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Comparison Identifying Imaging Diagnosis Methods in Multifocal and Multicentric Breast Cancer Patients

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Abstract **Background:** Breast cancer is the second important cause of cancer-related adults that mostly affects female. There are different diagnostic methods for detecting breast lesions, the specificity and sensitivity of which are very important in identifying multifocal lesions, since very few studies have been done on this issue so far, this study was done with the aims to Comparison identifying imaging diagnosis methods in multifocal and multicentric breast cancer patients. **Materials and Methods:** The current systematic review was done based on the Strengthening the Reporting of Observationally Studies in Epidemiology and Meta-Analyses of Observational Studies in Epidemiology. The primary keywords were published in reliable databases such as Pubmed , Elsevier, SID, Wiley in English were searched until the end of 2022. Two authors independently examined the articles in terms of data extraction, inclusion criteria, and quality assessment of the articles. **Results:** The age range from 496 samples was 57.3. Using the results of 5 published articles for MG and CESM, the overall specificity and sensitivity were 89% and 85% , respectively and for MRI, the overall specificity and sensitivity were 81% and 85% , respectively. **Conclusion:** The MRI method is the most sensitive tool for diagnosing BC in patients, but if a combination of new methods is used together, we will definitely achieve better results.

Key Words breast cancer, multifocal, multicentric, imaging diagnosis

1. Introduction

Breast cancer (BC) is the second important cause of cancer-related death a leading cause of death in female adults that mostly affects females [1]. In 2021, 280,000 cases of BC were diagnosed in the US, leading to over 43,000 deaths [2]. The BC prevalence in Iranian women is nearly 120 per 100000 people with an age-standardized rate of 33.21 per 100 000 people. The BC peak age is in the 4th and 5th decades [3].

The selection of systemic and local treatment for patients with BC depends on factors such as tissue type and tumor grade, primary tumor progress, lymph node status, presence of metastasis, and the status of tumor markers at the time of diagnosis [3], [4]. The Multicentric and Multifocality of neoplastic lesions are decisive factors in choosing the type of treatment [5], [6]. When there are 2 or more foci in one-quarter of the breast, it is called multi-focal type lesions, and when foci occur in different quadrants, it is called multi-focal type lesions [7], [8]. The prevalence of multicentric and multifocal BC varies highly in the literature (6 - 60%) [9]. The main imaging modalities are magnetic resonance imaging (MRI), ultrasound (US), mammogram (MGM), and. Each modality has specific weaknesses and strengths in breast tumor evaluation [10], [11]. Thus, multifocal (MF) and multicentric (MC) BC cases are increasing [12].

Among different attainable imaging techniques, mammography can detect neoplastic lesions in the breast as an inexpensive, reproducible, and available method [13]. Mammography (MG) sensitivity is associated with the breast structure. It reduces and ranges between 45% and about 60% in breasts, with a predominance of glandular tissue [14]. Particularly in women with dense breasts and young women, US is superior to MG, and differentiation between cysts and solid tumors is easier [15]. The specificity and sensitivity of US or MG are higher if US and MG are combined [16].

MRI, MG, extended with diffusion imaging (DWI/ADC) has a high level of septicity and sensitivity (over 85%) (18-20). In Akbari et al.'s study, the high sensitivity of MRI in identifying benign and malignant lesions is emphasized. Nonetheless, it has some limitations, such as false-positive results, leading to more aggressive treatment and management than necessary [17]. Opposite to MG, which under-

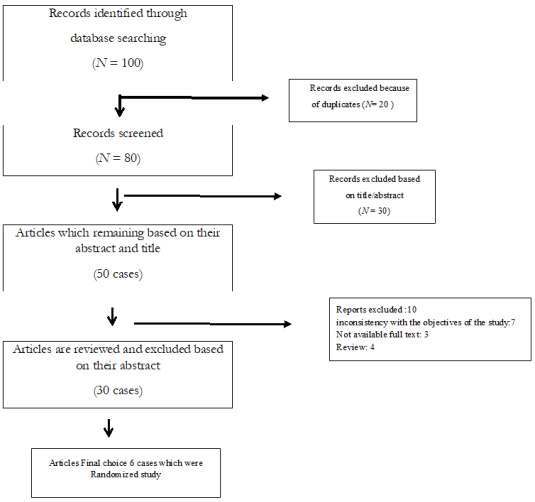


Figure 1: Flow of information through the various phases of the systematic review

estimates the tumor size leading to incomplete resection, MRI is highly precise for the local extent of BC, carcinoma region, and tumor size. Also, some foci and carcinomas can be observed merely on breast MRI images [18].

