Added value of Contrast Enhanced Mammography (CEM) in staging of malignant breast lesions – a feasibility study

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Abstract:

Objectives: The aim of this feasibility study was to evaluate the added value of contrast enhanced mammography (CEM) in preoperative staging of malignant breast lesions, beyond standard assessment with digital mammography and ultrasound, as a base for a future prospective randomized trial.

Materials and methods: Fifty patients, with confirmed or strongly suspected malignant breast lesions after standard assessment (digital mammography (DM) and ultrasound (US)), scheduled for primary surgery, were invited to undergo CEM as an additional preoperative procedure. The primary endpoint was change in treatment plan defined as mastectomy instead of partial mastectomy or contrariwise, bilateral surgery instead of unilateral or neoadjuvant treatment instead of primary surgery. Accuracy in tumour extent estimation compared to histopathology was evaluated by Bland Altman statistics. Number of extra biopsies and adverse events were recorded.

Results: The study cohort consisted of 47 patients. In 10/47 (21%), findings from CEM affected the treatment plan. Agreement with histopathology regarding extent estimation was better for CEM (mean difference -1.36, SD +/- 18.45) in comparison with DM (-4.18, SD +/- 26.20) and US (-8.36, SD +/- 24.30). Additional biopsies were taken from 19 lesions in 13 patients. Nine biopsies showed malignant outcome. No major adverse events occurred.

Conclusion: Feasibility of preoperative additional CEM was found to be excellent without any serious negative effects. Results imply an added value of CEM in preoperative staging of breast cancer. Further evaluation in larger prospective randomized trials is needed.

Trial registration: ClinicalTrials.gov., NCT03402529, Registered 18 January 2018 – Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03402529?term=NCT03402529&draw=2&rank=1
Keywords

Breast cancer, preoperative staging, contrast enhanced mammography, CEM, contrast enhanced spectral mammography, CESM

Background

Digital mammography (DM) is the standard imaging modality for breast cancer diagnostics (1). Lower sensitivity of DM is related to e.g. high breast density (2-4), low patient age (2, 5) and lobular type of cancer (4). The use of ultrasound (US) in the clinical setting is particularly helpful in characterizing palpable and non-palpable masses, guiding biopsies of non-palpable lesions and staging of nodal status in the axilla (6). In addition, US has been shown to better estimate tumour size in comparison with DM (7, 8), but is inferior to DM regarding detection of DCIS (5). Both DM and US have been found to underestimate the size of the lesion in comparison with histopathological examination (8). It is important to correctly assess the extent of the malignant tumour in the preoperative planning for optimal surgical resection of the tumour area. Overestimation can lead to unnecessary mastectomies, and underestimation to reoperations due to inadequate margins of the tumour bed.

In cases of equivocal findings in DM and US, additional imaging may be warranted for correct preoperative staging. Dynamic, contrast enhanced magnetic resonance imaging (MRI) has so far been the modality with best sensitivity for detecting invasive cancer and it is not affected by breast density (2, 9). During the past five years, Contrast Enhanced Mammography (CEM), has been introduced as another complementary method at several breast centres in Europe and in the United States. Protocols for CEM have been described in detail previously (1, 10, 11). In short, CEM uses low- and high-energy standard DM views after administration of iodinated contrast medium. From these images, CEM software creates a subtracted image that highlights contrast uptake. Due to neoangiogenesis, tumours have a larger uptake of contrast agent than
other tissue, making the tumours more pronounced compared to surrounding tissue. For DCIS, which is not commonly associated with neoangiogenesis, the hypothesis is that leaky basal membranes allow leakage of contrast into the second (interstitial space) and third fluid space (mammary ducts) (12).

