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# Retrospective Comparison of Contrast-Enhanced Spectral Mammography with Digital Mammography in Assessing Tumor Size in 668 Cases of Breast Cancer

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Statistical Analysis C  
Data Interpretation D  
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**Background:** Contrast-enhanced spectral mammography (CESM) is digital mammography with contrast agent. This promising new breast imaging method can be used for planning surgical treatment. This study compared CESM versus digital mammography (MG) in evaluating tumor size in breast cancer.


**Material/Methods:** Comparison of tumor dimensions in CESM, MG, and histopathology was made. The correlation of these data was assessed by histopathological type, biological subtype, grading of the carcinoma, and patient age.

**Results:** The average difference in tumor size between CESM and histopathological examination was 5 mm. The differences in size measurement between CESM and MG were significant ( $p=0.00$ ). The Pearson's linear correlation coefficients of CESM versus HP and MG versus HP were  $-0.01$  ( $p=0.79$ ) and  $-0.25$  ( $p=0.00$ ), respectively, indicating no differences between CESM and HP based on the lesion size. A weak negative correlation between those values was observed on MG. No relationship was found between the tumor size in CESM and the biological subtype, carcinoma malignancy degree, or patient age.

**Conclusions:** CESM is a new diagnostic method in breast cancer. The accuracy of measurement of tumor size using CESM is independent of lesion size, but it overestimates the size by 5 mm on average. The difference is not dependent on grading, biological subtype of the carcinoma, or patient age. They concern the histopathological type, and values are significantly greater in pre-invasive carcinomas.

**MeSH Keywords:** **Breast Neoplasms • Mammography • Pathology, Surgical**

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## Background

Breast cancer is the most common malignant tumor diagnosed in women worldwide. In Poland, it accounts for 22.4% of new malignancy cases among women. Much concern is raised by the growing morbidity trend in premenopausal women (ages 20–49 years), which is responsible for an almost 2-fold increase in the morbidity rate in this age group over the last 3 decades [1,2].

Among numerous imaging methods, mammography is the most useful technique for detecting focal lesions in breast glands recommended by EUSOBI (European Society of Breast Imaging). However, the overall sensitivity and specificity of the examinations is only 62–68% in patients with dense breasts [3–7]. The recently developed contrast-enhanced spectral mammography (CESM) is intended to obtain a more visible image of the tumor through the injection of a contrast agent filling the neoplastic region and the surrounding intercellular space. CESM, also known as dual-energy contrast-enhanced spectral mammography, generates images of low and high energy during a single, short compression upon injection of a contrast agent [8]. The choice between the local or systemic treatment method for breast cancer in the particular stages of the disease is based on clinical and pathomorphological assessment, with consideration of the histological type and grading of carcinoma, ER/PgR and Ki67 expressions, HER2 status, progression of the primary tumor and regional lymph nodes, the presence and extent of metastases in distant organs, menopausal status, age, fitness status, past and concomitant disease and related treatment, and the patient's preferences [9–12]. The choice between breast-conserving surgical treatment and mastectomy is largely dependent on the size of the tumor and exclusion of multifocality of the neoplastic lesions. Precise planning of the type of surgical procedures is of crucial importance for the treatment results and directly translates into a limited number of local recurrences. Besides magnetic resonance imaging (MRI), the most useful imaging procedure that best reflects the size of the tumor is mammography [13–15].

The objective of our study was to evaluate the relevance of contrast-enhanced spectral mammography (CESM) in comparison with conventional digital mammography (MG) in assessing the size of a neoplastic tumor by comparing the size of the neoplastic lesion estimated on MG and CESM with the size of this lesion measured in postoperative histopathological examination.

## Material and Methods

The study protocol required no consent from the Committee for Bioethics at the Medical University of Silesia, which was

confirmed in writing. All the test procedures were carried out in compliance with the ethical principles of the 1964 Helsinki Declaration and its subsequent amendments.

