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# Quantitative Assessment of Contrast Enhancement on Contrast Enhancement Spectral Mammography (CESM) and Comparison With Qualitative Assessment

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**Abstract.** *Background/Aim: Contrast enhanced spectral mammography (CESM) is a novel method of breast cancer diagnosis. Benign lesions are enhanced after contrast injection on both CESM and breast magnetic resonance imaging (MRI). Kinetic curves on breast MRI facilitate differentiation between benign and malignant lesions, while on CESM there is no such possibility and we need to asses lesions based only on their level of enhancement and its patterns. The aim of this study was to compare two subjective assessments of enhancement level on CESM with numerical values measured using the region of interests (ROIs) and to categorize obtained enhancement level values. Patients and Methods: Patients with suspicious findings on previously performed examinations were qualified for CESM. The qualitative assessment was based on the subjective classification of visible contrast enhancement as weak, medium or strong. The quantitative assessment was obtained by measurements of an average enhancement value and sigma value within the ellipsoidal shape ROI, inserted into the evaluated contrast enhancing lesion. Results: The study group included 151 patients with total of 195 lesions diagnosed. It was verified how the classification based on the threshold values of %RS (percentage signal difference between enhancing lesion and background) and SDNR (signal-difference-to-noise Ratio) corresponds to a subjective assessment. Conclusion: Quantitative assessment of contrast enhancement on CESM is helpful in making decisions whether a lesion requires a biopsy. This can reduce the number of unnecessary biopsy procedures and reduce the cost of diagnostics.*

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*Key Words:* Breast cancer, contrast-enhanced spectral mammography (CESM), mammography (MG).

Breast cancer was the most common cancer in women worldwide, contributing 25.4% of the total number of new cases diagnosed in 2018 according to worldwide cancer data (1). The incidence of the disease is still increasing. Due to the fact that the incidence of breast cancer is increasing, new methods are being developed to detect breast cancer at an early stage and correctly assess cancer stage (2-4). contrast enhanced spectral mammography (CESM) is a novel method of breast cancer diagnosis. Recently, this method significantly gained popularity, so there is an increasing number of Medical Centers performing CESM. Literature data show that this methodology is much better than digital mammography (DM), DM combined with ultrasound (US) and comparable to breast magnetic resonance imaging (MRI) (3, 5, 6). Several studies comparing sensitivity, specificity and accuracy of CESM and breast MRI have been published (4, 7). The sensitivity of CESM in breast cancer detection is high, similar to breast MRI, but its specificity is slightly lower (8, 9). Nevertheless, recent reports indicate that in many cases CESM may replace breast MRI in the breast cancer diagnosis.

Based on the analysis of spectral mammography images, we aimed to gain information that allows us to distinguish between malignant and benign lesions. As it is known benign lesions in breasts can show enhancement on CESM images as well as in MRI. Kinetic curves in breast MRI facilitate differentiation between benign and malignant lesions (10), in CESM there is no such possibility. We can only subjectively assess the level of enhancement.

