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Contrast-Enhanced Mammography Accuracy in Assessing Preoperative Breast Tumor Size

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Abstract

Background. Breast cancer is a leading type of cancer in women. Imaging techniques (ultrasound, mammography, and magnetic resonance imaging (MRI)) play a crucial role in tumor detection and evaluation. The last emerging technique is contrast-enhanced mammography (CEM) which provides both morphological and functional information.

Objective: to evaluate CEM accuracy in measuring breast tumor lesions.

Material and methods. The study involved 69 patients followed by the Breast Unit from January 2018 to September 2023. Breast tumor dimensions measured in CEM in the pre-operative stage by three experienced radiologists were compared to the dimension obtained at the histological examination, the current gold standard in assessing tumor size.

Results. We observed a slight overestimation by CEM compared to histology, with a difference between the two measurements not more than 10 mm. CEM underestimated the dimensions in 12 of 69 cases.

Conclusion. The study demonstrated excellent CEM accuracy in preoperative assessment of breast tumors, consistent with previous findings in the literature. CEM could prove to be a valid and safer alternative to MRI in preoperative breast tumor measuring.

Keywords: breast tumor; breast cancer; contrast-enhanced mammography; CEM; CEM accuracy; tumor size.

Conflict of interest. The authors declare no conflict of interest.

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Точность маммографии с контрастным усилением при определении предоперационного размера опухоли молочной железы

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Резюме

Актуальность. Рак груди – основной вид онкологических заболеваний у женщин. Методы визуализации (ультразвуковое исследование, маммография и магнитно-резонансная томография (МРТ)) играют решающую роль в обнаружении и оценке размера опухоли. Последним новым методом визуализации является маммография с контрастным усилением (contrast-enhanced mammography, CEM), которая дает как морфологическую, так и функциональную информацию.

Цель: оценка точности CEM при измерении опухолевых поражений молочной железы.

Материал и методы. В исследовании приняли участие 69 пациенток, наблюдавшихся в отделении, занимающимся лечением заболеваний молочной железы, с января 2018 г. по сентябрь 2023 г. Размеры опухоли молочной железы, измеренные методом CEM на дооперационном этапе тремя опытными радиологами, сравнивались с размерами, полученными при гистологическом исследовании, являющемся в настоящее время «золотым стандартом» оценки размеров опухоли.

Результаты. Мы отметили незначительное преувеличение размеров опухоли при использовании метода CEM по сравнению с гистологическим исследованием, при этом разница между двумя измерениями не превышала 10 мм. При применении метода CEM размеры опухоли были недооценены в 12 из 69 случаев.

Заключение. Исследование продемонстрировало отличную точность CEM при предоперационной оценке опухолей молочной железы, что согласуется с результатами, приведенными в научной литературе. Метод CEM может оказаться надежной и более безопасной альтернативой МРТ при предоперационном измерении опухолей молочной железы.

Ключевые слова: опухоль молочной железы; рак молочной железы; маммография с контрастированием; точность маммографии с контрастированием; размер опухоли.

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Introduction / Введение

Breast cancer is one of the leading malignancies among women. Early diagnosis is crucial in reducing mortality, leading to the availability of various imaging techniques such as mammography (MX), ultrasound (US), and magnetic resonance imaging (MRI) [1, 2]. MX plays a crucial role in screening due to its sensitivity and specificity. At the same time, US aids in detecting lesions not visible in mammography, especially in dense breasts, and is utilized in interventional procedures [3].

MRI shows high sensitivity in detecting invasive tumors and is recommended for high-risk patient screening. However, each technique has its limitations: MX has limited sensitivity in studying dense breasts; US suffers from high interobserver variability; MRI poses issues with reduced specificity due to intense breast enhancement, which can be physiological or benign [4].