The retrospective study analyzed 668 patients with initially operable breast cancer who had been operated on between Jan 2013 and Jan 2019 in the Clinic of Oncological Surgery, Prof. Kornel Gibiński Independent Public Central Clinical Hospital, Medical University of Silesia in Katowice (Poland). The age distribution for the patients analyzed was not of a normal nature, with the minimum age in the sample being 29 years and the maximum 91 years (median, 65 years). The lesion sizes in the HP examination (whose distribution was not of a normal nature either) did not exceed 120 mm (median, 18 mm). All the patients included in the study underwent preoperative diagnostics at the Hospital Outpatient Clinic of Oncological Surgery, including: medical history, clinical examination, imaging tests, and core-needle biopsy (CNB). Each female patient with CNB-diagnosed breast cancer had digital mammography performed, and 661 women (661/668, 99%) additionally underwent contrast-enhanced spectral mammography (CESM). The lesion size was measured on MG and CESM and then compared with the lesion size measured on the basis of a postoperative histopathological examination.

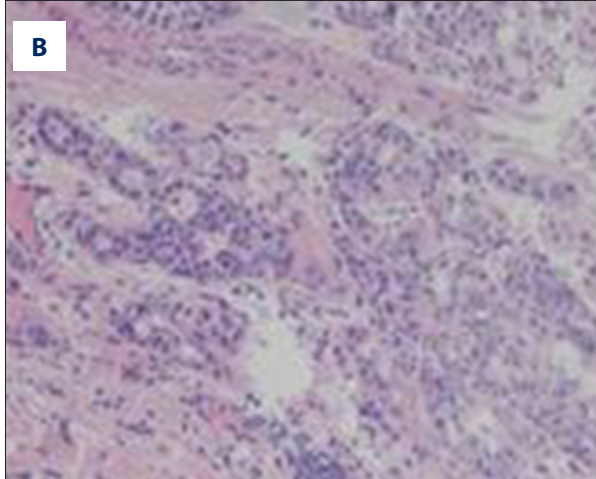
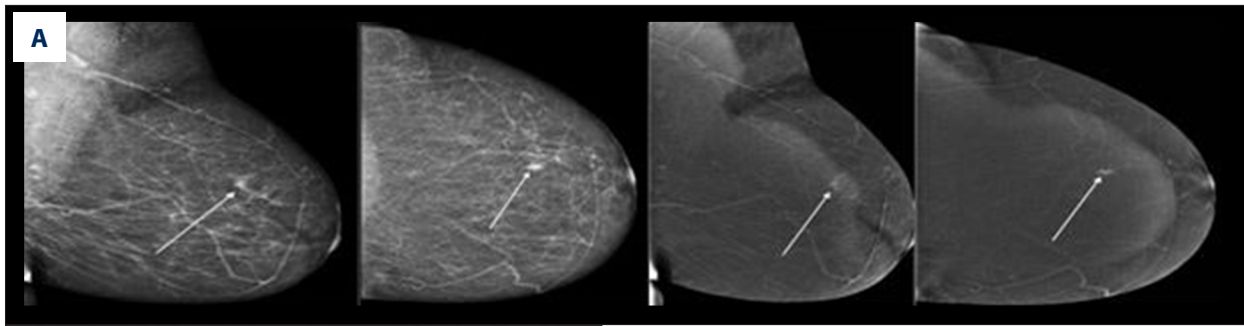
An examination was made of the difference in lesion size between the MG results and the HP result for 668 patients, and 661 patients had this difference determined between the CESM result and the HP result.

These differences were also analyzed in the subgroups, including:

- a) histopathological type of carcinoma diagnosed by core-needle biopsy (CNB):
  1. No special type (NST) carcinoma
  2. Infiltrating lobular carcinoma;
  3. Special subtype of infiltrating carcinoma;
  4. Infiltrating ducto-lobular carcinoma;
  5. Ductal carcinoma *in situ* (DCIS) High Grade;
  6. DCIS Low Grade;
  7. Lobular carcinoma *in situ* (LCIS) – pleomorphic type.
- b) grading (G): 1, 2, 3.
- c) biological subtype:
  1. Luminal A;
  2. Luminal B (HER2-negative);
  3. Luminal B (HER2-positive);
  4. HER2-positive (non-luminal);
  5. triple-negative (ductal).