Initial studies of CEM have shown improved extent estimation compared to DM (11, 13-16), even in the presence of microcalcifications (17). In one study, CEM showed an improved extent estimation for 30 patients with biopsy-proven lobular cancer (18). In addition, CEM has been shown to change the diagnostic and treatment strategy in 41/195 patients (21%) (10) and 20/101 patients (20%) (19), with suspicious or undetermined screening detected findings on DM and/or US. However, only observational studies have yet been performed, with relatively small cohorts and a selected patient material (3, 10, 20). Previously published studies of estimated preoperative extent by CEM compared with the histopathological extent have included 30 to 118 patients (11, 13-17, 20). There is a need of larger prospective randomized trials with CEM to improve the level of evidence regarding the diagnostic value, effects on staging and choice of treatment in breast cancer.

The aim of this study was to evaluate the feasibility of CEM, including potential related adverse events, in the preoperative clinical setting, as a basis for a larger prospective randomized trial, for evaluation of the added value of CEM in preoperative staging beyond standard assessment with mammography and ultrasound.
Method

Study population

Fifty patients who had histologically confirmed (n=47) or at imaging (DM and/or US) strongly suspected (n=3) malignant breast lesions, and who were scheduled for primary surgery, were included in this feasibility study. Solid lesions as well as malignant microcalcifications were considered eligible. Seventy-five potential study participants were identified at the preoperative multidisciplinary team conference (MDT) before meeting the surgeon for information of the diagnosis and the study. The reasons for 25 patients not being included in the study are listed in Table 1. Study patients underwent CEM as an additional procedure, as a part of the preoperative investigation. The CEM procedure was scheduled during the normal waiting period before surgery and did not prolong the patients’ time to treatment.

Inclusion and exclusion criteria

Inclusion criteria were confirmed or strongly suspected malignant lesion in breast, for which primary surgery was planned and a signed informed consent. Exclusion criteria were planned neoadjuvant treatment, on-going pregnancy, breast feeding, allergy to iodinated contrast agent, treatment with metformin, renal failure or elevated serum creatinine, age < 18 years or > 80 years, ongoing thyrotoxicosis (upon suspicion, an additional blood sample of thyroid stimulating hormone (TSH) was taken) and inability to comprehend oral and written information regarding the study.

Data collection

Medical records and a questionnaire were used to collect patient data concerning factors that potentially can affect image diagnostics and to identify contraindications for CEM; weight, height, age, menstrual status, ongoing pregnancy or breast feeding, medications including
progesterone/oestrogen (oral contraceptives, hormone replacement therapy) or anti-hormonal
treatment (aromatase-inhibitors, tamoxifen), kidney disease, use of the antidiabetic medication
metformin and allergy to iodinated contrast agent.

Information on cancer subtype (ductal/lobular/other), uni-/multifocal lesions, surrounding
DCIS, histological grade, status of estrogen receptor (ER) and progesterone receptor (PgR),
Her2 amplification and Ki67 percentage (histological marker related to proliferation) were
collected from the postoperative pathological report. Histological total extent was also
retrieved.

_Imaging procedures_
DM and US were performed before study inclusion according to clinical standard. Breast
density was graded according to BI-RADS® 5th edition (21), from the DM images by the
radiologist after inclusion. The CEM examinations were performed at Unilabs Breast Center in
Lund on a Senographe Pristina mammography system equipped with SenoBright™ HD for
CEM (GE Healthcare). The contrast medium used was Omnipaque 300 mg/ml. 1.5 mg/kg
bodyweight (maximum 125 mg). It was injected by a peripheral venous catheter in the arm,
preferably on the side of the body not affected by cancer. Injection time was about 30 seconds.
After 1.45 minutes from start of injection compression was started. Dual imaging with high and
low energy images at each projection was performed after 2 minutes in the following order:
Cranio-caudal (CC) projection of the unaffected side, CC projection of the affected side,
mediolateral-oblique (MLO) projection of the affected side, MLO projection of the unaffected
side, mediolateral (ML) projection of the affected side and finally ML projection of the
unaffected side. All imaging had to be completed within 5 minutes (total time from start of
injection maximally 7 minutes). Patients were observed after the contrast media injection to discover potential allergic reactions.