Currently, MRI stands as the most sensitive method in diagnosing breast tumors, although it has lower specificity compared to mammography due to its higher rate of false positives. Moreover, its high costs, limited availability in certain regions, and absolute contraindications in specific cases significantly limit its application. New techniques have been developed to overcome these limitations, such as contrast-enhanced mammography (CEM) which is a recent technique utilizing tumor angiogenesis to detect neoplasms early [5]. CEM provides two types of information: morphological, similar to traditional mammography, and functional, based on the intensity of contrast enhancement accumulated in the breast gland. Among other advantages, it has a low number of false positives [6].

Recent literature has focused extensively on comparing CEM and MRI in evaluating tumor extent, despite some limitations associated with MRI under certain circumstances [7, 8]. This study aims to compare tumor dimensions measured in CEM with those measured in the histological examination, the gold standard for breast cancer diagnosis. Factors that might contribute to a difference between the two measurements (histological type, histological grading, proliferation index, enhancement characteristics) have been taken into consideration and analyzed [9].

Objective: to evaluate CEM accuracy in measuring breast tumor lesions.

Material and methods / Материал и методы

The study involved retrospectively 69 patients with breast carcinoma, taken care by the Breast Unit from January 2018 to September 2023. All 69 patients underwent an MX and CEM examination which detected breast lesions, confirmed histologically by further biopsy/cytology. Patients were aged from 33 to 86 years old (with an average age of 55,8 years). All patients provided informed consent before imaging examination.

The exclusion from the study occurred when a) the index lesion extended beyond the field of view of the CEM (deep lesions); b) the patients confirmed allergies or renal insufficiency. Ethics approval was not required for this study.

The CEM examination was performed using a MX system (GE Healthcare, Solingen, Germany) equipped with an automatic injector. For the CEM examination, after the injection of iodinated contrast medium (Iohexol 350 mg/mL, 1.5 mL/kg), two projections were acquired: cranio-caudal (CC) two minutes post-injection, and medio-lateral-oblique (MLO) three minutes post-injection, starting with the breast affected by the neoplasm and then proceeding to the contralateral breast. The images at low and at high energy were thus obtained according to standard parameters to capture early enhancement, aiming to minimize potential false negatives resulting from early washout. Exposure parameters were adjusted based on breast size and glandular density using a predefined value table. The image subtraction process allowed for the elimination of glandular tissue, improving the contrast resolution of the contrast enhancement accumulation.

Three radiologists specialized in breast imaging, with respective experience of 6, 15, and 30 years, analyzed the exams on a high-resolution workstation. They measured the dimensions of the index lesions, reporting the maximum diameter in the early scans and looking for washout in the late scans, where applicable. If there was a lack of enhancement, the index lesions were measured as 0 mm. In cases of multicentric and multifocal disease, all areas showing suspicious enhancement characteristics were measured to compile a comprehensive report for each patient, detailing the features of the index lesions (size and extent). Additionally, for each index lesion, the degree of visualization on CEM was noted as intense enhancement, moderate enhancement, or mild enhancement, along with the homogeneity or heterogeneity of the lesions. To evaluate the type of enhancement, the following criteria were used: mass enhancement (lesion occupying space), non-mass enhancement (NME, lesion without mass effect), and ring enhancement (a subtype of mass enhancement) (Fig. 1).

A dedicated breast pathologist performed histological analysis: tumor dimensions were assessed macroscopically and/or microscopically on hematoxylin/eosin-stained sections. In cases of ductal carcinoma *in situ* around foci of invasive carcinoma, dimensions including the maximum diameter of both lesions were reported. For multicentric and multifocal invasive carcinoma cases, the extent of the larger and smaller foci was reported. Histotype, histological grade, and proliferation index (Ki67) were also evaluated.

A particular note is made for microcalcifications, as CEM allows us to differentiate between positive/negative, but especially provides more precise information about the extent in cases of Tis characterized by isolated microcalcifications without opacity.