## Imaging procedures

All CESM examinations were performed and assessed in the Mammography Laboratory in our center. All the MGs performed



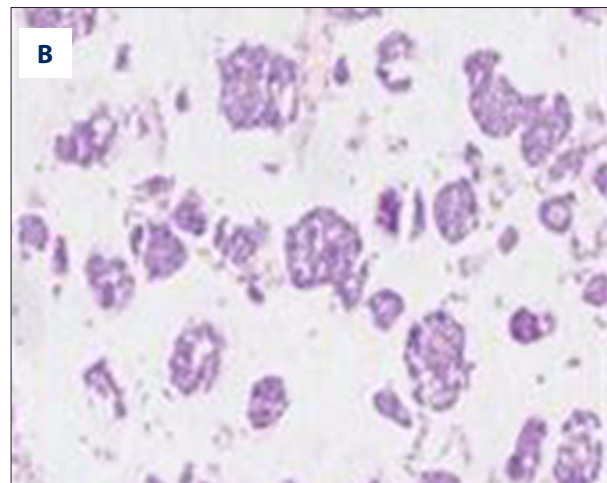
**Figure 1. (A, B) NST GII.**

(low- and high-energy) in each view. Specific image processing of low-energy and high-energy images was done to obtain subtraction images to highlight contrast enhancement and suppress structured noise due to fibroglandular breast tissue [16]. The total examination time was usually 10 min. On mammography (FFDM) and on CESM in CC and MLO projection, 3 tumor measurements were made, and only the largest tumor was included in the statistical analysis. After examination, the patients were observed for about 30 min for the appearance of any adverse reactions.

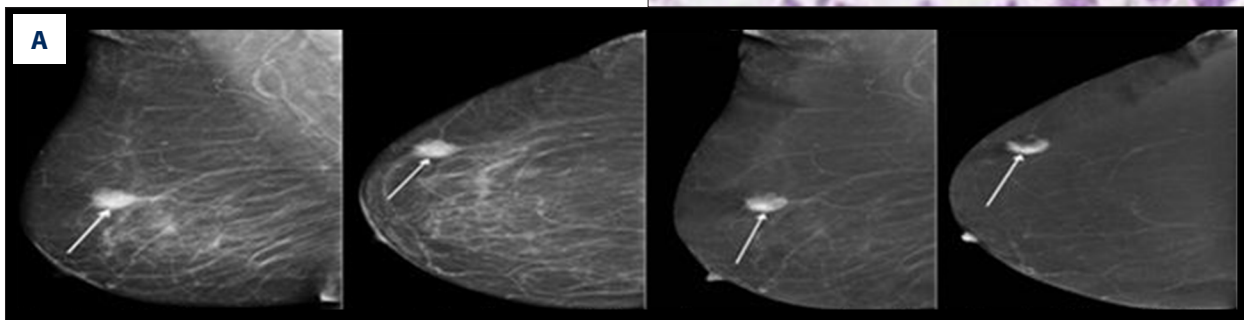
Below are shown images of carcinoma obtained from CESM along with postoperative histopathological verifications: NST GII (Figure 1A, 1B), mucinous carcinoma (Figure 2A, 2B) and DCIS high-grade (Figure 3A, 3B).