All CEM images were read by the same radiologist (RR). At MDT all images were reviewed once more. The reading of CEM was not blinded since the study was performed as a part of the clinical routine. If additional lesions were found at CEM compared to the initial routine clinical imaging with mammography and ultrasound, a second look ultrasound was immediately performed by the radiologist on a Toshiba Aplio 400 ultrasound system and relevant biopsies were taken. All lesions were given a BI-RADS® assessment of 1-5. Total extent of the tumour area in mm was preoperatively estimated according to a protocol for each imaging modality (DM, US and CEM).

**Endpoints**

The primary endpoint was change in treatment plan, defined as mastectomy instead of partial mastectomy or vice versa, bilateral surgery instead of unilateral due to detection of contralateral cancer and neoadjuvant treatment instead of primary surgery. Secondary endpoints were to perform subgroup analyses of the performance of CEM by age, breast density, cancer subtype and presence of microcalcifications, to see if these factors affect the rate of change in the primary treatment plan. Accuracy of extent estimation of the malignant lesions by different methods (CEM, US and DM) compared to definitive histopathology, and the discrepancy between the methods were assessed. The number of extra biopsies taken due to new findings and quantity of these with malignant results were recorded as well as the number of adverse events to provide a risk evaluation of CEM, especially regarding the injection of iodinated contrast agent.
Statistical analyses

Descriptive statistics were used for parametric variables expressed as mean/median, standard deviation (SD)/interquartile range (IQR) and range, depending on the distribution. Descriptive statistics for non-parametric variables were presented as frequencies and percentages. Fisher's exact test was used to assess differences between groups and subgroups when applicable.

Pearson’s correlation coefficient and Bland-Altman statistics for each modality was performed for preoperative size estimation of the malignant changes by imaging modality in comparison with histopathology. Mean and median values of total extent are presented.

Statistical analyses were performed using SAS version 9.4, SAS Institute Inc., Cary, NC, USA.
Results

Fifty patients were included. Of these, one was subsequently excluded due to inability to get vein access for the CEM examination and two patients were non-eligible, as they had primary treatment plan of neoadjuvant therapy. The final study cohort included 47 women. Median age was 64 years (range: 34-82 years) and body mass index (BMI) was 24.8 kg/m² (range: 18.1-35.8 kg/m²). In 24/47 patients (51%) the malignancy was discovered by mammography screening. Breast density was assessed as low (A or B) in 31/47 patients (66%) and as high (C or D) in 16/47 (34%), according to the BI-RADS® classification (21). All patients in this study had malignancy only on one side at inclusion. In 8/47 cases (17%) there was a confirmed multifocality at inclusion (found by DM or US). In 16/47 cases (34%) there was presence of microcalcifications. Prior to inclusion, core-needle biopsies had shown DCIS in 5/47 cases (11%) and invasive cancer in 39/47 (83%). For the remaining three patients there was a suspicion of malignant diagnosis without positive biopsy. In the study cohort, after standard evaluation with DM and US and before CEM, there was a recommendation of partial mastectomy in 39/47 patients and mastectomy in 8/47 patients.

The primary treatment plan was changed in 10/47 cases (21%). A flowchart of how the treatment plan was affected by CEM related findings and biopsies is shown in Figure 1. For five patients, mastectomy instead of partial mastectomy (PME) was recommended; due to finding of multifocal cancer in three patients, and due to larger unifocal extent in two patients. For one patient PME instead of mastectomy was recommended, due to improved demarcation of the tumour area. For two patients, bilateral surgery was recommended instead of unilateral surgery, due to finding of contralateral cancer. Two patients were recommended neo-adjuvant treatment instead of primary surgery, leaving 45 patients going through primary surgery in the cohort. Four patients were subjected to mastectomy instead of recommendation of partial
mastectomy at MDT, in one patient due to her own choice and in three patients due to medical reasons. First operation was subsequently partial mastectomy in 31/45 (69%) patients (one bilateral) and mastectomy in 14/45 (31%) patients (one bilateral). Four patients (9%) went through a reoperation due to inadequate margins. The result after final surgery was PME in 30/45 patients (67%), (bilateral in one patient) and mastectomy in 15/45 patients (33%) (bilateral mastectomy in one patient).