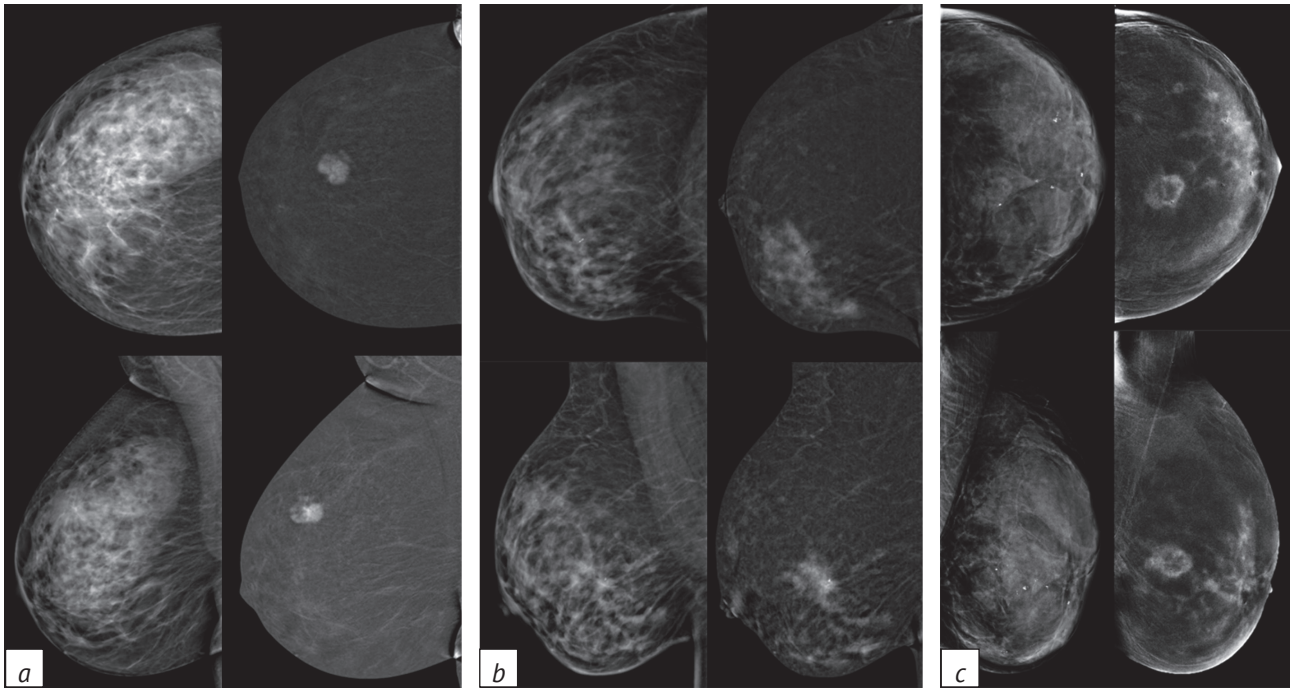

Fig. 1. Contrast-enhanced mammography (CEM) examinations:
a – mass enhancement type of pattern; *b* – non-mass enhancement type of pattern; *c* – ring enhancement type of pattern

Рис. 1. Маммография с контрастным усилением (contrast-enhanced mammography, CEM):
a – тип рисунка с массовым усилением; *b* – тип рисунка без массового усиления; *c* – тип рисунка с кольцевым усилением

Descriptive analysis was employed to explore and summarize the dataset. Measures such as medians and means provided valuable insights into the central tendencies of the variables under examination, enabling us to interpret the recorded values. Additionally, graphical representations, including histograms and charts, were utilized to visualize the data distribution and identify potential outliers. Normality was assessed for the different lesion diameters using the Shapiro–Wilk test. Since the variables did not follow a normal distribution pattern, a signed-rank test was applied to determine if there were significant differences in the data distributions between groups. The Pearson correlation test was applied to investigate any further statistically significant correlations.

Results / Результаты

All 69 patients, with a mean age of 54 years, were diagnosed with neoplastic breast mass and underwent MX and CEM. The diagnosis was confirmed histologically by cytological or biopsy analysis. A comprehensive description of the incidence of these characteristics is listed in (Fig. 2).