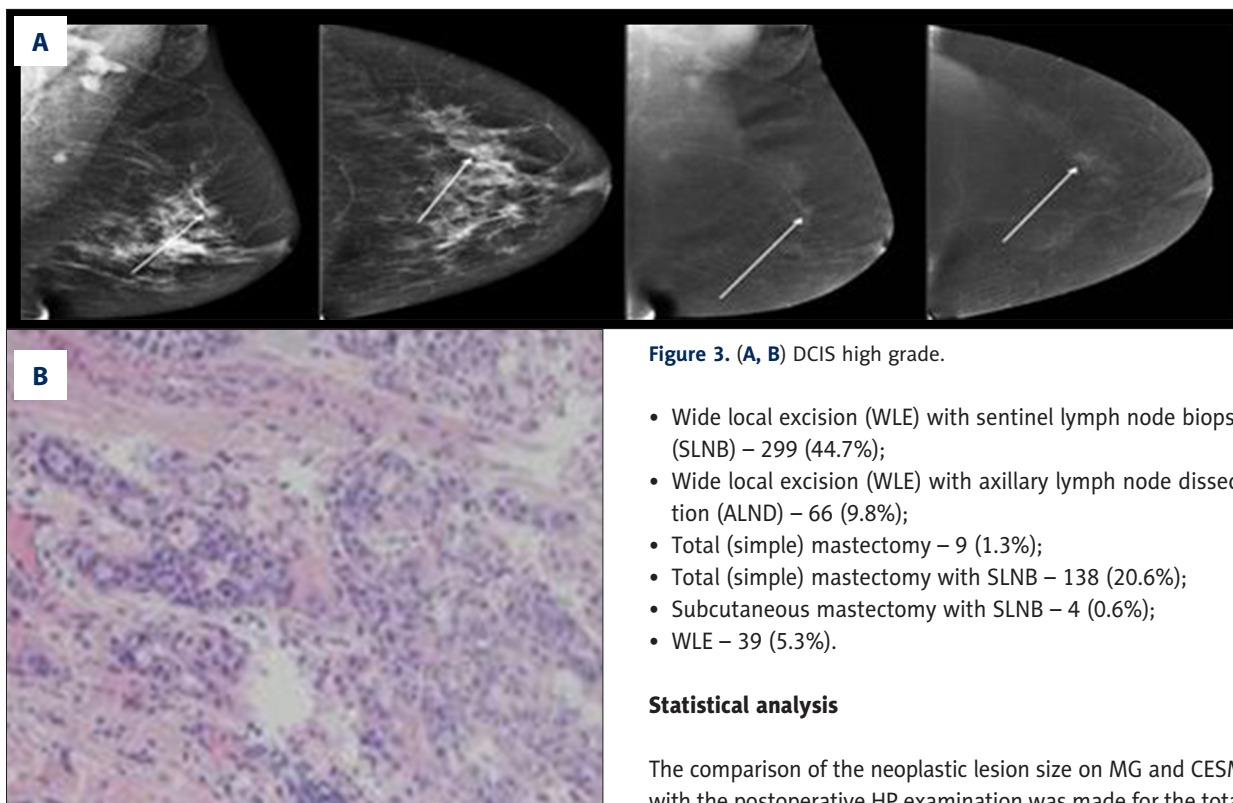
in our center and those performed outside were assessed by consultant radiologists having at least 15 years of experience in the diagnosis of breast diseases. Prior to the qualification for CESM, all the patients filled out a survey, which was used as the basis for eliminating those with a risk of allergic reactions and potential pregnancy. Each patient also had her creatinine and GFR levels assessed. All CESM examinations were carried out with a digital mammography device dedicated to perform dualenergy CESM acquisitions (SenoBright, GE Healthcare).

An intravenous injection of 1.5 ml/kg of body mass of non-ionic contrast agent was performed using a power injector at a rate of 3 ml/s with a bolus chaser of 30 ml of saline. In CESM mode, the device automatically performed a pair of exposures



**Figure 2. (A, B) Mucinous carcinoma.**





**Figure 3. (A, B) DCIS high grade.**

- Wide local excision (WLE) with sentinel lymph node biopsy (SLNB) – 299 (44.7%);
- Wide local excision (WLE) with axillary lymph node dissection (ALND) – 66 (9.8%);
- Total (simple) mastectomy – 9 (1.3%);
- Total (simple) mastectomy with SLNB – 138 (20.6%);
- Subcutaneous mastectomy with SLNB – 4 (0.6%);
- WLE – 39 (5.3%).

#### Statistical analysis

The comparison of the neoplastic lesion size on MG and CESM with the postoperative HP examination was made for the total number of patients and in the subgroups divided by carcinoma subtype and grading (G). For all statistical tests conducted during the analysis, the level of significance was set at 5%. We also examined whether the average results obtained in each of the measurement methods differed significantly from one another. Next, the difference was determined for each female patient between the size of the neoplastic lesion measured by each tested method and it was examined whether the obtained values differ significantly. The next stage involved determining the average values of differences in the above-mentioned subgroups (CNB, grading, and biological subtype). After analyzing the results obtained in the classification subgroups, the dependence of these parameters on patient age and HP results was checked.

#### Results

In our study the tumor size in HP ranged from 2 to 120 mm (median, 18 mm), in MG from 4 to 121 mm (median, 19 mm), and in CESM from 5 to 123 mm (median, 22 mm).

