RESEARCH LETTER

Efficacy of mammography and contrast-enhanced spectral mammography in women with multifocal and multicentric breast cancer

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Introduction Breast cancer is the most common malignancy in women worldwide.[1] Multifocality and multicentricity of the neoplastic lesions are the decisive factors determining the surgical choice between breast-conserving therapy and mastectomy. Among many imaging methods available, mammography is the best modality for detecting neoplastic foci in breasts due to its low cost and wide accessibility.

Contrast-enhanced spectral mammography (CESM) is a new technique which has been intensely developed over the last few years. The technology involves the use of a chelated iodine-based X-ray contrast agent to visualize tumor neoangiogenesis.[2] It provides morphological information available in conventional mammography, with additional visualization of the breast areas that exhibit enhanced uptake of the contrast agent, most commonly related to neoangiogenesis. The sensitivity of CESM is estimated at 90%.[3]

In the present paper, multifocal and multicentric cancers were commonly referred to as MFMCCs.

The objective of the study was to assess the usefulness of mammography and CESM for visualizing other (additional) cancer foci in women diagnosed with breast cancer, before surgical treatment. We also aimed to evaluate impact of the imaging modality on treatment decision.

Patients and methods This was a retrospective analysis of 71 medical records of patients with initially operable breast cancer who had been treated from January 2013 to April 2019 at the Department of Oncological Surgery, University Clinical Center prof. K. Gibiński of the Medical University of Silesia in Katowice, Poland.

Diagnostic workup was carried out in accordance with Polish and European standards. The gold standards for each patient were mammography, ultrasonography (of the breast, regional lymph nodes, and abdomen), core needle biopsy, and chest X-ray.

The inclusion criteria comprised diagnosed breast cancer (confirmed with core needle biopsy) and a complete set of imaging examinations (digital mammography and CESM). Magnetic resonance imaging (MRI) was an additional inclusion criterion; however, it was not part of in the present analysis. Before qualification for CESM, all patients completed a questionnaire designed to exclude women who were pregnant or allergic to contrast agents. Patients with estimated glomerular filtration rate values of less than 30 ml/min/1.73 m^2 were also excluded.

Ethics committee approval was not required due to the retrospective design of the study and the fact that it was not a medical experiment (Bioethics Commission decision no. PCN/0022/KB/189/20).

Imaging procedures All CESM examinations were performed at our center. Mammography examinations were carried out in external medical facilities (in most cases as a screening test), but they were verified by 2 consultant radiologists from our center.

As outlined in previous papers,[3,4] all CESM examinations were carried out on a digital mammography device dedicated to performing dual-energy CESM acquisitions (SenoBright, GE Healthcare, Waukesha, Wisconsin, United States). An intravenous nonionic contrast agent in the amount

TABLE 1 Efficacy of mammography and contrast-enhanced spectral mammography in detecting multifocal/multicentric breast cancers confirmed with postoperative histological examination

Assessment		Histopathological examination		Predictive value, % (95% CI)
		Multifocal	Unifocal	
Mammography	Multifocal	16	2	PPV, 88.8 (65.29–98.62)
	Unifocal	22	31	NPV, 58.5 (44.13–71.86)
Sensitivity and specificity, % (95% CI)		Sensitivity, 42.1 (26.31–59.18)	Specificity, 93.9 (79.77–99.26)	–
CESM	Multifocal	32	3	PPV, 91.4 (76.94–98.2)
	Unifocal	6	30	NPV, 83.3 (67.19–93.63)
Sensitivity and specificity, % (95% CI)		Sensitivity, 84.2 (68.75–93.98)	Specificity, 90.9 (75.67–98.08)	–

Abbreviations: CESM, contrast-enhanced spectral mammography; NPV, negative predictive value; PPV, positive predictive value

of 1.5 ml per 1 kg of body mass was injected using a power injector at a rate of 3 ml/s. Specific image processing of low-energy and high-energy images was carried out to obtain subtraction images highlighting contrast enhancement and suppressing structured noise due to fibroglandular breast tissue. The total examination time was usually 10 minutes.

The mammography and CESM images were assessed using the Breast ImagingReporting and Data System (BI-RADS) scale.[5] Lesions that had already been confirmed as malignant with core needle biopsy were classified as BI-RADS 6, while additional foci suspected of multifocal or multicentric neoplastic process were categorized as BI-RADS 4 or 5.

Surgical treatment In the analyzed group of 71 patients, breast-conserving surgeries were performed in 40 women (56%) and different types of mastectomy in 31 (44%).