Contrast-enhanced spectral mammography (CESM) as a novel recently developed technique was accepted by the FDA for clinical application in the US in 2011 [19]. It works based on imaging of tumor neoangiogenesis using a contrast compound (chelated iodine-associated X-ray contrast compound) [20]. The CESM sensitivity in diagnosing BC is over 90% [21]. As a result, in the present meta-analysis study, we had a comparison identifying imaging diagnosis methods such as ultrasound, MG, and MRI methods that were investigated for patients with multifocal and multicentric BC.

2. Methods

The current systematic review was done based on the Strengthening the Reporting of Observationally Studies in Epidemiology (STROBE) and Meta-Analyses of Observational Studies in Epidemiology (MOOSE) instructions for the review of analytical observational articles (cohort and case-control) [22], [23].

A. Search strategy

All original studies were searched in Web of Science, Medline (PubMed), EMBASE, Scopus, and CINHAL from January 2017 to June 2022 with no language limitation. The keywords were BC, MRI, MG, US, and Multifocal. The included studies were observational studies on humans.

The initial search findings were reviewed, leading to the removal of some papers. Exclusion and inclusion criteria were set by two investigators separately (Figure 1).

B. Eligibility criteria

(1) The original article, (2) human population, (3) Studies that only examined multifocal lesions in BC patients, (4) Studies that investigated the sensitivity and specificity of the methods considered in this study in multifocal lesions. (5) The detection power in the tumor size was not considered, only in the efficiency studies, the sensitivity and specificity of the method were the criteria for selecting the articles. Studies that investigated lesions other than multifocal in BC patients and did not report the sensitivity and specificity of the methods in identifying multifocal lesions were excluded from the study.

C. Search Outcome

We detected 100 articles in databases. Duplicates (N = 20) were excluded. Based on the selection criteria, 80 abstracts were screened and 30 Records were excluded based on title/abstract. We detected 50 relevant published articles but after reading their full texts, 30 cases were excluded because of Reports excluded (n = 10), inconsistency with the objectives of the study (n = 7), not available full text (n = 3), and Review article (n = 4). Finally, 6 articles remained which include 1 cohort and 4 retrospective and 1 prospective (Figure 1).

The Quality Assessment Tool [24] assessed the quality of the quantitative studies. Using the STROBE list (Table 1), the quality of 30 articles was evaluated, and at least six appropriate articles were included. The examination of full-text articles was done before data extraction. The used list is the version developed based on an instrument designed by the Effective Public Health Practice Project [24].

The articles were evaluated independently by two researchers who evaluated the possible disagreement, and when no agreement was made, a third author (LS) assessed the study. Data extraction was done by two independent matched reviewers based on a uniform Excel sheet. A checklist was applied to extract data, like (1) publication year, (2) author, (3) country (4) type of study, (5) Number sample, (6) age (7), Assessment (N) (8) MG, (9) MRI, (10) CESM and (11) US. Data has been assembled in Table 2.

D. 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.

Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed
		(c) Explain how missing data were addressed
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Cohort study—Summaries follow-up time (eg, average and total amount)
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summaries key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Table 1: STROBE Statement—checklist of items that should be included in reports of observational studies

3. Results

Overall, 6 studies were analyzed and their characteristics are shown in Table 2. All patients in this study underwent imaging examination prior to operation to screen those suspected of having multifocal/multicentric BCs. The final diagnosis was made considering pathology, so all studies had a histopathologic examination and were cross-sectional, originating in China (N = 1), Italy (N = 2), Poland (N = 2), and Nederland (N = 1) .1 of these studies were cohort studies and 4 were retrospective studies and 1 was prospective. The age range from (pooled data) 496 samples was 57.3. Statically designed studies for comparing imaging methods with the histopathologic examination were as fellow: 4 studies MRI and CESM (29-32),4 studies MG and MRI (31-34),1 study MG, MRI, and CESM (29), and 1 study MRI, CESM, and US (30). And finally, Feng's (29) US results had been excluded from analyses because None of the other studies had investigated this issue.

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):

Using the results of 5 published articles for MG and CESM, the overall specificity and sensitivity were 89% (95% CI: 84-93) and 85% (95% CI: 81-88), respectively (Figure 1). The pooled positive and negative likelihood ratios (LRs) were respectively 5.47 (95% CI: 2.53-11.83) and 0.24 (95% CI: 0.12-0.48) (Figure 2). Pooled diagnostic odds ratios (dOR) were high, at 49.90 (95% CI: 17.76-94.21) (Figure 3). The AUC for MG and CESM was 0.94 (Figure 4).