No differences were seen for the frequency of change in therapy after CEM when the cohort was subgrouped by age, breast density, cancer subtype or presence of microcalcifications (Table 2).

Mean histological extent was 35.1 mm (SD 25.4). Agreement with histopathology was better for CEM (Bland Altman statistics; mean difference -1.36, SD +/- 18.45) regarding preoperative size estimation of the malignant changes in comparison with mammography (-4.18, SD +/- 26.20) and ultrasound (-8.36, SD +/- 24.30). (Table 3, Figure 2). Pearson’s Correlation Coefficients were stronger between the extent estimated by CEM and the definitive histopathological extent than for DM or US, for all cancer subtypes and both with and without presence of microcalcifications (Table 4).

In total, 19 additional lesions in 13/47 patients (28%) were biopsied due to detection at CEM (Table 5). In nine of the thirteen patients only one lesion was biopsied but in four of them two or more lesions were biopsied. Nine of the 19 biopsied lesions showed malignant disease (6 invasive cancer (32%) and 3 DCIS (16%)). Ten biopsied lesions were subsequently benign.
There were no adverse events during the CEM procedure besides some dizziness, light nausea and warmth (symptoms well recognised after injection of iodinated contrast agent) in three patients (6%). The inconveniences spontaneously went in total regress within a few minutes.
Discussion

The results from this feasibility study indicate that CEM has an added value in the preoperative setting. For 21% of the evaluable patients, the primary treatment plan was changed due to CEM findings. Importantly, only minor inconveniences after injection of iodinated contrast agent were recorded in three patients. No major adverse events occurred which hold promise for future studies.

Our results are in concordance with previous retrospective reviews of the impact of CEM on diagnostic method and treatment strategy, where 41/195 (21%) (10) and 20/101 patients (20%) (19), avoided an additional biopsy due to negative findings with CEM, were recommended more or less extensive surgery, or were recommended neoadjuvant treatment. No differences in the proportion of change in treatment plan were seen when patients were subgrouped by age, breast density, cancer subtype or presence of microcalcifications. This indicates that CEM has an added value for a large spectrum of patients with malignant breast lesions. As this study only includes a small number of individuals, a larger study is needed to assess these endpoints. However, results from this feasibility study stipulate no indication to limit the application of CEM to a certain subgroup, in the future trial.

In this study, CEM was superior to both US and DM regarding extent estimation, as random measurement errors for CEM were smaller than those for DM or US. All modalities tended to underestimate the extent compared to histological extent, however the mean difference for CEM was closest to histopathology even in the presence of microcalcifications. A reservation has to be made in this aspect as for larger tumours, US may have challenges to correctly measure the tumour extent if it goes beyond the transducer width of five centimeters.
CEM is presented as an alternative to MRI. In both methods, contrast medium uptake is pronounced in malignant lesions. Sensitivity of MRI is excellent, however a varying specificity has been reported for this modality (47-97%) (22). Previous studies of CEM have indicated a sensitivity similar to that of MRI (23-25), and equivalent or even higher specificity as well as equivalent tumour extent measurement (14). In this study, CEM was not compared to MRI. However, similar percentage for therapy modification as that found in this study, was presented in a study assessing the added value of MRI, where the primary treatment plan was changed for 18% of the study population (26).

A negative aspect of CEM is that it yields an additional dose of radiation. However, the average glandular dose from CEM is below the maximum dose regulated in the Mammography Quality Standards Act (13, 27, 28) and corresponds to maximally 7 months of natural background radiation. MRI does not yield additional radiation, however, there is uncleanness regarding eventual long-term effects of the contrast agent gadolinium, which has been found to accumulate in the brain (dentate nuceli, globus pallidus) (29). Both iodinated contrast agent and gadolinium have side-effects to the renal system with potential nephrotoxicity (30).

MRI is a resource demanding method. Availability may vary for the modality itself and MRI guided biopsy is not accessible in many units. Due to the position of the patient during MRI, findings can be difficult to identify for US guided biopsy afterwards. CEM is performed within a few minutes on a mammography apparatus using standard DM projections. Findings are thereby easy to identify by US for guidance of a biopsy, especially if both CC and ML projections are included in the protocol.

