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Early, delayed, or combined contrast-enhanced mammography for detecting residual disease after neoadjuvant chemotherapy in breast cancer

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Abstract

Objectives To evaluate the diagnostic performance of contrast-enhanced mammography (CEM) for detecting residual disease (RD) and assessing residual tumor size after neoadjuvant chemotherapy (NAC) in breast cancer, comparing early-only, delayed-only, and combined acquisition protocols.

Materials and methods This retrospective single-center diagnostic performance study included consecutive women with biopsy-proven breast cancer who underwent pre- and post-NAC CEM with both early and delayed acquisitions and subsequent surgery (2016–2024). Patients without complete CEM protocols or surgical pathology were excluded. CEM images were independently analyzed for each protocol by two experienced breast radiologists in consensus. Radiological response was categorized per RECIST and dichotomized as complete response versus RD. Pathological tumor staging (ypT) at surgery was the gold standard; pathologic complete response (pCR) was defined as ypT0/ypTis. Diagnostic performance in predicting RD was calculated for each protocol with sensitivity and negative predictive value (NPV) as primary endpoints (χ^2 test). Bland–Altman analysis compared imaging-measured and pathological tumor sizes.

Results Of 202 women included (mean age, 54.7 ± 12.7), 83 (41.1%) achieved pCR. Sensitivity for detecting RD was higher for delayed (85.7%, 95% CI 78.1–91.5%) and combined protocols (86.6%, 79.1–92.1%) compared to early (68.1%, 58.9–76.3%; $p < 0.0001$). NPV improved from 58.2% (95% CI 48.3–67.6%) to 71.2% (62.3–79.0%; $p = 0.04$) with delayed acquisitions. Bland–Altman analysis showed slightly better agreement between early images and pathology (mean difference 5.7 mm) than for delayed acquisitions (11.8 mm).

Conclusions Delayed CEM images significantly improved sensitivity and NPV in predicting RD, supporting the inclusion of delayed acquisitions in the neoadjuvant setting.

Key Points

Question *Can contrast-enhanced mammography protocols be optimized after neoadjuvant chemotherapy to improve the detection of pathological residual disease and residual tumor size assessment?*

Findings *Delayed contrast-enhanced mammography acquisitions significantly improved sensitivity and negative predictive value for residual disease detection, whereas early acquisitions provided slightly better agreement for residual tumor size.*

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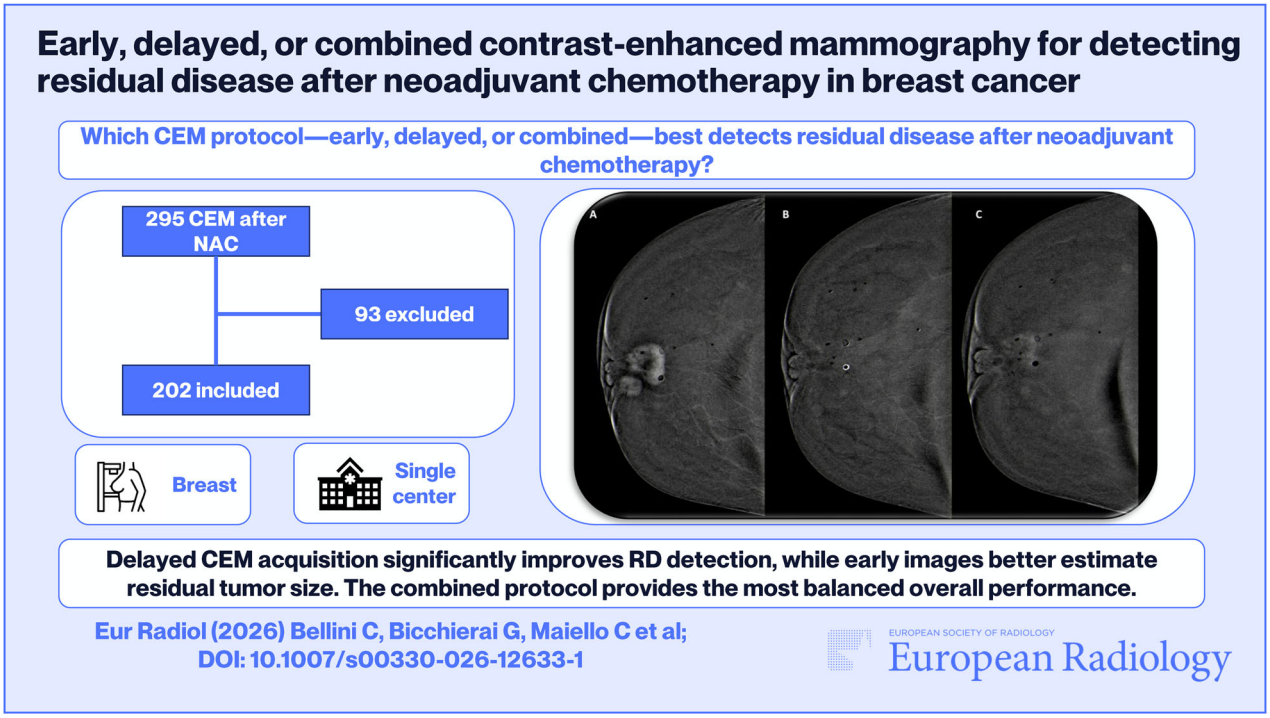
Clinical relevance *Including delayed images in post-neoadjuvant contrast-enhanced mammography improves detection of residual invasive disease, supporting surgical planning, while early images remain useful for tumor size estimation.*