Measurements of the overall accuracy of MRI compared with a histopathologic examination in the detection of multifocal and multicentric breast cancer (MMBC):

Using the results of 5 published articles for MRI, the overall specificity and sensitivity were 81% (95% CI: 73-87) and 85% (95% CI: 81-88), respectively (Figure 5). The pooled positive and negative likelihood ratios (LRs) were also 4.67 (95% CI: 1.81-12.09) and 0.07 (95% CI: 0.03-0.19), respectively (Figure 6). The pooled diagnostic odds ratios (dOR) were high and were 91.70 (95% CI: 37.59-223.69) (Figure 7). The AUC for MRI was 0.96 (Figure 8).

4. Discussion

BC is a very common reason for death in adult females (35,36) with a prevalence of 1 out of 8 women and a risk of developing during the whole lifetime of 12.5% (37,38). As a result, considering the high prevalence of BC, examining diagnostic methods is of great importance. Following the development of pathology and imaging, there has been an increase in the detection rates of MC and MF BCs [25]. The main aim of this meta-analysis study was to compare diagnostic methods in identifying multifocal/multicentric lesions in BC patients.

Most recent studies have considered comparing the specificity and sensitivity of MRI and CESM for the detection of

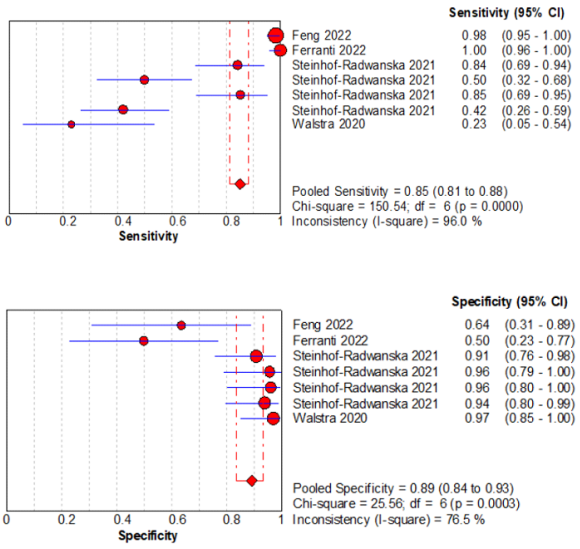


Figure 2: Forrest plot of sensitivity and specificity of mammography and contrast-enhanced spectral mammography (CESM) in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

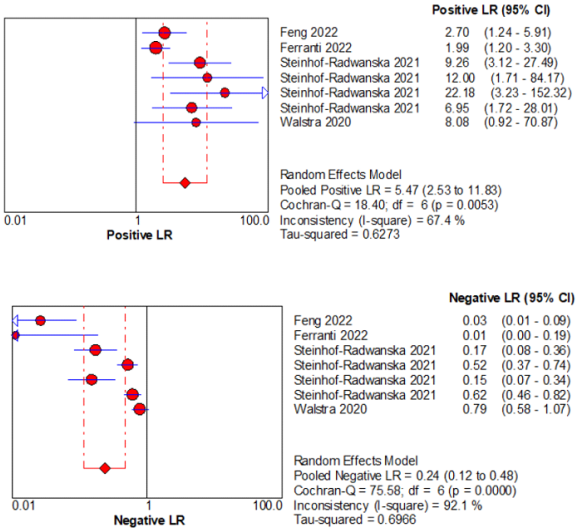


Figure 3: Forrest plot of positive and negative likelihood ratios of mammography and contrast-enhanced spectral mammography (CESM) in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

N			Type of study	Number sample	Age	Assessment (N)						%																				
Author					(Mean)	MG (multifocal)	MG(unifocal	CESM(multifocal	CESM(unifocal	MRI(multifocal)	MRI(unifocal)	Mammography					MRI					CESM					Sonography				
												Specificity	Sensitivity	PPV	NPV	AUC	Specificity	Sensitivity	PPV	NPV	AUC	Specificity	Sensitivity	PPV	NPV	AUC	Specificity	Sensitivity	PPV	NPV	AUC
Feng(29)	2022	China	retrospective	54	48.7	-	-	178	-	183	-						36.4	99.4	-	-	95.7	63.6	98.3	-	-	96.3					
Ferranti(30)	For Country 2022	Italy	Prospective	118	48.5	Multifocal 20											47	99	88	90	-	50	10	92	100	-	76	97	-	-	-
Steinhof R- (31)	2021	Poland	retrospective	71	65	16	2	32	3	36	2	84.2	84.2	88.8	58.5	-	93.9	94.7	94.7	93.9	-	90.9	84.2	91.4	83.3	-					
Steinhof-R (32)	2021	Poland	retrospective	60	62	17	1	29	1	31	2	95.8	50	94.4	57.5	-	92.31	91.18	93.94	88.89	-	96.15	85.29	96.67	83.3	-					
Walstra (33)	2020	Netherland	Cohort	159	62	10	34	-	-	3	32	97.1	23.1	25	77.3		91.4	76.9	76.9	91.4	-										
Petrillo 34)	2019	Italy	retrospective	34	58	3	20	-	-	1	12	79.6	81.5	84.1	76.5	-	83.7	90.8	88.1	87.2	-										