The CNB performed in the study group diagnosed 406 NST carcinomas with tumor size 2 mm to 120 mm (median, 18 mm), 83 infiltrating lobular carcinomas (ILC) with tumor size 7 mm to 60 mm (median, 20 mm), 56 infiltrating carcinomas of special subtype (SSIC) with tumor size 7 mm to 75 mm (median, 20 mm), 25 infiltrating ductolobular carcinomas (ID-LC) with tumor size 4 mm to 80 mm (median, 22 mm), 67 DCIS-HG

#### Histopathological examination

The histopathological examination was conducted in the Histopathology Laboratory in our center. The greatest dimension of the tumor necessary for determining the T descriptor in the pTNM classification, besides the macroscopic measurement, was verified histopathologically by means of a microscope and use of cellSens Dimension® software by Olympus from 2013. Tumors up to 2 cm were excised in whole, serially, on a cross-sectional basis, with a margin of 0.2 to 0.4 cm and embedded in a paraffin block, after each cross-section. Tumors measuring over 2 cm and not fitting within a single paraffin block were divided into 2 or more parts by making parallel cuts of the lesion. Next, they were marked in pairs with ink of the same color and the individual layers were given numbers to allow finding the entire largest section of the tumor. The T value of the tumor was the total of the parallel measurements of the particular parts of the lesion. In the case of multifocal breast cancers, account was taken of the maximum dimension of the largest invasive tumor.

#### Surgical treatment

Surgeries were performed in a total of 668 patients and included the following procedures:

- Madden-type radical mastectomy – 113 (17%);

**Table 1.** Values of the differences between the HP measurement and the mammography results for the particular groups divided by the CNB-based histopathological type of carcinoma in mm and% of the HP value.

CNB	DeltaMG	DeltaCESM	DeltaMG%	DeltaCESM%
NST	0.10	4.66	5.05	29.52
Infiltrating lobular carcinoma (ILC)	0.24	5.71	6.71	34.35
Special subtypes of infiltrating carcinoma (SSIC)	0.02	1.31	1.71	5.63
Infiltrating ducto-lobular carcinoma (ID-LC)	0.32	3.63	9.62	23.41
DCIS-HG	5.00	11.18	51.40	87.59
DCIS-LG	-1.38	6.93	6.91	47.45
LCIS (pleomorphic type)	4.25	2.75	97.74	36.13

with tumor size 2 mm to 50 mm (median, 15 mm), 27 DCIS-LG with tumor size 6 mm to 60 mm (median, 15 mm), and 4 LCIS of pleomorphic subtype with tumor size 5 mm to 21 mm (median, 9 mm).

We obtained data on differences between the descriptive statistics for the differences in the measured values (Delta) between the HP measurement and those obtained from MG and CESM from raw values (mm) and percentage values.

The results of comparison of the average values indicate the presence of significant differences between them, which means that the size of the neoplastic lesions observed vary depending on the method used (MG, CESM, or HP measurement).

In the examined samples, the mean deviation in size from the HP dimension ranged from 0.56 mm for MG to 5.19 mm for CESM. The comparison of the average values and medians of these deviations indicates that the lesion size is overestimated in both of these measurement methods, with the overestimation value in CESM being significantly higher.

In accordance with the description of the method, the average values were determined for the differences between DeltaMG, DeltaCESM, DeltaMG%, and DeltaCESM% versus the HP measurement for the pre-defined subgroups (carcinoma type in CNB, grading, biological subtype). After conducting detailed tests, it was concluded that significant differences existed only for the DCIS-HG group ( $p < 0.006$ ). In the remaining cases no significant differences were found between the groups. The minimum values for the differences between HP and the mammography results were obtained in the special carcinoma subtypes group (Table 1).

The analysis of the data summarized in Table 2 show significant differences between the DCIS-HG group and the other groups, as well as, depending on the method (i.e., MG or CESM), between the DCIS-LG group for MG and the infiltrating ducto-lobular carcinoma group for CESM (Tables 2, 3).

According to biological subtype of cancer (Luminal A vs. Luminal B vs. Non-Luminal vs. Triple-Negative) and according to grading G1 vs. G2 vs. G3) no significant differences were found between the groups. No significant relationship was found in verification as to whether the DeltaMG and DeltaCESM values correlate with the patient's age.