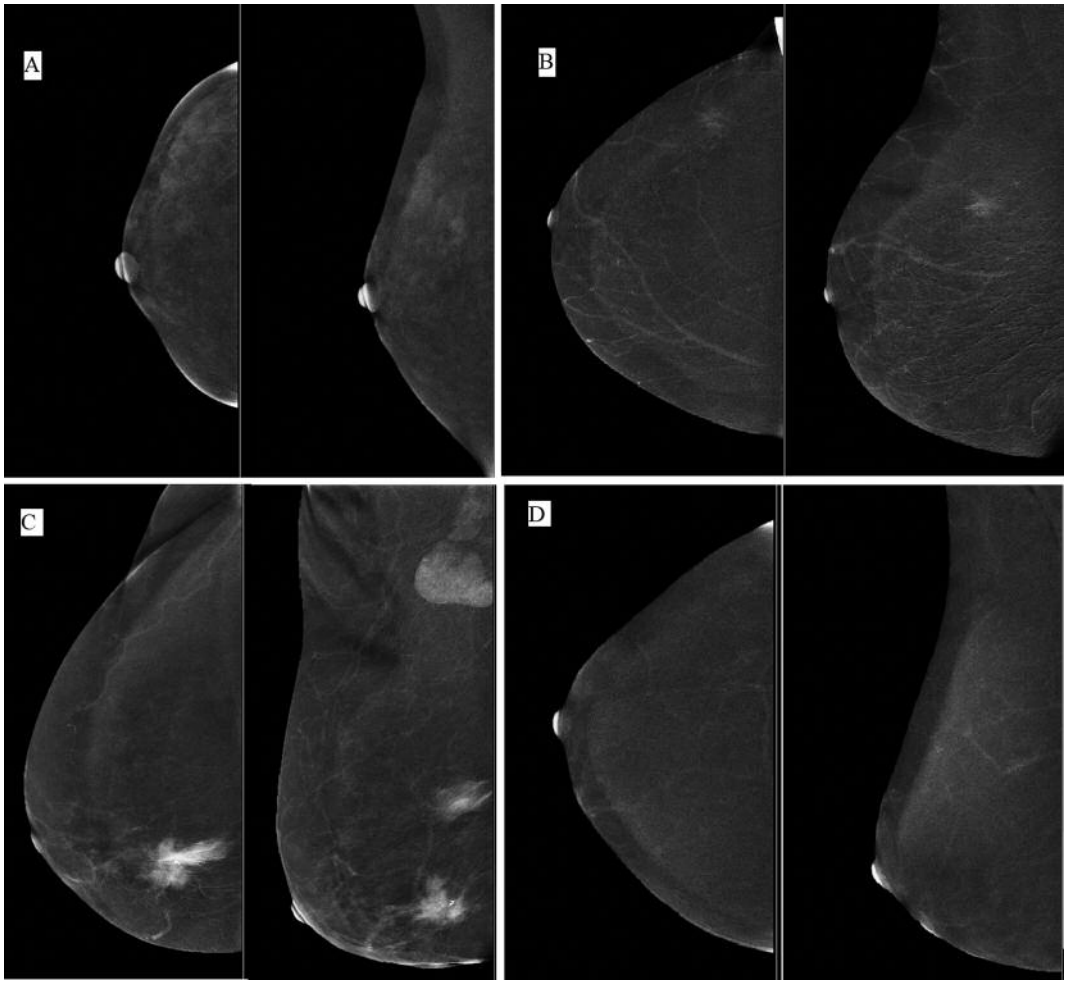


Figure 1. *Example contrast enhanced spectral mammography (CESM) images in cranio-caudal (CC) and medio-lateral (MLO) projections. (A) Lesion with weak level of enhancement visible. (B) Lesion with medium level of enhancement visible. (C) Lesion with strong level of enhancement visible. (D) Example CESM images of a normal breast, with no enhancement visible.*

The aim of this study was to compare two subjective assessments of enhancement levels on CESM with numerical values measured using the region of interests (ROIs – virtually selected area inside a lesion that provides quantitative information about the pixel brightness in the selected boundaries such as minimum and maximum, average and SD value) and categorize obtained enhancement level values into strong, medium and weak.

## Patients and Methods

*Patient eligibility.* Patients qualified for the CESM examination in the previous diagnostic imaging procedures received Breast Imaging-Reporting and Data System (BI-RADS) 4, 5 or 0 categories. CESM examination was performed according to the protocol used by the local Unit and also described in previous publications (5, 11). Patients with no contraindications, with normal TSH and eGFR levels were enrolled in the study. This study was performed in compliance with the Declaration of Helsinki and it received the approval of the Ethical Committee at the Regional Medical Chamber (acceptance No. OIL/KBL/17/2018).

*CESM assessment.* Iodine contrast agent (Iopromidum) was given intravenously at a dose of 1.5 ml/kg with the use of an automatic syringe. Two minutes after the contrast injection, the low- and high-energy acquisitions of each breast were performed in 2 projections: cranio-caudal (CC) and mediolateral-oblique (MLO). The radiologist supervising the examination indicated the breast from which the acquisition was started, based on the documentation that showed which breast had a lower risk of cancer. The order of acquisition was as follows: MLO projection of a less suspicious breast, MLO projection of a more suspicious breast, CC projection of a less suspicious breast and CC projection of a more suspicious breast. The study timing was set to be finished within 7 minutes