The median size of the lesions varied slightly among the three analyzed methods: MX, CEM, and definitive histology. Histological examination, considered the gold standard for measuring lesions, showed a mean measurement of 1.4 cm (SD=2.24), while CEM and MX techniques recorded measurements of 1.5 cm (SD=2.46) and 1.6 cm (SD=2.21), respectively. MX underestimated the size of the neoplastic mass in 21 out of 69 cases, while CEM underestimated it in 28 out of 69 cases. In 8 out of 69 cases (11.6%), histological evaluation of lesion size reported the same size with both instrumental techniques. In both cases, the minimum and maximum differences were –4.8 and 7.9, respectively (Tables 1, 2).

Concerning the identification of multiple lesions, out of 13 multifocal masses found in definitive histology, 12 out of 13 (92.3%) were identified using CEM, while only 7 out of 13 (58.3%) were identified mammographically. Other obtained results indicate that out of the 69 observations, 34 patients were found to have mass-like neoformations using CEM, accounting for 49.27% of the total, while 33.3% were found to have homogeneous contrast enhancement. In the study of contrast enhancement characteristics using CEM, all neoplastic masses demonstrated high, medium, and low contrast intensity values, accounting for 12%, 31.3%, and 56.7% of the total, respectively. In nearly all patients with high contrast enhancement intensity (97%), the Ki67 ranged between 50 and 65. Overall, Ki67 ranged from 3 to 65 across all observations.

The majority of neoplasms (58 out of 69) were classified in definitive histology as infiltrating ductal carcinoma (IDC), 7 as infiltrating lobular carcinomas, and 4 as others. Two of the IDC formations showed an *in situ* component with the identification of microcalcifications, resulting in an increase in size using CEM compared to the tumor lesion size taken in histology examination,