Table 2: Characteristics of the studies

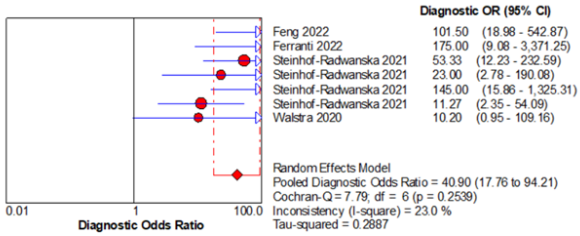


Figure 4: Forrest plot of diagnostic odds ratios (dOR) of mammography and contrast-enhanced spectral mammography (CESM) in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

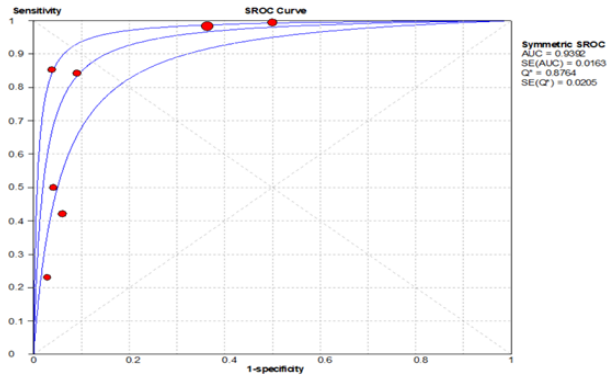
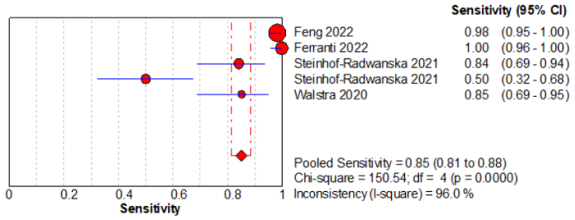


Figure 5: Receiver operating characteristics curve for all comparative studies between mammography and contrast-enhanced spectral mammography (CESM) and histopathologic examination for the detection of multifocal and multicentric breast cancer (MMBC)

singular BC areas and omit additional neoplastic areas affecting the scope of surgical procedures [26], The occurrence of multicentric and multifocal BCs is between 9 and 75% [27], which differs because of using various imaging modalities or the histopathological sample collection method. Tot et al. [28] reported that 40% of BC showed simple (unifocal) subgross appearance, whereas 60% showed complex appearance with diffuse or multifocal components. Steinhof-Radwań ska et al. (2021) confirmed multi-centrality and multifocality of the lesions in 38 cases (38/71, which is 53.5% of all the tested cases) [29].

CESM offers a low-energy mammogram (LE-MG) and is a combined subtracted mammogram (RSM) following



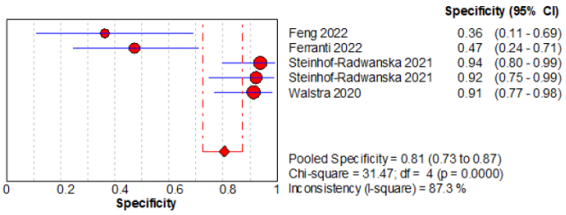


Figure 6: Forrest plot of sensitivity and specificity of MRI in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

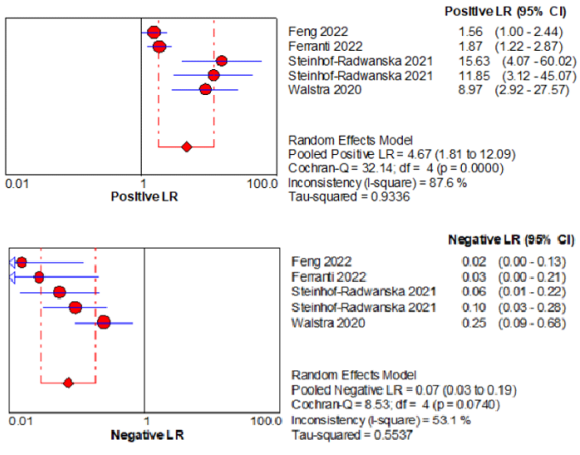


Figure 7: Forrest plot of positive and negative likelihood ratios of MRI in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

