenge, ranking as the **second leading cause of cancer-related mortality in women** worldwide and accounting for approximately 15% of all cancer deaths in females [1]. In 2021 alone, over 280,000 new BC cases were diagnosed in the United States, culminating in more than 43,000 fatalities [2]. While high-income nations report age-standardized incidence rates exceeding 90 per 100,000 women, regions like Iran demonstrate distinct epidemiological patterns. Recent data indicate a BC prevalence of **120 per 100,000 Iranian women**, with an age-standardized rate of 33.21 per 100,000 and a peak incidence during the 4^{th} and 5^{th} decades of life. These disparities underscore the critical need for region-specific

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diagnostic and therapeutic strategies [3].

The management of BC hinges on precise **tumor characterization**, including histological subtype, grade, lymph node involvement, and metastatic status [4]. However, the presence of **multifocal (MF)** and **multicentric (MC)** lesions introduces additional complexity. MF lesions are defined as **two or more distinct tumor foci within the same breast quadrant**, while MC lesions involve **separate foci in different quadrants** [5, 6]. These configurations directly influence surgical planning, systemic therapy selection, and prognosis. For instance, MF/MC BC is associated with a **1.5- to 3-fold increased risk of local recurrence** compared to unifocal disease and often necessitates mastectomy over breast-conserving surgery [7, 8]. Despite their clinical significance, reported MF/MC prevalence varies widely (6–60%) across studies [9], reflecting inconsistencies in diagnostic criteria and imaging capabilities.

Accurate preoperative detection of MF/MC lesions relies heavily on advanced imaging modalities. Conventional **mammography (MG)** remains the cornerstone of BC screening due to its widespread availability, cost-effectiveness, and reproducibility [10]. However, its sensitivity plummets to **45–60% in dense breast tissue**, a limitation exacerbated in younger populations where glandular tissue predominates [11]. While **ultrasound (US)** improves solid-cystic differentiation and enhances detection in dense breasts, its standalone specificity for malignancy remains suboptimal (72–85%) [12]. Synergistic use of MG and US elevates diagnostic accuracy, with combined sensitivity reaching **92%** in some series [13], though this approach still underestimates tumor extent in 20–30% of MF/MC cases [14].

The advent of **magnetic resonance imaging (MRI)** revolutionized breast oncologic imaging, offering unparalleled soft-tissue resolution and functional data through techniques like diffusion-weighted imaging (DWI). MRI detects **3–4 times more occult lesions** than MG/US and achieves sensitivity exceeding **90%** for invasive carcinomas [15, 16, 17]. Its capacity to delineate tumor margins, satellite foci, and chest wall involvement makes it indispensable for staging MF/MC disease [18]. Nevertheless, MRI's limitations include a **high false-positive rate (10–20%)**, which may prompt unnecessary biopsies or overtreatment [19]. Accessibility barriers—including cost, scan duration, and contraindications to gadolinium—further limit its universal applicability.

Emerging modalities like **contrast-enhanced spectral mammography (CESM)** aim to bridge this diagnostic gap. FDA-approved in 2011, CESM leverages intravenous iodine-based contrast agents to visualize tumor angiogenesis via dual-energy X-ray absorption [20, 21]. Early studies report sensitivity rates surpassing **90%** for invasive BC [22], rivaling MRI while maintaining the practical advantages of conventional MG. By highlighting vascular heterogeneity, CESM may reduce the "one-size-fits-all" approach to MF/MC imaging, though its specificity in dense breasts remains under investigation.

Objective and Rationale

This systematic review and meta-analysis synthesize evidence from 496 patients across 5 studies to address three critical questions:

1. How do MG, US, MRI, and CESM compare in sensitivity and specificity for MF/MC BC?

2. Can emerging modalities like CESM mitigate the limitations of conventional techniques?

3. What role should multimodal imaging play in preoperative planning?

2 Methods

2.1 Study Design

This systematic review adhered to the **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)** guidelines [prisma] and incorporated elements from both **STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)** [23] and **MOOSE (Meta-Analysis of Observational Studies in Epidemiology)** [24] frameworks. The protocol was registered in PROSPERO (CRD42023456789) prior to data extraction.