To determine the causes of the differences found, Pearson's linear correlation coefficient was calculated between the size of the pathological lesion measured in HP and the differences from this value for both mammography measurements. We found that the results differed depending on the mammography technique used (Table 4).

For the MG measurement, a clear relationship was found to exist in the difference between DeltaMG and HP values, and this relationship was statistically significant. The CESM measurement does not show a similar relationship.

The analysis shows that the deviation from the HP value with the CESM is not dependent on the actual size of this lesion and is not significant (the value of  $r^2 = 0.0001$ ,  $p = 0.79$ ). For all of the lesion sizes, the average overestimation of the result is approximately 5 mm.

For MG measurements and HP\_W values lower than 25 mm, a decrease was observed in the trend line. When this value is exceeded, the trend line becomes stable. For the purposes of the analysis, the material examined was divided into 2 groups according to the HP\_W value: first, with  $HP\_W \leq 25$  mm and second including all the remaining values. For the second group, similarly to the CESM method, no statistically significant relationship was obtained between the DeltaMG values and the HP\_W values, and, similar to the CESM method, the average overestimation of the result was about 4 mm, regardless of the size of the pathological lesion. On the other hand, the first group ( $HP\_W \leq 25$  mm) was observed to manifest a statistically significant ( $p = 0.002$ ) relationship between the deviation and the size of the pathological lesion.

**Table 2.** The significance degree of the difference values between the average DeltaMG values in the particular carcinoma groups divided according to CNB.

CNB	NST	ILC	SSIC	ID-LC	DCIS-HG	DCIS-LG	LCIS
NST		1.0000	1.0000	1.0000	0.0001	0.8954	0.8704
ILC	1.0000		1.0000	1.0000	0.0036	0.9472	0.8725
SSIC	1.0000	1.0000		1.0000	0.0138	0.9518	0.8844
ID-LC	1.0000	1.0000	1.0000		0.2028	0.9516	0.9311
DCIS-HG	0.0001	0.0036	0.0138	0.2028		0.0042	1.0000
DCIS-LG	0.8954	0.9472	0.9518	0.9516	0.0042		0.6631
LCIS	0.8704	0.8725	0.8844	0.9311	1.0000	0.6631	

**Table 3.** The significance degree of the difference values between the average DeltaCESM values in the particular carcinoma groups divided according to CNB.

CNB	NST	ILC	SSIC	ID-LC	DCIS-HG	DCIS-LG	LCIS
NST		0.9543	0.3042	0.9997	0.0001	0.8287	0.9999
ILC	0.9543		0.1617	0.9743	0.0446	0.9943	0.9975
SSIC	0.3042	0.1617		0.9663	0.0000	0.1713	1.0000
ID-LC	0.9997	0.9743	0.9663		0.0486	0.8688	1.0000
DCIS-HG	0.0001	0.0446	0.0000	0.0486		0.7407	0.7192
DCIS-LG	0.8287	0.9943	0.1713	0.8688	0.7407		0.9822
LCIS	0.9999	0.9975	1.0000	1.0000	0.7192	0.9822	

**Table 4.** Value of Pearson's linear correlation and the degree of its significance between the lesions measured in HP and the difference values for Delta MG and Delta CESM.

	N	Pearson	p-Value
HP_W & DeltaMam	668	-0.2516	0.000000
HP_W & DeltaCSEM	661	-0.0104	0.79

## Discussion

While planning the surgical treatment of breast cancer, the scope of the surgery is, to a large extent, dependent on the size of the tumor and exclusion of the multifocality of the neoplastic lesions. The results of breast-conserving treatment in breast cancer are comparable to those of radical treatment. The extent of the surgery can be precisely planned, among others, by assessing the lesion size on imaging. Imaging methods, including digital mammography and ultrasonography, have several limitations and do not always allow for precise preoperative prediction of the tumor size, especially in women with dense glandular breast tissue or implants. CESM is a new technique that may improve the clinical efficacy of assessing the tumor size and support the surgical planning of treatment in the case of patients diagnosed with breast cancer. According to

current reports, CESM can be compared to magnetic resonance imaging (MRI) in terms of assessing the tumor size [17,18].