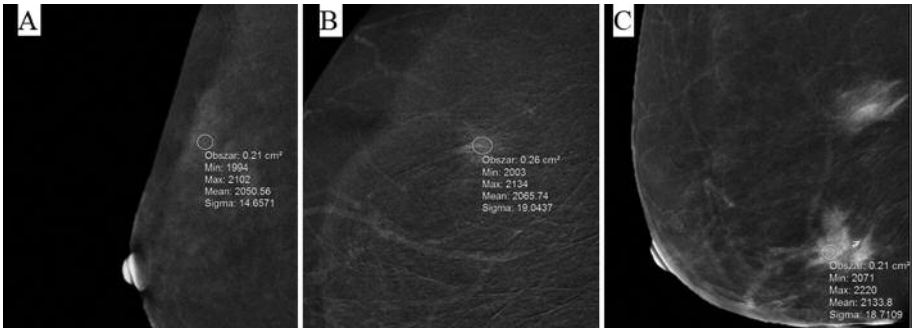


Figure 2. *Example region of interest (ROI) inserted into the lesion with: (A) weak enhancement level; (B) medium enhancement level; (C) strong enhancement level.*

after the contrast injection (12). Studies were evaluated by two independent radiologists. The first (No.1), with greater experience (over 10 years in CESM) made the qualitative evaluation. The second one (No.2), less experienced (over 5 years of CESM assessment) first performed the qualitative and then quantitative assessment. The qualitative assessment was based on the subjective classification of visible contrast enhancement as weak, medium or strong. To visualize the level of enhancement we provide a study with no enhancement at all (Figure 1).

The quantitative assessment was obtained by measurements of an average enhancement value and sigma value within the ellipsoidal shape ROI, inserted into the evaluated contrast enhancing lesion. Optimal ROI placement and shape depended on homogeneity (the higher the better), shape and size of the enhancement. The ROI area never exceeded the boundaries of the assessed lesion (Figure 2).

Both qualitative and quantitative assessment included the same area of enhancement in the CC and MLO projections.

Histopathological verification of the lesions visible in the achieved images that received the code BI-RADS 4 or BI-RADS 5 was obtained through:

- core needle biopsy (CNB) - if lesions were visible in ultrasound,
- vacuum assisted breast biopsy (VABB) - in case of microcalcifications visible in mammography or contrast enhancement is observed in breast MRI,
- surgical biopsy - in case of ambiguous results of percutaneous biopsies.

*Histopathological verification*. The obtained tissue samples underwent formalin fixation followed by paraffin embedding. Next, they were cut into sections up to 5 μm thick using a microtome and stained with hematoxylin and eosin. Specimens were evaluated by pathologists with experience in breast cancer detection. In case of a malignant tumor, the expression of progesterone, estrogen, herceptin receptors and the Ki-67 index were additionally evaluated.

*Statistical analysis*. In this study the subjective, qualitative assessment of CESM images by two independent Readers was compared to quantitative evaluation (numerous values measured within ROIs). The following parameters were analyzed: %RS (percentage signal difference between enhancing lesion and background) and signal-difference-to-noise ratio (SDNR), calculations were previously described (13). The level of contrast enhancement was compared to the value of background enhancement and its standard deviation, because different background values could influence the enhancement level parameters. Dependence between the qualitative assessment and the numerical value of enhancement level based on the Kruskal-Wallis test was examined. The description of the examined lesions consisted of the enhancement value, background level value, its standard deviations, and two subjective, independent assessments of the enhancement level – weak, medium and strong.

It was verified in what way the subjective assessments relate to the enhancement parameters and whether it is possible to determine, on their basis, the threshold values for classification of enhancement levels as weak, medium and strong. A comparison of both methods was also made with an appropriate non-parametric test. To compare the enhancement level values, a compatibility analysis based on Cohen's Kappa coefficient was used and its significance was checked. Significance level $\alpha$=0.05 was accepted for all tests.

## Results

The study group included 151 patients with a total of 195 lesions. Within the group, 133 patients were diagnosed with only one lesion, while 17 patients had two or more lesions. After a histopathological verification 142 lesions (73%) appeared to be malignant, including 122 infiltrating cancers in 122 cases while 53 lesions (27%) were benign. Figure 3 presents enhancement parameters distribution according to the lesion type. Higher values of enhancement are correlated with malignant lesions, particularly with infiltrating cancers. There are no significant differences between values of enhancement parameters for non-infiltrating cancers and benign lesions.

*Subjective evaluation – Reader No. 1*. Both parameters (%RS and SDNR) depend on the subjective assessment of Reader No.1 (the Kruskal-Wallis test $p<0.000$) – the higher the rating, the higher the parameter values (Figure 4). Based on the cut-off values of 95% confidence intervals (CI), the thresholds were divided in order to classify enhancement level as weak, medium and strong. Those threshold values are median between subsequent confidence intervals: 3.1% and 5.05% for %RS and 4.6 and 8 for SDNR. Therefore,