Keywords Breast neoplasms, Mammography, Contrast media, Neoadjuvant therapy

Graphical Abstract



Introduction

Neoadjuvant chemotherapy (NAC) is the standard of care for locally advanced breast cancer and selected early-stage tumors with triple-negative or HER2-positive phenotypes. Pathological complete response (pCR) is associated with improved long-term outcomes, and accurate preoperative identification of residual disease (RD) is critical for tailored surgical planning for de-escalation of surgery [1].

Contrast-enhanced MRI is the reference technique for assessing tumor response post-NAC due to its high sensitivity in detecting RD [2–4]; however, access is limited by cost, time and contraindications [5]. During NAC, patients typically require at least two MRI examinations—baseline and post-treatment—raising concerns about availability, cost, and patient tolerance [6]. Moreover, the increasing use of magnetic seeds for localizing non-palpable lesions can generate susceptibility artifacts, hindering reliable evaluation of RD [7, 8].

Contrast-enhanced mammography (CEM) has recently emerged as a promising alternative [9]: it combines morphologic and functional imaging through dual-energy acquisition after intravenous iodinated contrast injection to visualize tumoral neoangiogenesis [10]. CEM is faster, more accessible, and potentially more cost-effective than MRI [11–13], with several studies showing higher patient preference due to shorter examination times and improved comfort [14–16]. Clinical applications of CEM mirror those of MRI, with comparable diagnostic performance, particularly in problem-solving and presurgical staging [17–22], and with promising results in monitoring NAC response [23–26].

Despite its increasing use, evidence regarding standardized CEM acquisition protocols remains limited [27]. Typically, CEM includes a set of early images (~ 2 min) and optional delayed images (~ 8 min), but the clinical advantage of delayed images is unclear. In current clinical practice, the use of delayed CEM acquisitions after NAC is inconsistent across institutions, and their actual contribution to response assessment remains uncertain. As a result, CEM protocols vary substantially, limiting comparability across studies and everyday clinical implementation. We hypothesized that delayed acquisitions

could improve RD detection, as many chemotherapeutic agents, such as anthracyclines, taxanes, and HER2-targeted therapies, alter tumor vascularization [28, 29].

In breast MRI, systemic therapy reduces enhancement in fibroglandular tissue and tumors, and late enhancement in delayed imaging can indicate residual malignancy [6, 30].

Accordingly, delayed CEM images may enhance the identification of small foci of residual disease, potentially improving sensitivity for RD prediction. However, evidence comparing early, delayed, and combined CEM acquisition protocols after NAC remains limited, and standardized recommendations are currently lacking.