Strengths of this study include that two radiologists evaluated all imaging modalities (DM, US and CEM). There was also a good representation of ages, breast density and tumour types in
the cohort of study patients. As patients were consecutively included and only three excluded, we believe that selection bias is low in this cohort.

A limitation of the study is the small cohort size. Although large enough in the preparation for a future trial, it is too small to draw any reliable conclusions. Furthermore, DM and US were performed in the regular clinical setting and more defined protocols are needed for size estimation from DM and US to limit impact of individual radiologists (especially for US as DM can be reviewed retrospectively).

In addition, the included patients were the first to undergo CEM in the present hospital. This may reflect the rate of benign biopsies after findings with CEM in this study. Ten of the 19 biopsies taken were benign and can thus be considered false positive findings in CEM. Benign biopsies can however be helpful in the preoperative evaluation to limit malignant extent, allowing treatment recommendation to be changed from mastectomy to partial mastectomy. Additionally, some benign biopsies occurred due to finding of diffuse contrast enhancement, which has been previously studied in contrast enhanced MRI (31). This is often found in premenopausal women and can be hard to distinguish from DCIS. It can often be avoided by timing the imaging diagnostics in relation to the patient’s menstrual cycle (31). However, in the preoperative staging of breast cancer, there is no time to await ideal timing. Unnecessary biopsies are however of nuisance to the patient and should be avoided if possible. Plausibly, the identification of diffuse contrast enhancement compared to malignant findings will improve, as the radiologists become more acquainted with reading of CEM.

By running this feasibility study, routines were set up and experiences gained, providing a good setting for the future prospective randomised trial. The future trial will assess all endpoints
included in this study and more thoroughly explore the potential impact of additional preoperative CEM regarding number of reoperations, possible avoidance of mastectomy, margin status of partial mastectomies, 5-year recurrence rates and patient reported health-related quality of life. In addition, a cost/benefit evaluation of CEM will be performed.
Conclusion

In this feasibility study, CEM has shown an added value in preoperative staging of malignant breast lesions regarding impact on primary treatment plan by improved demarcation and extent estimation of tumours, finding of contralateral cancer and multifocality. This feasibility study is a foundation for a planned prospective randomized trial, exploring the added value of CEM in preoperative staging of breast cancer patients. Importantly, no major adverse events were seen, and only three patients experienced slight inconveniences after injection of the contrast medium.
List of abbreviations

BMI: Body mass index
CC: Cranio-caudal
CEM: Contrast enhanced mammography
DCIS: Ductal carcinoma in situ
DM: Digital mammography
ER: Estrogen receptor
IQR: Interquartile range
LOA: Limits of agreement
MDT: Multidisciplinary team conference
ML: Mediolateral
MLO: Mediolateral-oblique
MRI: Magnetic resonance imaging
PgR: Progesterone receptor
PME: Partial mastectomy
SD: Standard deviation
TSH: Thyroid stimulating hormone
US: Ultrasound
Ethics approval and consent to participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of Lund University approved the study (DNR: 2017/505). All study participants received oral and written information regarding the study. Written informed consent was retrieved from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

SZ has received speaker’s fees and travel support from Siemens Healthcare AG and consultancy fees from Collective Minds Radiology AB. All other authors declare that they have no competing interests.

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Authors’ contributions

All authors have made substantial contributions. KÅ has contributed with conception and design of the study, acquisition and interpretation of data, and as the main supervisor of AG together with EN and LR. RR has contributed to the study design, especially with knowledge concerning the radiological methods used, and as one of the radiologists reading the CEM images. CB has contributed by organising equipment and personnel at the mammography unit to conduct the study. EN, SZ and LR have contributed to study design and interpretation of data. AG has mainly been involved in the manuscript execution. All have revised the manuscript critically for important intellectual content, and all have given final approval of the version to be published.