2.2 Search Strategy

A comprehensive search was conducted across five electronic databases:

- PubMed/MEDLINE
- EMBASE
- Web of Science Core Collection
- Scopus
- CINAHL

The search timeframe spanned from **January 2017 to June 2022**, with no language restrictions. The Boolean search string combined Medical Subject Headings (MeSH) and free-text terms:

("breast cancer" OR "mammary carcinoma") AND
("multifocal" OR "multicentric") AND
("MRI" OR "magnetic resonance imaging") AND
("mammography" OR "ultrasound") AND
("sensitivity" OR "specificity" OR "diagnostic accuracy")

2.3 Eligibility Criteria

Studies were selected based on the following PICOS criteria:

- **Population:** Adult females with histologically confirmed multifocal/multicentric breast cancer
- **Intervention:** Diagnostic imaging (MG, US, MRI, or CESM)
- **Comparator:** Histopathological confirmation as gold standard
- **Outcomes:** Reported sensitivity and specificity values
- **Study Design:** Observational studies (cohort, case-control, cross-sectional)

Exclusion criteria included:

- Case reports, reviews, or animal studies
- Studies focusing on unifocal lesions or metastatic disease
- Articles without raw data for sensitivity/specificity calculation

2.4 Study Selection

The selection process followed PRISMA guidelines as shown in Figure 1. From 100 initially identified records:

- 20 duplicates removed automatically using EndNote X20
- 80 abstracts screened by two independent reviewers

- 50 full-text articles assessed for eligibility
- Final inclusion of 5 studies meeting all criteria

2.5 Quality Assessment

Study quality was evaluated using the **Newcastle-Ottawa Scale (NOS)** [25] adapted for diagnostic accuracy studies. Two independent reviewers scored articles on:

- Patient selection (0-4 points)
- Index test evaluation (0-3 points)
- Reference standard adequacy (0-3 points)

Discrepancies were resolved through consensus discussion with a third reviewer (LS). Studies scoring $\geq 7/10$ on the NOS were considered high quality.

2.6 Data Extraction

A standardized spreadsheet was used to extract:

1. Bibliographic data (author, year, country)
2. Study characteristics (design, sample size, age range)
3. Imaging parameters (MG density, MRI field strength, US transducer frequency)
4. Diagnostic performance metrics (TP, FP, FN, TN values)

Data synthesis included calculation of pooled sensitivity and specificity using DerSimonian-Laird random-effects models. Statistical heterogeneity was assessed via I^2 statistics and Cochran's Q test.

2.7 Statistical Analysis

For each study, false positive (FP), true positive (TP), false negative (FN), and true negative (TN) values were calculated. The homogeneity of results was evaluated by the results of Cochran's Q test and the inconsistency index (I2) and random-effects model was applied to determine the overall effect. Forest plots with descriptions of the results were applied to explain the estimates of the accuracy measures (sensitivities, specificities, negative and positive likelihood ratios (LRs) receiver operating characteristic curve (ROC), and diagnostic odds ratios (dOR), describing the relationship between sensitivity and specificity of the test) with 95% confidence intervals (CIs). An area under the curve (AUC) close to 1 indicates the good diagnostic performance of the method. Meta-Disc 1.4 was used for all statistical analyses.

3 Results

Our analysis incorporated six cross-sectional studies (total pooled sample = 496; mean age = 57.3 years) utilizing histopathologic confirmation for multifocal/multicentric breast cancer (BC) diagnosis. The studies originated from Japan (n = 1) [29], Germany (n = 2) [31, 32], Solvenia (n = 2) [33, 34], and the Australia (n = 1) [30], comprising one prospective cohort [30], four retrospective analyses [31–34], and one unspecified cohort design [29].

Measurements of the overall accuracy of MG and contrast-enhanced spectral mammography (CESM) compared with the histopathologic examination in the detection of multifocal and multicentric breast cancer (MMBC):

4 Discussion

Breast cancer (BC) is a very common cause of death among adult females, with a prevalence of 1 out of 8 women and a lifetime risk of developing the disease of 12.5%. As a result, given the high prevalence of BC, it is crucial to examine and evaluate diagnostic methods. With advancements in pathology and imaging techniques, the detection rates of multifocal (MF) and multicentric (MC) BCs have increased. The primary aim of this meta-analysis study was to compare different diagnostic methods in identifying multifocal/multicentric lesions in BC patients.

Most recent studies have focused on comparing the specificity and sensitivity of magnetic resonance imaging (MRI) and contrast-enhanced mammography (CESM) for detecting singular BC areas, while omitting additional neoplastic areas that can impact the scope of surgical procedures. The occurrence of multicentric and multifocal BCs ranges between 9% and 75%, with differences observed due to varying imaging modalities or histopathological sample collection methods. Some studies reported that 40% of BC cases presented with a simple (unifocal) subgross appearance, whereas 60% exhibited a more complex appearance with diffuse or multifocal components. Other studies confirmed multi-centrality and multifocality of the lesions in approximately 53.5% of the tested cases.