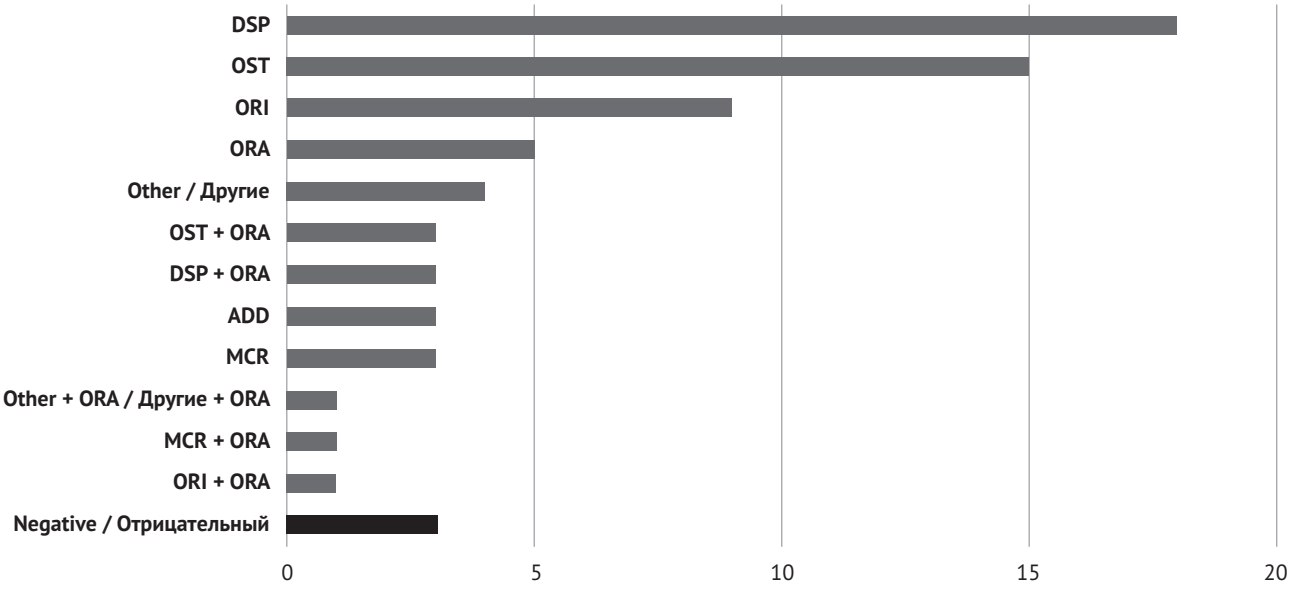

Fig. 2. Morphological distribution of lesions.
DSP – parenchymal distortion; OST – stellate opacity; ORI – irregular opacity; ORA – rounded opacity; MCR – microcalcifications; ADD – high breast density

Рис. 2. Морфологическое распределение поражений.
DSP – паренхимальное искажение; OST – звездчатое помутнение; ORI – неравномерное помутнение; ORA – округлое помутнение; MCR – микрокальцификаты; ADD – высокая плотность молочной железы

Table 1

The size of the lesion in histological examination compared to mammography

Таблица 1

Размер поражения при гистологическом исследовании по сравнению с маммографией

Variable / Переменная	Difference / Разница			
	Count / Подсчет	Minimum / Минимум	Average / Среднее	Maximum / Максимум
D_MX < D_IST	40	–4.8	–0.94175	–0.1
D_MX = D_IST	8	–	–	–
D_MX > D_IST	21	0.1	0.9761905	7.9
Jointly defined / Определено совместно	69	–4.8	–0.2488408	7.9
Total / Итого	69	–	–	–

Note. MX – mammography; IST – histology.

Примечание. MX – маммография; IST – гистология.

for the determination of the surrounding peritumoral area. Among the 69 patients, 3 cases were classified as G1, 33 as G2, and 31 as G3, 1 was a Tis, and 1 was not classified.

The Shapiro–Wilk test revealed a non-normal distribution of the collected data. The variables of interest were studied through the Wilcoxon test. The Wilcoxon signed-rank test between D_IST and D_MX showed a statistically significant difference between the two datasets, as indicated by the small p-value (0.0098). This suggested that it was unlikely for the differences between D_IST and D_MX to occur by chance alone. On the other hand, the Wilcoxon signed-rank test between D_IST and D_CEM did not show any statistically significant difference between the two datasets, as indicated by the large p-value (0.9928). This suggested that the differences between D_IST and D_CEM might be due to random variations (Table 3).

Discussion

The main purpose of the study was to evaluate the diagnostic accuracy of CEM in the dimensional assessment of breast tumors and its predictive value in preoperative staging, comparing it with histological results

Table 2

The size of lesion in histological examination compared to CEM

Таблица 2

Размер поражения при гистологическом исследовании по сравнению с CEM

Variable / Переменная	Difference / Разница			
	Count / Подсчет	Minimum / Минимум	Average / Среднее	Maximum / Максимум
D_CEM < D_IST	32	–4.8	–0.75	–0.1
D_CEM = D_IST	9	–	–	–
D_CEM > D_IST	28	0.03	1.133214	7.9
Jointly defined / Определено совместно	69	–4.8	0.112029	7.9
Total / Итого	69	–	–	–

Table 3

Variables of interest studied through the Wilcoxon test

Таблица 3

Переменные, представляющие интерес и изученные с помощью теста Вилкоксона

Variable / Переменная	Observations / Число наблюдений	W	V	z	Prob>z
D_MX	69	0.73418	16.172	6.048	0.00000
D_CEM	69	0.73135	16.344	6.071	0.00000
D_IST	69	0.76829	14.097	5.749	0.00000

after surgery. The study demonstrated excellent accuracy of the method in the preoperative assessment of breast tumors, consistent with previous findings in the literature [6, 7, 10–13].