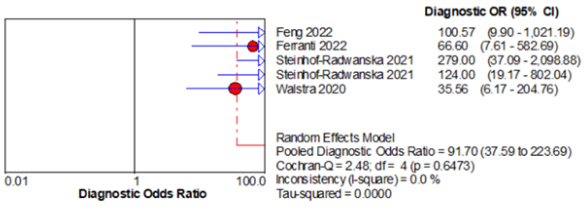


Figure 8: Forrest plot of diagnostic odds ratios (dOR) of MRI in the detection of multifocal and multicentric breast cancer (MMBC), confirmed by histopathologic examination

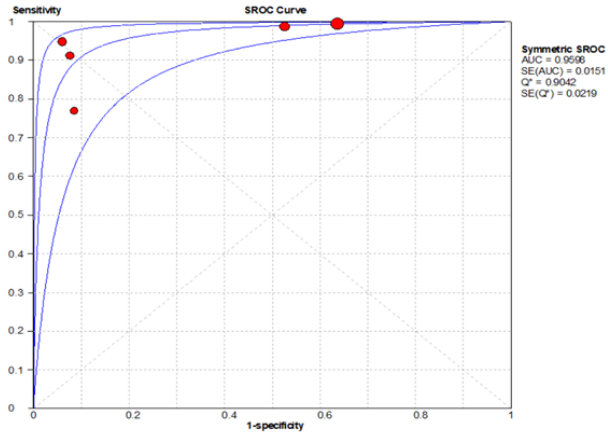


Figure 9: Receiver operating characteristics curve for all comparative studies between MRI and histopathologic examination for the detection of multifocal and multicentric breast cancer (MMBC)

intravenously administration of iodinated contrast medium images in the examination session within a short duration [28]. CESM offers a morphologic assessment similar to routine digital MG and simultaneous tumor neovascularity evaluation as an indicator of malignancy. CESM exhibited an extremely high sensitivity to BC [30], [31].

In our study, the overall specificity and sensitivity of mammography (CESM) were respectively 89% (95% CI: 84-93) and 85% (95% CI: 81-88) . In Taylor et al.'s study (2023), the sensitivity of the CEM method was reported to be up to 95% to identify breast lesions [32]. Tagliafico et al. [33] in their meta-analysis, declared a pooled sensitivity of 98% for CESM to detect BC, including over 900 lesions.

MRI method is widely used in BC patients because of its high specificity and sensitivity [34]. In such patients, in contrast to MG, MRI provides a doubled or even tripled sensitivity. MRI is helpful in patients who have lobular cancer and case with enhanced breast density. In such female patients, the MG efficacy is underestimated, and neoplastic lesions can be missed. Women who have high breast density can provide with systematic abbreviated MRI for screening [35].

In our study, the overall specificity and sensitivity of the MRI method were 81% (95% CI: 73-87) and 85% (95% CI: 81-88), respectively. In the study of Ahmed (2023), in the examination of breast lesions in patients, she introduced the MRI method as a suitable method for multifocal lesions [36]. In the study of Farghadani et al. (2021), the Specificity and accuracy of MRI were reported as 93.02 and 93.75%, respectively [37].

In the study of Feng [38] and Ferranti [39], the highest percentage was reported for the sensitivity of the MRI method. In the study of Akbari et al. (2019) with the aim of evaluating the diagnostic capabilities of different methods of BC, the sensitivity, accuracy, and specificity were 24.7%, 40.2%, specificity 82%, and the sensitivity, accuracy, and specificity of ultrasound were 26%, respectively. 41.44, a specificity of 58.2% was reported [40].

Generally, CESM can detect multifocal malignancies and its sensitivity has been widely reported as comparable to MRI breast with superior specificity [41], [42]. Lee-Felker et al. declared an equal sensitivity for MRI and CESM (respectively 94% vs. 99%,) to detect index lesions as well as higher sensitivity for CESM than MRI (100% vs 91%, respectively) to detect secondary cancers [43].

Generally, CESM can detect multifocal malignancies, and its sensitivity has been reported comparable to MRI breast and with superior specificity [41], [42], Lee-Felker et al. reported that CESM and MRI have similar sensitivity (94% vs 99%, respectively) in detecting index lesions and higher sensitivity of CESM (100% vs. 91%, respectively) in detecting secondary cancers [43].

Our study articles showed that in MG and CESM, the overall sensitivity and specificity were 85% and 89% (84-93), and on the other hand, in MRI, the overall sensitivity and specificity were 85% and 81%. But Radwanska's study suggested that MRI and CESM provide better results in the diagnosis of MFMCC than MG, significantly affecting surgical decisions (31). Of course, the MRI method is the most sensitive tool for diagnosing BC in patients, but if a combination of new methods is used together, we will definitely achieve better results [44], [45].