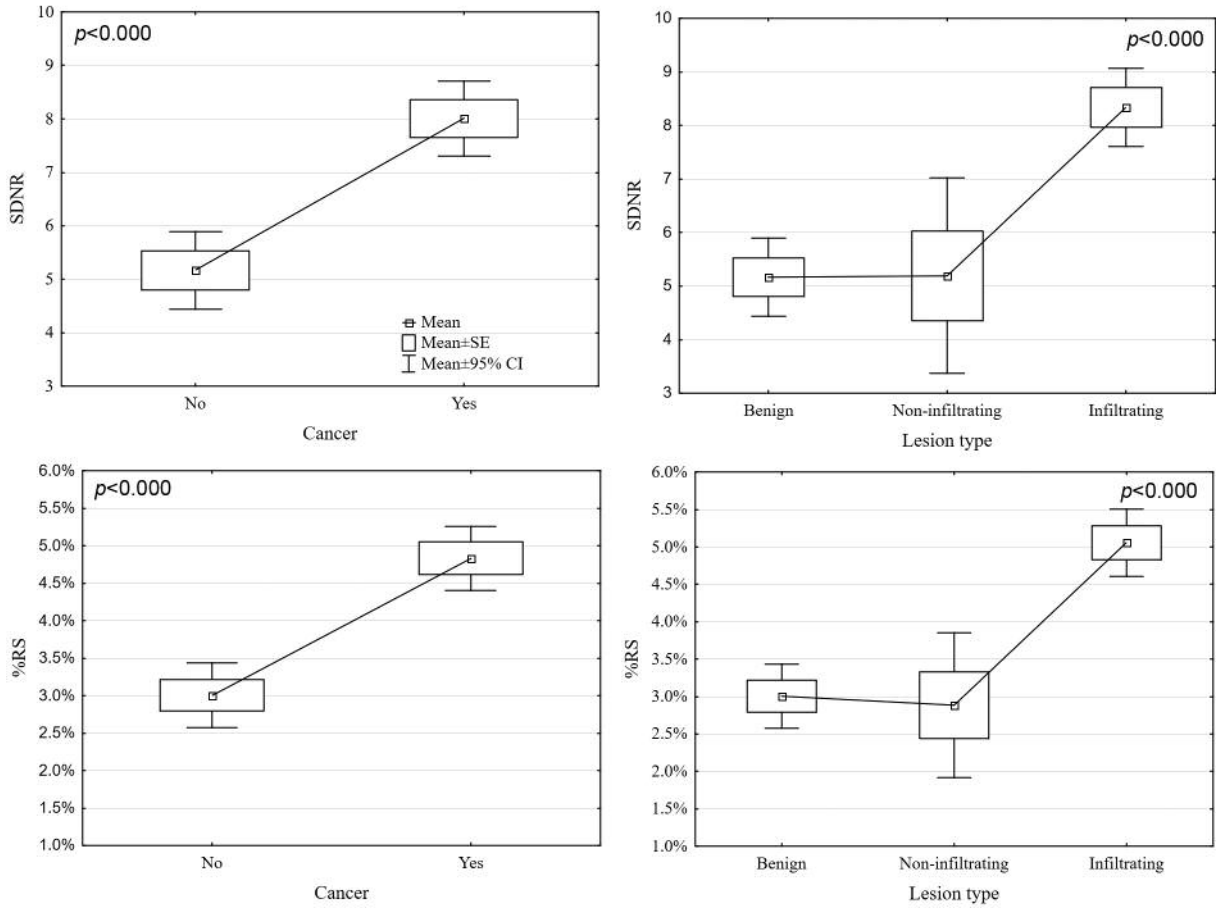


Figure 3. *Comparison of the enhancement value parameters with histopathological results.*

weak CESM enhancement level would be between (Table I). The next step involved verification of the relation between the classification based on %RS and SDNR threshold values to the subjective evaluation. The percentage of consistent ratings was counted, and the compatibility analysis based on Kappa coefficient was performed.

The compatibility of the enhancement assessment determined on the basis of the SDNR parameter and the subjective evaluation was better than that based on the %RS parameter and the subjective rating (the Kappa coefficient is 0.79 and 0.69, respectively). Nevertheless, the compatibility of both assessment methods based on enhancement parameters correlated with the subjective evaluation is reliable and statistically significant ($p<0.001$, detailed results are shown in Table II). Their comparison shows high correlation (Kappa coefficient 0.92) (Table II).