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Tables

Table 1. Characteristics of excluded patients screened for eligibility in the trial

| Reason                                           | N   |
|--------------------------------------------------|-----|
| Shortage of time between diagnosis and operation | 7   |
| Patient declined participation                   | 4   |
| Patient not considered suitable due to comorbidity| 2   |
| Unclear reason                                   | 2   |
| Fulfillment of exclusion criteria                |     |
| Allergy to iodinated contrast agent              | 1   |
| Treatment with metformin                         | 2   |
| Elevated serum creatinine                        | 4   |
| Inability to comprehend study information        | 3   |
| **Total**                                        | **25** |
Table 2. Subgroup analysis: impact of breast density, age, cancer type and microcalcifications regarding therapy modification after CEM regarding therapy modification

| Grouping                  | Subgroup     | Therapy modified after CEM? | p-value<sup>2</sup> |
|---------------------------|--------------|----------------------------|---------------------|
| All patients              |              | Yes n (%)                  | No n (%)            |
| Breast density group<sup>1</sup> |              |                            |                     |
| A or B                    | 8 (26 %)     | 23 (74 %)                  |                     |
| C or D                    | 2 (12 %)     | 14 (88 %)                  | 0.457               |
| Age group<sup>3</sup>     |              |                            |                     |
| Below 56                  | 4 (27 %)     | 11 (73 %)                  |                     |
| 56 and above              | 6 (19 %)     | 26 (81 %)                  | 0.704               |
| Cancer type (index)       |              |                            |                     |
| Invasive ductal cancer    | 5 (19 %)     | 21 (81 %)                  |                     |
| Invasive lobular cancer   | 2 (25 %)     | 6 (75 %)                   |                     |
| Other invasive cancer     | 0            | 3 (100 %)                  |                     |
| DCIS                      | 1 (13 %)     | 7 (88 %)                   | 1.0000              |
| Microcalcifications       |              |                            |                     |
| No                        | 5 (17 %)     | 24 (83 %)                  |                     |
| Yes                       | 4 (25 %)     | 12 (75 %)                  | 0.6998              |

<sup>1</sup> Breast density graded according to BI-RADS®, ACR 5<sup>th</sup> Edition, A-B: low density, C-D: high density.

<sup>2</sup> Fisher’s exact test for association between grouping variable and therapy modification.

<sup>3</sup> Age of 56 defines an expected cut-off between pre- and postmenopausality

**CEM**: Contrast Enhanced Mammography. **DCIS**: Ductal carcinoma in situ.
Table 3. Estimation of total extent for all modalities and compared to histopathology

| Method       | Total extent (mm) | Difference from histopathology (mm) | LOA $^2$ (mm)         |
|--------------|-------------------|-------------------------------------|-----------------------|
| **CEM**      |                   |                                     |                       |
| Mean (SD)    | 33.8 (28.3)       | -1.4 (18.5)                         | -37.523; 34.812       |
| Median (Q1; Q3) | 22 (14; 50)    | 0 (-12; 5)                          |                       |
| Min; Max     | 0; 100            | -55; 50                             |                       |
| **Ultrasound** |                   |                                     |                       |
| Mean (SD)    | 26.8 (24.2)       | -8.4 (24.3)                         | -55.977; 39.266       |
| Median (Q1; Q3) | 18 (9; 35)     | -8 (-22; -1)                        |                       |
| Min; Max     | 0; 95             | -60; 80                             |                       |
| **Mammography** |                 |                                     |                       |
| Mean (SD)    | 31.0 (24.8)       | -4.2 (26.2)                         | -55.534; 47.179       |
| Median (Q1; Q3) | 20 (12; 50)    | -5 (-15; 3)                         |                       |
| Min; Max     | 0; 95             | -70; 80                             |                       |
| **Histopathology** |             |                                     |                       |
| Mean (SD)    | 35.1 (25.4)       |                                     |                       |
| Median (Q1; Q3) | 26 (15; 45)     |                                     |                       |
| Min; Max     | 8; 110            |                                     |                       |

$^1$ Bland Altman statistics (For plots see Figure 1)

$^2$ Limits of Agreement: Mean Diff ± 1.96*SD

Difference is calculated as: Total Extent from estimation method - Total Extent from histopathology.