To our knowledge, only one prior study investigated this topic in NAC, reporting promising results in a small cohort [25]. The aim of our study was to compare early-only, delayed-only, and combined CEM protocols for their sensitivity and negative predictive value (NPV) in predicting RD in a larger patient population, providing evidence to support protocol standardization; secondary objectives included evaluation of tumor size assessment and other diagnostic accuracy metrics.

Materials and methods

Study design and patient population

This single-center retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (AOU Careggi, #16.251_AOUC). Informed consent was waived due to the retrospective design. Consecutive women with biopsy-proven breast cancer who underwent pre- and post-NAC CEM, including both early and delayed acquisitions, and subsequent surgery between September 2016 and December 2024, were retrospectively identified from our institutional PACS and electronic medical records at a tertiary care hospital. Inclusion criteria were biopsy-proven breast cancer, completion of neoadjuvant chemotherapy, availability of pre- and post-NAC contrast-enhanced mammography with early and delayed acquisitions, and subsequent surgery with histopathological assessment. Exclusion criteria were incomplete CEM datasets or the absence of post-neoadjuvant CEM and/or surgical pathology. Patient selection is detailed in Fig. 1.

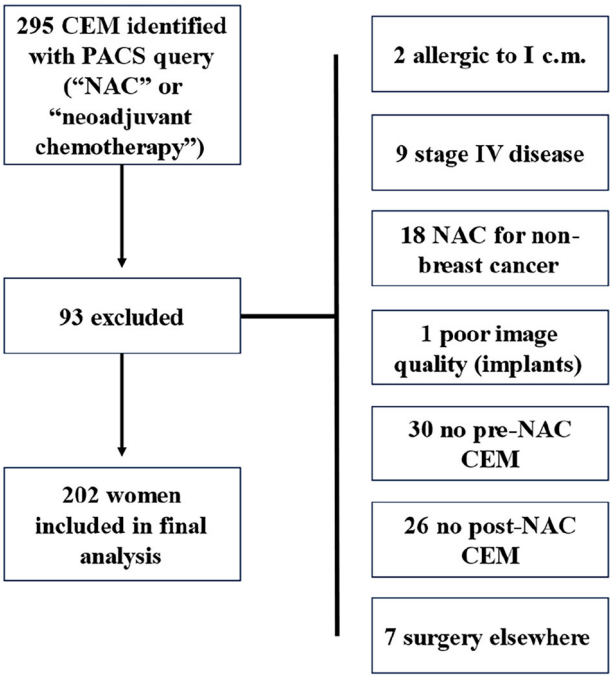


Fig. 1 Flowchart showing patient selection for inclusion in the study. From an initial cohort of 295 women identified through a PACS query for "neoadjuvant chemotherapy" or "NAC" who underwent CEM between September 2016 and December 2024, several were excluded for predefined criteria, resulting in a final study population of 202 patients

CEM protocol

CEM was executed with a commercial mammography system (Selenia Dimensions, Hologic) after intravenous injection of 1.5 cc/kg of iodinated contrast (Iopromide 370 mg/mL; Bayer HealthCare or Iopamidol 370 mg/mL; Bracco Imaging S.p.A) at 3 cc/s followed by 20 mL of saline flush with an automated power injector. Early images were acquired 2 min post-injection, obtaining in sequence craniocaudal (CC) and mediolateral oblique (MLO) views of both breasts within 5 min, starting from the affected side. For each CEM view, a low-energy image (LE) and a high-energy image were performed serially, at 26–31 kVp with rhodium and silver filters and at 45–49 kVp with a copper filter, respectively. A recombination algorithm was used to subtract the unenhanced breast tissue and provide a recombined image (RC) for highlighting the areas of relative contrast enhancement. Delayed images were obtained at 8 min post-injection following the same order. The complete CEM examination required approximately 12 min from contrast injection to completion of delayed acquisitions. The detailed workflow of the protocol is illustrated in Fig. 2.

Image analysis

Two experienced breast radiologists (C.B., G.B.), with 10–17 years of experience in breast imaging and 9 years' experience in contrast-enhanced mammography (CEM), independently reviewed all recombined CEM image sets (early, delayed, and combined) in randomized reading sessions, blinded to histopathological results; discrepancies were resolved by consensus. For each acquisition protocol, radiological response was assessed according to RECIST 1.1 criteria by comparison with the pre-neoadjuvant chemotherapy examination [31].