Statistical analysis Age distribution of patients was analyzed and tested for normality using the Kolmogorov–Smirnov test. Median, minimum, and maximum values in the sample were determined for the variable in question. Subsequently, contingency tables were constructed for the results of MFMCC detectability for both diagnostic methods under analysis as compared with histopathological examination. The analysis of these tables served as a basis for calculating the values of sensitivity, specificity as well as negative and positive predictive values (NPV and PPV) for mammography and CESM. Proportional 95% CIs for sensitivity, specificity, and predictive values were shown. Intervals were calculated using the Clopper–Pearson method. The diagnostic accuracy of both imaging methods were used as a basis for determining the rate of decision change regarding the treatment procedure. The data were analyzed using Excel (Microsoft, Redmond, Washington, United States) and the STATISTICA software (StatSoft Inc, Tulsa, Oklahoma, United States).

Results The median age of patients was 65 years (range, 29–91 years). The consistency of histological examination with the results of digital mammography and CESM in terms of detecting MFMCC is presented in **TABLE 1**.

The sensitivity of mammography in detecting MFMCC was 42.1% (95% CI, 26.31–59.18), while the specificity, PPV, and NPV of this method were 93.9% (95% CI, 79.77–99.26), 88.8%, and 58.5%, respectively. For CESM, the sensitivity was 84.2% (95% CI, 68.75–93.98), whereas the specificity, PVV, and NPV amounted to 90.9% (95% CI, 75.67–98.08), 91.4%, and 83.3%, respectively.

Based on the results of mammography, 53 breast-conserving surgeries were planned in the study group. Contrast-enhanced spectral mammography detected 13 cases of MFMCCs, which resulted in a change of the planned treatment to different types of mastectomy. The rate of change regarding treatment decision was 24%.

Among the 13 patients in whom MFMCCs were detected by CESM, the histopathological examination confirmed the diagnosis in 12 women (92.3%). In a single case, the obtained results were false positive, but preoperative core needle biopsy revealed atypical ductal hyperplasia.

Discussion Multifocal and/or multicentric neoplastic process is diagnosed in approximately 5% to 11% of female patients.[6] In our analysis, these types of lesions were confirmed in 38 women (53.5%). These results are alarming, but they are compatible with those obtained by other researchers who noticed the same trend. Tot et al[7] found that 60% of breast carcinomas had complex morphology manifested by multifocal or diffuse components.

Surgery plays a fundamental role in breast cancer therapy. Approximately 60% of patients with early-stage breast cancer should be referred for breast-conserving therapy.[8] However, it should be noted that accurate preoperative knowledge about the extent, size, and location of the neoplastic lesions is a prerequisite for a proper surgical intervention.

The sensitivity of digital mammography in detecting multiple breast lesions depends on breast structure. It seems that both glandular and adipoglandular breast structures as well as tumor density similar to that of the surrounding glandular

tissue were responsible for such a low sensitivity in detecting additional cancer foci. During re-evaluation, there was no significant increase in sensitivity.

The issue of insufficient sensitivity of mammography and ultrasonography in detecting additional breast cancer foci was raised by Bozzini et al[9] in 2008. The authors determined the sensitivity of mammography and ultrasonography for assessing additional cancer foci at the level of 45.5% and 52.9%, respectively.[9] Our results are similarly alarming—mammography failed to detect over 50% of additional cancer foci.

Contrast-enhanced spectral mammography is highly sensitive in detecting breast cancer (comparably to MRI), but there are no recommendations for its use. Moreover, the cost of CESM is lower than that of MRI, and finally, the time needed to perform the procedure and interpret the results is shorter than for the former method. Unlike MRI, CESM has an important limitation, namely, ionizing radiation. It seems that indications for both examinations are similar, except for women with high risk of breast cancer, in whom an MRI examination should rather be performed due to lack of exposure to ionizing radiation, and patients with cardiac pacemaker, metal implants and claustrophobia, who would benefit more from CESM.

After breast-conserving surgery, postoperative radiotherapy prevents recurrence of the disease in terms of both local recurrence and the formation of distant foci of the malignant process. For about a decade, there has been a tendency to limit the irradiated area according to the accelerated partial breast irradiation strategy, which has a cardioprotective effect.[10] Currently, according to the American Society for Radiation Oncology Guidelines,[11,12] such method is acceptable in patients over the age of 50 years, with postoperative margins following resection of tumor measuring over 2 mm and staged Tis or T1N0. Accelerated partial breast irradiation takes definitely less time, is less burdensome for patients, and causes fewer radiation-related side effects. Therefore, it is a standard treatment in many countries worldwide. However, due to the possibility of leaving additional cancer foci outside the therapeutic area, few patients receive this type of radiation therapy, even though it significantly reduces radiation-induced skin reactions.[11,12]

Accurate breast imaging and visualization of additional cancer foci may, in the future, reduce the volume of postoperative breast radiotherapy after breast-conserving therapy in a much larger group of patients. Wider use of CESM would not only lead to a reduction in the number of complications among patients, but it would also significantly lower the treatment costs. Therefore, we believe that precise assessment of the tumor extent is of great importance for treatment qualification.

The main limitation of the analysis is the small size of the study group.

In summary, among patients with multifocal / multicentric breast cancer, CESM is highly sensitive in detecting additional cancer foci and may influence the extent of surgical intervention in every fourth patient.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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