5. Limitation

Precise breast imaging as well as visualization of additional cancer foci possibly decreases the postoperative breast radiotherapy quantity following conserving treatment in many patients. This procedure reduces the number of complications in patients, and consequently, treatment costs. Most of the studies compared the examined diagnostic methods on breast lesions in general, and few studies focused only on multifocal lesions, and the ultrasound method was mostly used to detect the mass by considering its size. Most studies of new methods such as CESM and its combination with MRI were investigated in the diagnosis of multifocal lesions.

We suggest that radiologists who wish to report on MG should be trained in this particular subject, and breast surgeons should be fully trained in breast ultrasound examination, and according to the results of this study, use the CEsM

method and even combine it with MRi can be very effective in diagnosing multifocal lesions.

Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

References

[1] Haghighi, F., Naseh, G., Mohammadifard, M., & Abdollahi, N. (2017). Comparison of mammography and ultrasonography findings with pathology results in patients with breast cancer in Birjand, Iran. *Electronic Physician, 9*(10), 5494-5498.

[2] Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. CA: *A Cancer Journal for Clinicians, 68*(1), 7-30.

[3] Akbari, M. E., Khayamzadeh, M., Khoushnevis, S. J., Nafisi, N., & Akbari, A. (2008). Five and ten years survival in breast cancer patients mastectomies vs. breast conserving surgeries personal experience. *Int J Cancer Manag, 1*(2), e80407.

[4] Nash, R., Goodman, M., Lin, C. C., Freedman, R. A., Dominici, L. S., Ward, K., & Jemal, A. (2017). State variation in the receipt of a contralateral prophylactic mastectomy among women who received a diagnosis of invasive unilateral early-stage breast cancer in the United States, 2004-2012. *JAMA Surgery, 152*(7), 648-657.

[5] Veronesi, U., Cascinelli, N., Mariani, L., Greco, M., Saccozzi, R., Luini, A., ... & Marubini, E. (2002). Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New England Journal of Medicine, 347*(16), 1227-1232.

[6] Hartmann-Johnsen, O. J., Kåresen, R., Schlichting, E., & Nygård, J. F. (2017). Better survival after breast-conserving therapy compared to mastectomy when axillary node status is positive in early-stage breast cancer: a registry-based follow-up study of 6387 Norwegian women participating in screening, primarily operated between 1998 and 2009. *World Journal of Surgical Oncology, 15*, 1-10.

[7] Salgado, R., Aftimos, P., Sotiriou, C., & Desmedt, C. (2015, April). Evolving paradigms in multifocal breast cancer. In *Seminars in Cancer Biology* (Vol. 31, pp. 111-118). Academic Press.

[8] Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershenwald, J. E., Brookland, R. K., ... & Winchester, D. P. (2017). The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: A Cancer Journal for Clinicians, 67*(2), 93-99.

[9] Masannat, Y. A., Agrawal, A., Maraqa, L., Fuller, M., Down, S. K., Tang, S. S. K., ... & Heys, S. D. (2020). Multifocal and multicentric breast cancer, is it time to think again?. *The Annals of The Royal College of Surgeons of England, 102*(1), 62-66.

[10] Mousa, D. A., Ryan, E. A., Mello-Thoms, C., & Brennan, P. C. (2014). What effect does mammographic breast density have on lesion detection in digital mammography?. *Clinical Radiology, 69*(4), 333-341.

[11] Sardanelli, F., Giuseppetti, G. M., Panizza, P., Bazzocchi, M., Fausto, A., Simonetti, G., ... & Del Maschio, A. (2004). Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in fatty and dense breasts using the whole-breast pathologic examination as a gold standard. *American Journal of Roentgenology, 183*(4), 1149-1157.

[12] Girardi, V., Carbognin, G., Camera, L., Baglio, I., Bucci, A., Bonetti, F., & Mucelli, R. P. (2011). Multifocal, multicentric and contralateral breast cancers: breast MR imaging in the preoperative evaluation of patients with newly diagnosed breast cancer. *La Radiologia Mdica, 116*(8), 1226-1238.

[13] Farshid, G. (2017). Routine reporting of mammographic density from screening mammograms. *ANZ Journal of Surgery, 87*(12), 965-967.

[14] Yadav, P., & Chauhan, S. (2018). Effectivity of combined diffusion-weighted imaging and contrast-enhanced MRI in malignant and benign breast lesions. *Polish Journal of Radiology, 83*, e82.

[15] Farina, R., & Sparano, A. (2012). Errors in sonography. *Errors in Radiology,* 79-85.