Figure 5 presents the distribution of the SDNR parameter and enhancement assessment based on the SDNR parameter. Lesions with a medium enhancement level are marked as triangles on the plot - for SDNR values ranging from 5.3 to 8.35, with the extreme enhancement values between 2,052 and 2,120. Weak (for lower values) and strong enhancements (for higher values) are also included within this range. This is due to the fact that SDNR is a relative parameter related to background enhancement and its standard deviation. Therefore, the SDNR parameter cannot be unambiguously related to the enhancement levels or enable division of cases only on the basis of enhancement level into weak, medium and strong. However, below the enhancement value of 2,052 we can definitely describe the enhancement as weak, while above 2,120 as strong. If the enhancement value is below 2,052, in 74% of cases lesions presented weak enhancement, according to the subjective evaluation of Reader No.1, while above enhancement value of 2,120 85% cases were classified as strong.

*Subjective evaluation – Reader No. 2.* An analogous analysis was performed for subjective evaluation by Reader No.2. Similarly, threshold values were set enabling categorization of cases into weak, medium and strong basing on the SDNR and %RS parameters (2.7% and 4.8%; 4.6 and 8

Table I. *Enhancement parameters values depending on subjective assessment performed by Reader No.1. %RS: Percentage signal difference between enhancing lesion and background; SDNR: signal-difference-to-noise ratio.*

| | All | CESM enhancement level | | |
|---|---|---|---|---|
| | | Weak | Medium | Strong |
| N | 170 | 49 | 57 | 64 |
| %RS | | | | |
| Medium value ±SE | 4.4±0.2% | 2.4±0.1% | 4.0±0.2% | 6.2±0.3% |
| Confidence interval | (4.0-4.7) | (2.1-2.6) | (3.6-4.5) | (5.6-6.8) |
| SDNR | | | | |
| Medium value ±SE | 7.3±0.3 | 4.1±0.2 | 6.8±0.4 | 10.1±0.5 |
| Confidence interval | (6.7-7.8) | (3.6-4.5) | (6.1-7.5) | (9.2-11.0) |

Table II. *Classification based on the enhancement parameters - Reader No. 1. %RS: Percentage signal difference between enhancing lesion and background; SDNR: signal-difference-to-noise ratio.*

| The compatibility assessment | Compatibility (%) | Kappa interval | Confidence | *p*-Value |
|---|---|---|---|---|
| Evaluation for %RS | 65 | 0.69±0.08 | (0.55-0.84) | 0.000 |
| Evaluation for SDNR | 74 | 0.79±0.07 | (0.65-0.94) | 0.000 |
| Both evaluations | 90 | 0.92±0.08 | (0.77-1) | 0.000 |

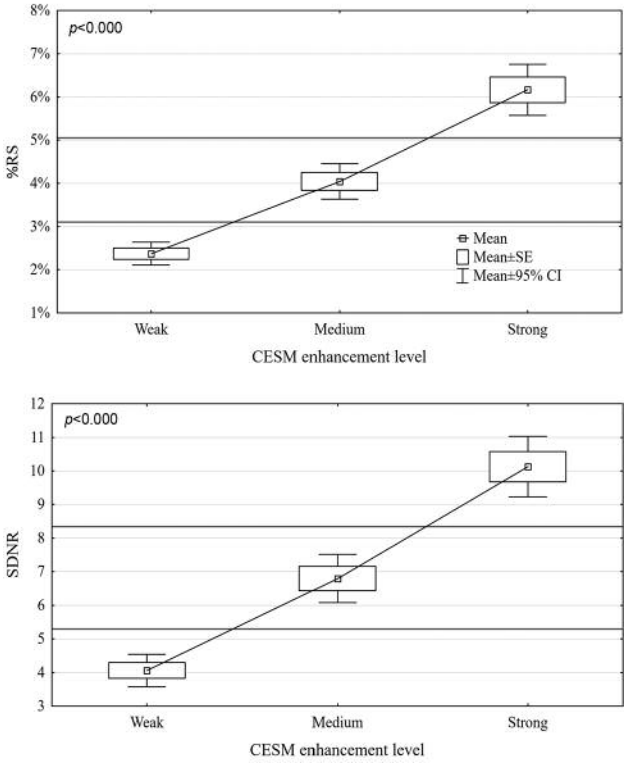


Figure 4. *Distribution of the percentage signal difference between enhancing lesion and background (%RS) and signal-difference-to-noise ratio (SDNR) parameters depending on the enhancement evaluation by Reader No. 1.*

respectively). It is worth noticing that the thresholds for No. 2 evaluation were lower than those for No.1 (Table III). Figure 6 presents the distribution of the %RS and SDNR parameters in correlation with the enhancement evaluation by Reader No. 2 (with threshold values).