We observed a slight overestimation by CEM compared to histology. However, in most cases, the difference between the two measurements was no more than 10 mm. Further analysis revealed a prevalence of mass-like enhancement, with a predominance of low-intensity ductal tumors. In CEM, ductal carcinoma *in situ* appeared as an area of subtle and delayed contrast enhancement because the contrast agent reaches the neoplastic focus through diffusion, without actual angiogenesis [6]. Consequently, performing scans with a delay from the start of contrast injection allows for greater enhancement and better visibility of the in-situ lesion. Our results are consistent with previous observations, although most studies focus on MRI. We also noted an overestimation of tumor mass in CEM compared to definitive histology, in cases of microcalcifications with a focus on carcinoma in situ, confirming a wider area of peritumoral tissue. We observed a varied distribution of histological grades, indicating that histological grade does not influence tumor size; however, this result requires a larger sample size for confirmation.

The study's results showed that MX and CEM performed similarly in assessing tumor size, but CEM typically provides more accurate measurements due to its use of contrast agents, which enhance the visibility of tumors, particularly in dense breast tissue or in cases where the tumor is more difficult to delineate (Fig. 3).

The comparable performance observed in this study could be attributed to specific factors such as the study's design, sample characteristics, or the nature of the tumors assessed, rather than a genuine equivalence between the two methods. At all, the superior diagnostic capabilities of CEM remain well-established, especially in cases requiring precise tumor delineation for treatment planning. Although the study was not designed to directly compare the two modalities, the observation of similar performance in tumor size assessment between CEM and MX raises important considerations. Discussing this comparison provides valuable context, highlighting that while CEM is generally superior due to its advanced imaging capabilities, the results of this study suggest that, under certain conditions, MX can offer comparable accuracy. However, in many other scenarios, particularly in cases of dense breast tissue or *in situ* tumors, CEM remains the gold standard for accurately determining the true size of the lesion. This underlines the critical role of CEM

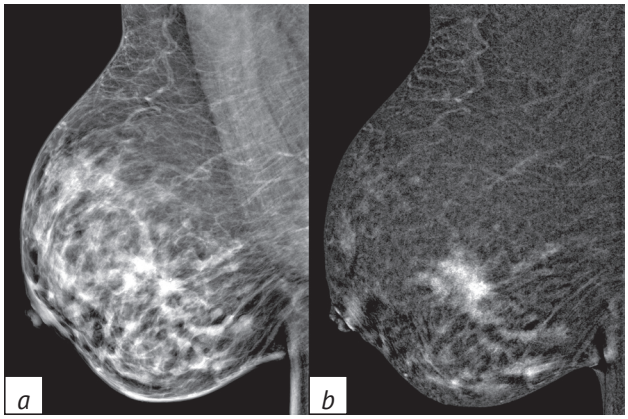

Fig. 3. Comparison between MX (*a*) and CEM (*b*) in case of invasive ductal carcinoma. It is challenging to assess the tumor size in the MX image of the right breast in the oblique projection. However, the extent of the tumor is immediately clear in the CEM image

Рис. 3. Сравнение результатов маммографии (*a*) и CEM (*b*) в случае инвазивной протоковой карциномы. Трудно оценить размер опухоли на маммографическом изображении правой молочной железы в косой проекции. Однако на CEM-изображении размеры опухоли видны сразу

in clinical practice, where its enhanced sensitivity and specificity are crucial for precise diagnosis and treatment planning.

Conclusion / Заключение

Given the satisfactory results obtained with CEM examination in terms of pre-surgical staging, both regarding the number of foci and the extent of individual lesions and considering the well-known limitations of MRI such as its limited availability, long acquisition times, and high costs, there are strong encouragement for the use of CEM as a valid preoperative method. Therefore, its speed and relative technical simplicity make it more tolerable for patients; moreover, it is burdened with lower expenses compared to MRI. Indeed, the lower cost of CEM compared to MRI should not be underestimated; according to some authors, the cost of CEM is approximately 80% lower than that of MRI and only 9% higher than that of digital mammography. CEM could prove to be a valid and safer alternative to MRI, characterized by higher specificity and offering advantages in terms of time, costs, and patient compliance.

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