[16] Lai, H. W., Chen, D. R., Wu, Y. C., Chen, C. J., Lee, C. W., Kuo, S. J., ... & Wu, H. K. (2015). Comparison of the diagnostic accuracy of magnetic resonance imaging with sonography in the prediction of breast cancer tumor size: a concordance analysis with histopathologically determined tumor size. *Annals of Surgical Oncology, 22*, 3816-3823.

[17] Mann, R. M., Veltman, J., Barentsz, J. O., Wobbes, T., Blickman, J. G., & Boetes, C. (2008). The value of MRI compared to mammography in the assessment of tumour extent in invasive lobular carcinoma of the breast. *European Journal of Surgical Oncology (EJSO), 34*(2), 135-142.

[18] Iacconi, C., Galman, L., Zheng, J., Sacchini, V., Sutton, E. J., Dershaw, D., & Morris, E. A. (2016). Multicentric cancer detected at breast MR imaging and not at mammography: important or not?. *Radiology, 279*(2), 378-384.

[19] Jochelson, M. S., & Lobbes, M. B. (2021). Contrast-enhanced mammography: state of the art. *Radiology, 299*(1), 36-48.

[20] Bhimani, C., Matta, D., Roth, R. G., Liao, L., Tinney, E., Brill, K., & Germaine, P. (2017). Contrast-enhanced spectral mammography: technique, indications, and clinical applications. *Academic Radiology, 24*(1), 84-88.

[21] Steinhof-Radwańska, K., Grażyńska, A., Barczyk-Gutkowska, A., Kajor, M., Powązka, P., Lorek, A., ... & Pilch-Kowalczyk, J. (2020). The new method, the old problem–role of contrast-enhanced spectral mammography in the diagnosis of breast cancer among Polish women. *Polish Journal of Radiology, 85*, e381.

[22] Hassold, T., Abruzzo, M., Adkins, K., Griffin, D., Merrill, M., Millie, E., ... & Zaragoza, M. (1996). Human aneuploidy: incidence, origin, and etiology. *Environmental and Molecular Mutagenesis, 28*(3), 167-175.

[23] Ramasamy, R., Chiba, K., Butler, P., & Lamb, D. J. (2015). Male biological clock: a critical analysis of advanced paternal age. *Fertility and Sterility, 103*(6), 1402-1406.

[24] Thomas, B. H., Ciliska, D., Dobbins, M., & Micucci, S. (2004). A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews on Evidence-Based Nursing, 1*(3), 176-184.

[25] Hlawatsch, A., Teifke, A., Schmidt, M., & Thelen, M. (2002). Preoperative assessment of breast cancer: sonography versus MR imaging. *American Journal of Roentgenology, 179*(6), 1493-1501.

[26] Li, L., Roth, R., Germaine, P., Ren, S., Lee, M., Hunter, K., ... & Liao, L. (2017). Contrast-enhanced spectral mammography (CESM) versus breast magnetic resonance imaging (MRI): a retrospective comparison in 66 breast lesions. *Diagnostic and Interventional Imaging, 98*(2), 113-123.

[27] Bakhtavar, K., Saran, M., Behzadifar, M., & Farsi, M. (2017). Magnetic resonance mammography in comparison with mammography in the discovery of multifocal, multicentric and bilateral lesions of breast cancer. *Electronic physician, 9*(8), 5083.

[28] Tot, T., Gere, M., Hofmeyer, S., Bauer, A., & Pellas, U. (2020). The subgross morphology of breast carcinomas: A single-institution series of 2033 consecutive cases documented in large-format histology slides. *Virchows Archiv, 476*(3), 373-381.

[29] Steinhof-Radwańska, K., Lorek, A., Holecki, M., Barczyk-Gutkowska, A., Grażyńska, A., Szczudło-Chraścina, J., ... & Gisterek, I. (2021). Multifocality and multicentrality in breast cancer: comparison of the efficiency of mammography, contrast-enhanced spectral mammography, and magnetic resonance imaging in a group of patients with primarily operable breast cancer. *Current Oncology, 28*(5), 4016-4030.

[30] Gilbert, F. J., & Pinker-Domenig, K. (2019). Diagnosis and staging of breast cancer: when and how to use mammography, tomosynthesis, ultrasound, contrast-enhanced mammography, and magnetic resonance imaging. Diseases of the Chest, Breast, Heart and Vessels 2019-2022: *Diagnostic and Interventional Imaging,* 155-166.