Similarly to the No.1 assessment of enhancement levels, the No. 2 assessment was also compared to the classification based on the enhancement parameters. As for No.1, there is a better compatibility of the No.2 evaluation based on SDNR than based on %RS. In this case, however, the difference between kappa coefficients is smaller (0.02 *versus* 0.1) (Table IV).

Figure 7 presents the distribution of the SDNR parameter in function of enhancement level. A group of lesions with their enhancement classified as medium were indicated (SDNR values between 4.6 and 8) with triangle markers on the graph. Their extreme (min and max) values were 2,044 and 2,120. As in the evaluation No. 1 lesions with enhancement level below 2,044 were classified as weak, and above 2,120 as strong. It is worth mentioning that the enhancement cut-off value for cases categorized as strong was exactly the same – 2,120 as in the No.1 subjective evaluation. Below the enhancement value of 2,044 75% of cases were lesions with weak enhancement according to the second subjective evaluation, while above the enhancement level value of 2,120 - all lesions were assessed as strong.

*Comparison of subjective evaluations (No. 1 vs. No. 2).* Subjective evaluations of the enhancement values performed by Reader No. 1 and No. 2 were compared. In 67% of cases inter-rater agreement was achieved, while 12% of cases were assessed more restrictive (higher) by the Reader No.1. In contrast, another 21% cases were assessed higher by the Reader No. 2. This leads to the conclusion that the second radiologist was more restrictive applying higher grades than No.1, what was confirmed by the lower threshold values for classification of cases based on the SDNR and %RS parameters (Table V). The kappa coefficient value for assessments compatibility was high, 0.71 ($p$<0.000) (Table VI).

## Discussion

In this study a quantitative evaluation of 195 contrast enhanced lesions was performed. All lesions detected on CESM were histopathologically verified by core needle biopsy (CNB), vacuum-assisted breast biopsy (VABB),

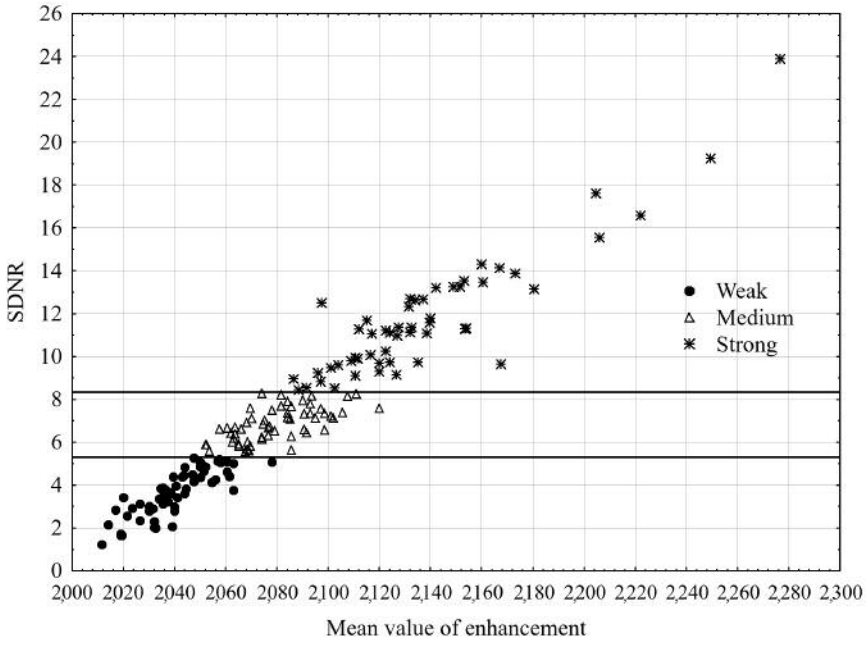


Figure 5. *The distribution of the signal-difference-to-noise ratio (SDNR) parameter in function of enhancement level given by Reader No. 1.*

Table III. *Enhancement parameters values depending on subjective assessment done by Reader No.2. %RS: Percentage signal difference between enhancing lesion and background; SDNR: signal-difference-to-noise ratio.*

| | All enhancing lesions | CESM enhancement level | | |
|---|---|---|---|---|
| | | Weak | Medium | Strong |
| N | 170 | 36 | 65 | 69 |
| %RS | | | | |
| Medium value ±SE | 4.4±0.2% | 2.0±0.1% | 3.4±0.1% | 6.5±0.2% |
| Confidence interval | (4.0-4.7) | (1.8-2.3) | (3.1-3.6) | (6.0-7.0) |
| SDNR | | | | |
| Medium value ±SE | 7.3±0.3 | 3.4±0.2 | 5.7±0.2 | 10.8±0.4 |
| Confidence interval | (6.7-7.8) | (3.0-3.9) | (5.3-6.0) | (10.0-11.5) |