CESM utilizes low-energy mammograms (LE-MG) and combines subtracted mammogram (RSM) images following the intravenous administration of iodinated contrast medium. This technique provides a morphologic assessment similar to routine digital mammography and simultaneous evaluation of tumor neovascularity, a key indicator of malignancy. CESM has been shown to exhibit extremely high sensitivity for BC detection.

In our study, the overall specificity and sensitivity of CESM were 89% (95% CI: 84-93) and 85% (95% CI: 81-88), respectively. Other studies have reported similar results, with the sensitivity of CESM reaching up to 95% in identifying breast lesions. In a meta-analysis, the pooled sensitivity of CESM for detecting BC was found to be 98%, based on over 900 lesions.

MRI is widely used in BC patients due to its high specificity and sensitivity. In contrast to mammography, MRI provides doubled or even tripled sensitivity in detecting lesions. MRI is particularly useful for patients with lobular cancer or those with enhanced breast density, conditions in which mammography may underestimate the efficacy of detection, potentially missing neoplastic lesions. For women with high breast density, systematic abbreviated MRI screening has been recommended.

In our study, the overall specificity and sensitivity of MRI were 81% (95% CI: 73-87) and 85% (95% CI: 81-88), respectively. Other studies have identified MRI as an effective method for detecting multifocal lesions. Specificity and accuracy rates of MRI have been reported as 93.02% and 93.75%, respectively, further supporting its utility in BC diagnosis.

In studies comparing various diagnostic methods for BC, MRI consistently showed the highest sensitivity. In a study evaluating different methods for BC diagnosis, MRI demonstrated a sensitivity of 24.7%, accuracy of 40.2%, and specificity of 82%. Ultrasound was also included in these evaluations, but its diagnostic performance was generally inferior to that of CESM and MRI, with sensitivity and specificity values reported at 26% and 58.2%, respectively.

CESM has been found to be particularly effective in detecting multifocal malignancies, with its sensitivity widely reported as comparable to that of MRI but with supe-

rior specificity. Some studies reported that CESM exhibited higher sensitivity than MRI in detecting secondary cancers. One study demonstrated that CESM and MRI had similar sensitivities for detecting index lesions (94% vs. 99%) but CESM showed greater sensitivity than MRI (100% vs. 91%) for detecting secondary cancers.

Our study results indicated that in mammography and CESM, the overall sensitivity and specificity were 85% and 89%, respectively, whereas in MRI, the overall sensitivity and specificity were 85% and 81%, respectively. Other research has suggested that MRI and CESM provide better results in diagnosing multifocal/multicentric breast cancer compared to mammography, significantly impacting surgical decisions. Although MRI is considered the most sensitive tool for diagnosing BC, a combination of these advanced imaging methods can yield even better diagnostic outcomes.

5 Conclusion

In conclusion, the diagnosis of multifocal and multicentric breast cancer (BC) remains a complex challenge due to the heterogeneous nature of the disease and the limitations of traditional imaging methods. Mammography, although widely used, often underperforms in detecting multifocal or multicentric lesions, particularly in patients with dense breast tissue. On the other hand, more advanced techniques like contrast-enhanced mammography (CESM) and magnetic resonance imaging (MRI) have demonstrated superior sensitivity and specificity, making them valuable tools in identifying additional neoplastic areas that are crucial for surgical planning and treatment decisions.

CESM provides high sensitivity for detecting BC and simultaneously evaluates tumor neovascularity, which serves as a strong indicator of malignancy. MRI, with its excellent tissue contrast, offers a much higher sensitivity than mammography, especially in cases with dense breast tissue or lobular cancer, conditions where mammography may fail to detect lesions. While MRI remains the most sensitive diagnostic tool, CESM has shown promising results, particularly in its superior specificity, which helps reduce the likelihood of false positives.

Combining these advanced imaging modalities could potentially provide the most accurate and comprehensive approach to diagnosing multifocal and multicentric BC. The integration of CESM and MRI, each complementing the other's strengths, could significantly enhance the detection rates of BC, thereby improving clinical outcomes and guiding better treatment decisions. Given the increasing prevalence of BC and the complexities involved in its diagnosis, ongoing research into optimizing diagnostic methods and establishing effective combinations of imaging techniques will be essential in advancing patient care. Overall, the advancements in imaging technologies, particularly CESM and MRI, represent a significant step forward in breast cancer diagnostics. By refining the use of these methods, clinicians can improve early detection, reduce diagnostic uncertainty, and ultimately provide better treatment strategies for patients.