[31] Li, L., Roth, R., Germaine, P., Ren, S., Lee, M., Hunter, K., ... & Liao, L. (2017). Contrast-enhanced spectral mammography (CESM) versus breast magnetic resonance imaging (MRI): a retrospective comparison in 66 breast lesions. *Diagnostic and Interventional Imaging, 98*(2), 113-123.

[32] Taylor, D. B., Burrows, S., Saunders, C. M., Parizel, P. M., & Ives, A. (2023). Contrast-enhanced mammography (CEM) versus MRI for breast cancer staging: detection of additional malignant lesions not seen on conventional imaging. *European Radiology Experimental, 7*(1), 8.

[33] Tagliafico, A. S., Bignotti, B., Rossi, F., Signori, A., Sormani, M. P., Valdora, F., ... & Houssami, N. (2016). Diagnostic performance of contrast-enhanced spectral mammography: systematic review and meta-analysis. *The Breast, 28*, 13-19.

[34] Azab, E. A., & Ibrahim, M. E. (2018). Diffusion weighted (DW) MRI role in characterization of breast lesions using absolute and normalized ADC values. *The Egyptian Journal of Radiology and Nuclear Medicine, 49*(2), 564-570.

[35] Yadav, P., & Chauhan, S. (2018). Effectivity of combined diffusion-weighted imaging and contrast-enhanced MRI in malignant and benign breast lesions. *Polish Journal of Radiology, 83*, e82.

[36] Ahmed, A. M., Zaky, M. M., Hegazy, M. A., & Zaky, S. M. (2023). The Role of Magnetic Resonance Imaging in Surgical Decision Making of Suspicious Breast Lesions in Dense Breast. *The Egyptian Journal of Hospital Medicine, 90*(2), 2556-2562.

[37] Farghadani, M., Barikbin, R., Rezaei, M. H., Hekmatnia, A., Aalinezhad, M., & Zare, H. (2021). Differentiating solid breast masses: comparison of the diagnostic efficacy of shear wave elastography and magnetic resonance imaging. *Diagnosis, 8*(3), 382-387.

[38] .Feng, L., Sheng, L., Zhang, L., Li, N., & Xie, Y. (2022). Comparison of Contrast-Enhanced Spectral Mammography and Contrast-Enhanced MRI in Screening Multifocal and Multicentric Lesions in Breast Cancer Patients. *Contrast Media & Molecular Imaging, 2022*(1), 4224701.

[39] Ferranti, F. R., Vasselli, F., Barba, M., Sperati, F., Terrenato, I., Graziano, F., ... & Vidiri, A. (2022). Diagnostic Accuracy of contrast-enhanced, spectral mammography (CESM) and 3T magnetic resonance compared to full-field digital mammography plus ultrasound in breast lesions: results of a (pilot) open-label, single-centre prospective study. *Cancers, 14*(5), 1351.

[40] RezaHaghighatkhah, H., & EsmaeilAkbari, M. Evaluation of Clinical Assessment, Mammography, and Ultrasonography in Diagnosis of Benign and Malignant Breast Lesions and Determining Their Cost-Effectiveness. *International Journal of Cancer Management, 12*(9), e69683.

[41] Neri, A., Marrelli, D., Megha, T., Bettarini, F., Tacchini, D., De Franco, L., & Roviello, F. (2015). Clinical significance of multifocal and multicentric breast cancers and choice of surgical treatment: a retrospective study on a series of 1158 cases. *BMC Surgery, 15*, 1-10.

[42] Kadioğlu, H., Özbaş, S., Akcan, A., Soyder, A., Soylu, L., Koçak, S., ... & Müslümanoğlu, M. (2014). Comparison of the histopathology and prognosis of bilateral versus unilateral multifocal multicentric breast cancers. *World Journal of Surgical Oncology, 12*, 1-9.

[43] Lee-Felker, S. A., Tekchandani, L., Thomas, M., Gupta, E., Andrews-Tang, D., Roth, A., ... & Rahbar, G. (2017). Newly diagnosed breast cancer: comparison of contrast-enhanced spectral mammography and breast MR imaging in the evaluation of extent of disease. *Radiology, 285*(2), 389-400.

[44] Xing, D., Lv, Y., Sun, B., Xie, H., Dong, J., Hao, C., ... & Chi, X. (2019). Diagnostic value of contrast-enhanced spectral mammography in comparison to magnetic resonance imaging in breast lesions. *Journal of Computer Assisted Tomography, 43*(2), 245-251.

[45] Yılmaz, E., Sarı, O., Yılmaz, A., Ucar, N., Aslan, A., Inan, I., & Parlakkılıc, U. T. (2018). Diffusion-weighted imaging for the discrimination of benign and malignant breast masses; utility of ADC and relative ADC. *Journal of the Belgian Society of Radiology, 102*(1).