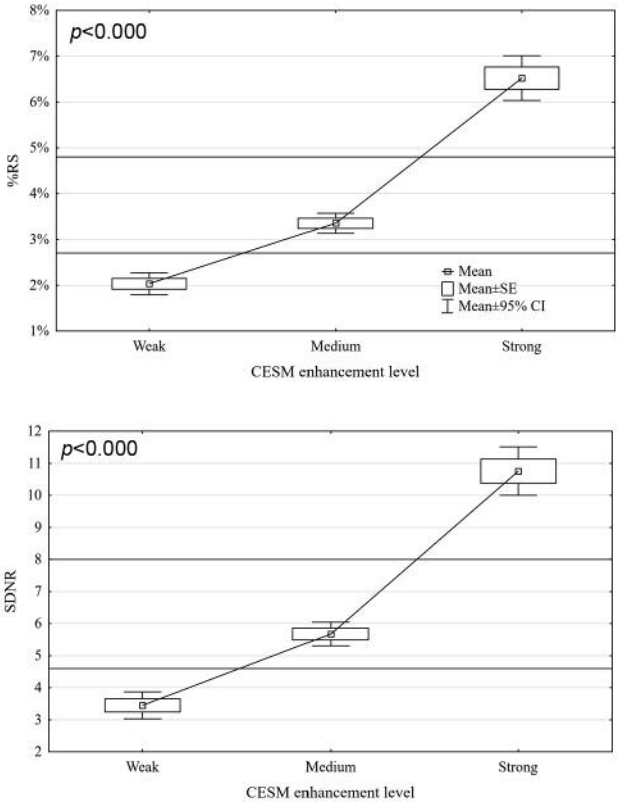


Figure 6. *Distribution of the percentage signal difference between enhancing lesion and background (%RS) and signal-difference-to-noise ratio (SDNR) parameters depending on the enhancement evaluation by Reader No. 2.*

tumorectomy or mastectomy. In the examined group of patients 122 lesions were invasive cancers, 28 fibroadenomas, 23 other types of benign lesions, 20 DCIS and 2 radial scar lesions. None of the visible contrast enhancement areas indicated a site verified as unchanged breast tissue.

The radiologist with less experience in CESM performing a qualitative and quantitative assessment obtained better results than the radiologist with greater experience in CESM performing only a qualitative assessment. The reader who used both methods was also more restrictive in his assessment, categorizing enhancement as strong more often than reader who used only qualitative method.