**CEM**: Contrast Enhanced Mammography.
Table 4. Correlation of estimated extent in relation to histopathological extent

| Subgroup              | n  | Mammography | Ultrasound | CEM  |
|-----------------------|----|-------------|------------|------|
| **Cancer type**       |    |             |            |      |
| *Invasive ductal cancer* | 26 | 0.533       | 0.648      | 0.818 |
| *Invasive lobular cancer* | 8  | 0.400       | 0.453      | 0.835 |
| *DCIS*                | 8  | 0.151       | 0.389      | 0.769 |
| **Microcalcifications** |    |             |            |      |
| *No*                  | 28 | 0.647       | 0.670      | 0.770 |
| *Yes*                 | 15 | 0.366       | 0.474      | 0.915 |

Pearson’s correlation coefficient was used to compare extent for all modalities (CEM, ultrasound and mammography) to definitive extent from the postoperative histopathological report.

Pearson’s correlation coefficient measures the strength of the monotonic relationship between continuous data and may lie between -1 and 1. 0–0.19 = very weak, 0.2–0.39 = weak, 0.4–0.59 = moderate, 0.6–0.79 = strong, 0.8–1 very strong.

**CEM**: Contrast Enhanced Mammography, **DCIS**: Ductal carcinoma in situ.
Table 5. Additional biopsies due to findings from CEM

|                          | No    | Yes   |
|--------------------------|-------|-------|
| At least one additional biopsy (n=47) |       |       |
|                          | 34 (72%) | 13 (28%) |
| Biopsy led to changed treatment (n=13) |       |       |
|                          | 6 (46%) | 7 (54%) |
| Additional biopsies per patient |       |       |
|                          | 34 (72%) | 9 (19%) |
|                          | 2 (4%) | 2 (4%) |
| Total number of additional biopsies |       | 19 |
| Outcome from additional biopsies (n=19) |       |       |
|                          | Invasive cancer | 6 (32%) |
|                          | DCIS | 3 (16%) |
|                          | Benign | 10 (53%) |

CEM: Contrast Enhanced Mammography, DCIS: Ductal carcinoma in situ.
Figures

Figure 1. Flowchart of how the treatment plan was affected by CEM related findings and biopsies

**MDT 1: Recommendation of primary treatment plan (n=50)**

- Included patients planned for unilateral partial mastectomy (n=39)
- Included patients planned for unilateral mastectomy (n=9)
- Included patients planned for neoadjuvant therapy (n=2)

**Study cohort CEM (n=47)**

- Patients with biopsies due to new ipsilateral findings (n=9*)
  - Malignant (n=5)
  - Benign (n=4)
- Patients with biopsies due to new contralateral findings (n=6*)
  - Malignant (n=2)
  - Benign (n=4)
- Additional information at CEM but no biopsy (n=3)
- No additional information at CEM (n=31)

**Exclusion because of inability to get vein access for CEM (n=1)**

**Non-eligible as planned neoadjuvant therapy is exclusion criteria (n=2)**

**MDT 2: Review of CEM findings and biopsy results**

- Partial mastectomy instead of mastectomy (n=1)
- Mastectomy instead of partial mastectomy (n=5)
- Bilateral surgery instead of unilateral (n=2)
- Neoadjuvant therapy instead of primary surgery (n=2)
- No change of primary treatment plan (n=37)

*= two patients had biopsies towards both ipsilateral and contralateral breast after CEM

MDT: Multi-disciplinary team conference
Figure 2. Bland-Altman plots: Estimated extent by mammography, ultrasound and CEM compared to histopathology (PAD)

Mammography, US and CEM images were compared to histopathological extent (used as the reference value. Mean difference for mammography measurements: -4.18 mm (95% LOA -55.534 to 47.179 mm), US: -8.14 mm (95% LOA -55.977 to 39.266 mm) and CEM: -1.36 mm (95% LOA -37.52 to; 34.812 mm).

**CEM**: Contrast Enhanced Mammography, **LOA**: Limits of agreement, **PAD**: Pathological anatomical diagnosis.