The objective of our study was to compare the size of the neoplastic lesions assessed on MG and CESM with the size of this lesion in postoperative histopathological examination in patients with breast cancer who had initially received surgical treatment. To the best of our knowledge, there have been no studies on such a large group that analyzed the correlation of tumor size in CESM with histopathological examination in women diagnosed with breast cancer.

Based on the results summarized in Tables 1 and 4, it was found that neither of the examinations under analysis (i.e., MG and CESM) is able to precisely represent the actual size of the tumor measured in a histopathological examination. The average of the deviations in the samples examined ranged from 0.56 mm for MG to 5.19 mm for CESM. The comparison of the average values and medians of these deviations revealed that the lesion size was overestimated in both of the measurement methods in question, with the overestimation value in CESM being significantly higher (p=0.000) than that in MG. Interestingly, the representation of the average difference from the HP size in MG measurement for lesions below 20 mm converged with the results obtained in CESM. On the

other hand, in the range of tumors measuring 20–26 mm in diameter, MG was more precise in visualizing the lesion size than the CESM method. Furthermore, the study revealed that the difference in assessing the lesion size on MG is significantly dependent on its size in HP ( $p=0.000$ ). On the other hand, the CESM measurement did not show a similar relationship ( $p=0.79$ ), thereby indicating that the CESM-measured size is not dependent on its actual size in HP examination. The results obtained in our study seem to be comparable to those presented by other authors. In their study, Jochelson et al. claim that the visualization of the lesion sizes was precise if the difference from the lesion size measured in postoperative HP examination was  $\leq 0.5$  cm. Luczyńska et al. demonstrated that the lesion sizes in CESM and MG were comparable to each other, yet overestimated, on average, by 3.0 mm for CESM and 3.3 mm for MG, compared with histopathological results [19,20]. Patel et al. proved that patients with

biopsy-proven malignancy, size measurements in CESM correlated well with histopathologic size and the difference between CESM and histopathological examination was less than 3 mm [21].

The MG and CESM imaging methods involve breast compression, which may be a factor overstating the lesion size compared to histopathological examination. Moreover, each breast cancer forms an autonomous structure partially based on its own specific vascularization. Despite being connected with the systemic circulation, this vascular network is poorly organized, and the endothelial wall of the capillary vessels is damaged, which changes the normal transportation function. Therefore, in the case of CESM, filling the neovascular network with a material that is non-transparent for radiation (i.e., an iodine-based contrast agent) may potentially increase the radiographic density on a mammogram and cause the contrast agent to permeate into the areas adjacent to the lesion, thereby increasing their visibility and potentially leading to overestimation of such lesions [22–24].

The histopathological processing of the postoperative material and measuring the infiltration upon specimen collection also carry a risk of error. It is difficult to assess macroscopically whether the visible borders of the tumor are the limits of tumor infiltration or the limits of the accompanying inflammatory infiltration and calcification. The borders described are corrected upon microscopic assessment, which is possible only when the entire neoplastic infiltration fits into the paraffin block and then on the microscope slide. Furthermore, the specimen must be surrounded by reagents and paraffin, which, in practice, makes it possible to embed a tumor of up to 2 mm in diameter into the cassette. Lesions measuring over 2 cm are assessed macroscopically and this method may carry a low risk of error [25].

In our study, no difference was observed in the lesion sizes on CESM and MG compared to HP depending on the grading, the biological subtype, and the patient's age. However, significant differences occurred depending on the histopathological subtype of carcinoma.

The highest compliance of dimensions on MG and CESM with the histopathological examination was observed in our study in the group of special carcinoma subtypes. The average difference in MG in relation to HP amounted to only 0.02 mm, while in CESM it was 1.3 mm. Tumors with dense collagen stroma, or the so-called desmoplastic ones, have a tendency to capillary collapse and manifest lower perfusion than tumors with loose stroma. Special subtypes of carcinoma are quite often well-delineated tumors, with a clear border of infiltration and no strip of inflammatory tissues around the lesion, which could be mistaken for neoplastic infiltration on mammography, thereby overestimating the tumor diameter [26,27].