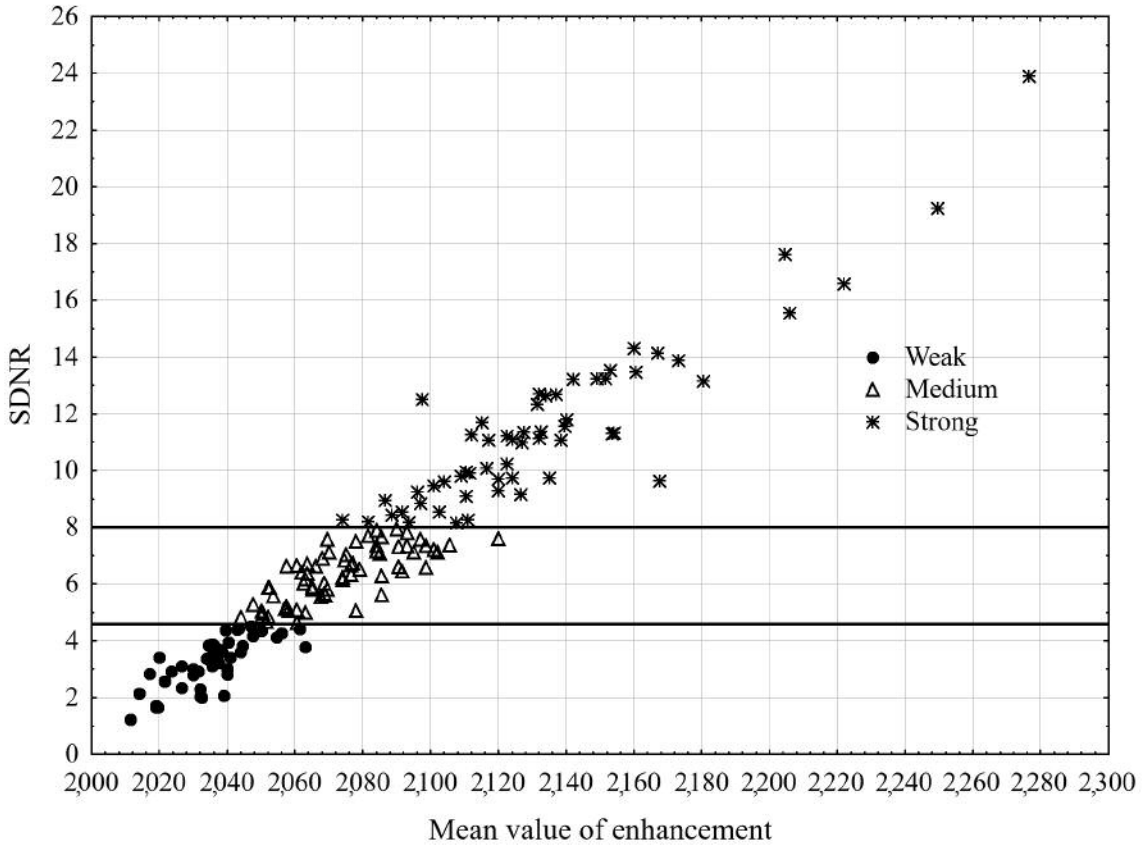


Figure 7. *The distribution of the signal-difference-to-noise ratio (SDNR) parameter in function of enhancement level given by Reader No. 2.*

Table IV. *Classification based on the enhancement parameters - Reader No. 2. %RS: Percentage signal difference between enhancing lesion and background; SDNR: signal-difference-to-noise ratio.*

| The compatibility assessment | Compatibility (%) | Kappa | Confidence interval | *p*-Value |
|---|---|---|---|---|
| Evaluation for %RS | 76 | 0.80±0.08 | (0.66-0.95) | 0.000 |
| Evaluation for SDNR | 78 | 0.81±0.07 | (0.66-0.96) | 0.000 |
| Both evaluations | 87 | 0.89±0.08 | (0.74-1) | 0.000 |

Table V. *Reader No. 1 and Reader No. 2 qualitative assessment comparison.*

| CESM enhancement level (Reader No.1) | CESM enhancement level (Reader No.2) | | | All |
|---|---|---|---|---|
| | Weak | Medium | Strong | |
| Weak | 30 | 17 | 2 | 49 |
| Medium | 6 | 34 | 17 | 57 |
| Strong | 0 | 14 | 50 | 64 |
| All | 36 | 65 | 69 | 170 |

Up until now, there were only few studies published describing the quantitative assessment of the CESM, so the possibility to compare parameters and extend the analysis with specific aspects of the evaluation was limited (13, 14). However, if there are more studies regarding aspects of the current study, we will look forward for a review of our results and compare them with new data.

This study has certain limitations. This was a retrospective study, so the amount of data that could be obtained from CESM

Table VI. *Reader No. 1 and Reader No. 2 qualitative assessment comparison threshold value of %RS. %RS: Percentage signal difference between enhancing lesion and background.*

| The compatibility assessment | Compatibility (%) | Kappa | Confidence interval | *p*-Value |
|---|---|---|---|---|
| Evaluation for %RS | 67 | 0.71±0.08 | (0.56-0.86) | 0.000 |

images was limited. The important limitation of this paper is the fact that one of the Readers assessed the acquired images only qualitatively, his evaluation was strictly subjective, and because of this the results were slightly overstated. However, analysis of the results indicated that there is no statistically significant difference between the qualitative assessment of the radiologist assessing patients only qualitatively and the assessment of the radiologist evaluating patients both qualitative and quantitative. Another limiting factor could be background parenchymal enhancement not being assessed. This value is not yet well examined in terms of CESM, but this is a topic of ongoing study which will be presented in the future. It should also be mentioned that the correlation between menstrual cycle phase and level of background parenchymal enhancement and potential fluctuations of lesions contrast uptake was not taken into consideration.

## Conclusion

Quantitative assessment of contrast enhancement in CESM is helpful in making decision whether a particular breast lesion requires a biopsy. This can reduce the number of unnecessary biopsy procedures and reduce the cost of diagnostics.

## Conflicts of Interest

The Authors declare that there are no conflicts of interest in terms of publication of this article.

## Authors' Contributions

W.R developed and researched the concept, collected and performed the data analysis and edited the text. All tree authors S.H., T.P. and Z.K contributed to the final version of the manuscript. E.L. edited text and supervised the study.

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