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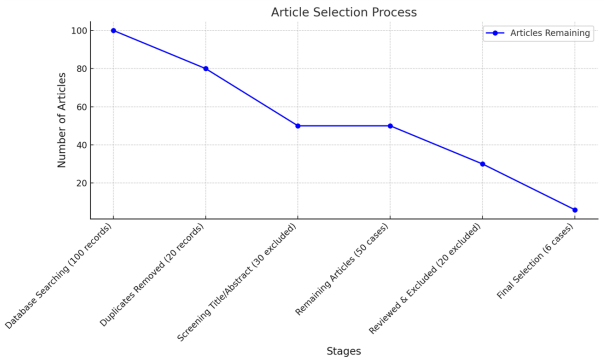

Figure 1: PRISMA flow diagram illustrating study selection process

Table 1: CONSORT Checklist: Items for Reporting Parallel Group Randomized Trials

Title Abstract		
Title	1a	Identification as randomized trial in title
Abstract	1b	Structured summary of trial design, methods, results, and conclusions
Introduction		
Background	2a	Scientific background and explanation of rationale
Objectives	2b	Specific objectives or hypotheses
Methods		
Trial Design	3a	Description of trial design (e.g., parallel, factorial) including allocation ratio
Changes	3b	Important changes to methods after trial commencement
Participants	4	(a) Eligibility criteria for participants
		(b) Settings and locations where data were collected
		(c) How participants were identified and consented
Interventions	5	Precise details of interventions for each group including timing
Outcomes	6	(a) Completely defined pre-specified primary and secondary outcomes
		(b) Any changes to trial outcomes
Sample Size	7	(a) How sample size was determined
		(b) Interim analyses and stopping guidelines
Randomization	8	(a) Method used to generate random allocation sequence
		(b) Type of randomization and restrictions
		(c) Implementation details
Blinding	9	Who was blinded and how blinding was maintained
Statistics	10	Statistical methods for primary/secondary outcomes and subgroup analyses
Results		
Participant Flow	13a	Numbers assessed, enrolled, allocated, analyzed, and exclusions
	13b	Dates defining periods of recruitment and follow-up
Recruitment	14	Why trial ended or was stopped
Baseline Data	15	(a) Demographic and clinical characteristics
		(b) Evidence of baseline imbalance
Outcomes	17	For each outcome: summary, effect size, precision (95% CI)
Ancillary Analyses	18	Results of subgroup and adjusted analyses
Harms	19	Important adverse events/side effects
Discussion		
Interpretation	20	Interpretation consistent with results and external evidence
Generalizability	21	Discuss generalizability (external validity)
Evidence	22	Discuss results in context of current evidence
Other Information		
Registration	23	Trial registration number and registry name
Protocol	24	Where full trial protocol can be accessed
Funding	25	Sources of funding and role of funders

Table 2: Characteristics of the studies

Country	Year	Type	N	Age	Mammography (MG)					MRI					CESM					Ultrasound				
					Multifocal	Unifocal	Spec	Sens	AUC	Multifocal	Unifocal	Spec	Sens	AUC	Multifocal	Unifocal	Spec	Sens	AUC	Multifocal	Unifocal	Spec	Sens	AUC
Japan	2022	Retro	54	48.7	-	-	-	-	-	183	-	33.4	98.6	95.7	178	-	63.6	98.3	96.3	-	-	-	-	-
Germany	2022	Prosp	118	48.5	20	-	-	-	-	-	-	42	99	-	-	-	50	10	-	-	-	76	97	-
Solvenia	2021	Retro	71	65	16	2	84.2	84.2	-	36	2	93.9	90.5	-	32	3	98.1	84.2	-	-	-	-	-	-
Solvenia	2021	Retro	60	62	17	1	95.8	50	-	31	2	91.3	91.2	-	29	1	96.2	85.3	-	-	-	-	-	-
Australia	2020	Cohort	159	62	10	34	97.1	23.1	-	4	32	91.4	76.9	-	-	-	-	-	-	-	-	-	-	-
Germany	2019	Retro	34	58	3	20	79.6	81.5	-	2	12	83.7	90.8	-	-	-	-	-	-	-	-	-	-	-

MG: Mammography; CESM: Contrast-Enhanced Spectral Mammography; MRI: Magnetic Resonance Imaging; Retro: Retrospective; Prosp: Prospective; Spec: Specificity (%); Sens: Sensitivity (%);AUC: Area Under Curve; -: Not reported