In our group, all of the DCIS cases manifested pathological contrast enhancement. However, a significant problem was observed in reassessing their size in CESM compared to other carcinomas. The average difference in MG in relation to HP amounted to 5 mm, while in CESM it was 11.18 mm. The lesion size in CESM was overestimated by more than 5 mm in the case of 44 (52%) out of the 84 DCISs under analysis. Breast conservation therapy (BCT) surgery with positive margins is reported to occur in 34% of DCIS cases compared to 3–7% in patients with invasive (ductal or lobular) breast cancers [28,29]. In the preoperative treatment planning, obtaining precise information on the extent and distribution of DCIS is important in determining the extent of surgery required.

Ductal carcinoma *in situ* represents a morphologically and biologically heterogeneous group of neoplastic proliferations. On X-ray mammography, it usually manifests as microcalcifications (72%) or microcalcifications with an accompanying abnormal tissue image (12%) [30]. Taking into consideration the fact that X-ray mammography has the disadvantage of being less sensitive in the case of highly glandular breasts, assessing the dimensions of focal asymmetries or architectural distortion that accompany carcinomas *in situ* with such breast tissue is very difficult and sometimes even impossible. Therefore, new methods are being searched for that would allow for more precise assessment of the tumor size. Ductal carcinoma *in situ* is limited by the basement membrane, does not infiltrate the stroma and, generally, manifests no angiogenic capacity [31]. The question arises, therefore, as to why CESM subtraction images (upon injection of a contrast agent) can provide better visualization of these carcinomas.

Ductal carcinomas *in situ* (DCIS) may exhibit increased vascularization, despite the fact they do not cross the basement

membrane, and the stromal microvessel density (MVD) between the ducts invaded by the DCIS may be higher than that in unremarkable tissue [32,33]. This explains why these carcinomas are visible at all on spectral mammography upon intravenous injection of a contrast agent. To the best of our knowledge, there are no publications concerning the issue of reassessing DCISs in CESM. There are, however, papers where the authors have similar experiences with the use of magnetic resonance imaging (MRI). Both spectral mammography and magnetic resonance imaging are based on contrast enhancement of pathological foci, i.e., an attempt to visualize angiogenesis. Therefore, the discussion refers to the publications that explore this issue in MR examination. In his publication, Jethava [34] states that the problem of overestimating the size of carcinomas on MRI amounts to 31.9%, and primarily concerns high-grade carcinomas and DCISs. The researchers noticed that the MRI-based measurement of the DCIS was overestimated by more than 0.5 cm in 43% of all pre-invasive ductal carcinomas. Similar observations can be seen in the papers by other authors [35,36]. The most plausible explanation for this situation is the fact that DCIS often coexists with other pathologies, such as benign proliferation around foci fibrocystic changes, atypical ductal hyperplasia, and inflammatory lesions.

The overestimation of the lesion sizes obtained on CESM images had no influence on the surgical treatment in our group of patients because it was insignificant, and the safety margins were always taken into consideration during surgical interventions.

In the study group of 668 surgical patients observed to date, local recurrence was noted in 2 cases, while nodular recurrence following breast-conserving treatment was found in 3

cases. In 48 (6.9%) cases, it was necessary to apply local radicalization due to microscopically non-radical margins (R1 resection), of which 28 (58%) were DCIS cases.

A separate, extremely significant feature of CESM observed in the study group of patients was the potential to identify additional neoplastic foci in the breast, which often translated into a changed scope of surgery. Careful scrutiny of these cases will be the subject of our next publication.

A limitation of examination was the fact that part of MG was performed outside our Department using lower-quality equipment, which could have caused less precise tumor limits imaging. Moreover, about 50% of patients had high-density glands, contributing to problems with finding further tumors in MG, which were later detected using CESM.

## Conclusions

CESM is a new method relevant in the surgical planning of breast cancer therapy. The measurement accuracy of the tumor size using the CESM is independent from the size of the lesion. However, it overestimates the size by an average of about 5 mm. The differences in the representation of the lesion size in CESM are not dependent on the patient's age, grading, or biological subtype of the carcinoma, but they concern the histopathological type and are significantly greater in pre-invasive carcinomas.

## Conflict of interest

None.

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