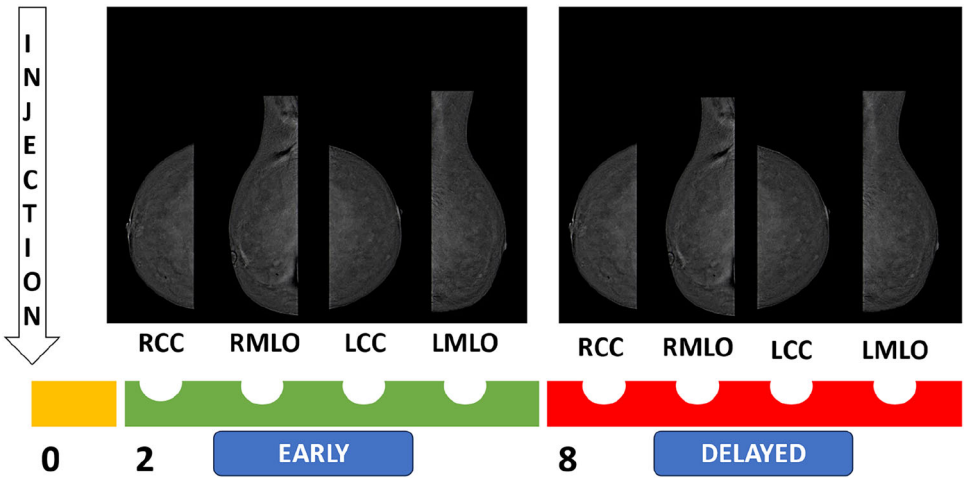


Fig. 2 Acquisition protocol for contrast-enhanced mammography, including early (2-min) and delayed (8-min) post-contrast images. Standard institutional contrast-enhanced mammography acquisition protocol. For this study, the affected breast was imaged first

RECIST response categories were recorded and subsequently dichotomized for the primary analysis as complete response versus residual disease (RD). Complete response was defined as the absence of residual enhancement. Partial response was defined as a ≥ 30% reduction in the longest lesion diameter, progressive disease as a ≥ 20% increase, and stable disease when neither criterion was met. For the combined (early + delayed) protocol, the presence of residual enhancement on either early or delayed images was considered indicative of residual disease. When residual enhancement was present, the largest lesion diameter was measured on recombined images. In cases of multifocal or multicentric disease, measurements were performed on the largest enhancing lesion.

Prior to the study readings, the two readers jointly reviewed a case set of 15 CEM cases excluded from the analysis, with the aim of standardizing measurement procedures for tumor size assessment.

Pathological assessment

All patients underwent surgery within 30 days of post-NAC CEM. Dedicated breast pathologists (5–20 years' experience) assessed surgical specimens (V.V., E.N.). Pathological tumor staging (ypT) at surgery served as the reference standard for response assessment. Pathological complete response (pCR) was defined as the absence of residual invasive carcinoma in the breast (ypT0 or ypTis), irrespective of nodal status, due to the known limitations of CEM in axillary evaluation. Cases showing ductal carcinoma in situ (DCIS) (ypTis) were documented. When multifocal or multicentric disease was present, measurements were performed on the largest lesion identified in the surgical specimen.

Neoadjuvant chemotherapy protocol

In our center, neoadjuvant treatments were administered according to established standard-of-care protocols for each breast cancer subtype. Patients with triple-negative disease received taxane–carboplatin chemotherapy followed by anthracyclines, with the addition of pembrolizumab when eligible, consistent with the KEYNOTE-522 regimen [32–34]. Patients with HER2-positive tumors were treated with anthracycline-free chemotherapy combined with trastuzumab and pertuzumab, in accordance with current clinical practice [35]. In HR+/HER2-negative disease, NAC was reserved for cases with high clinical or biological risk [36], whereas neoadjuvant endocrine therapy was considered for patients with molecularly low-risk profiles to increase the likelihood of breast-conserving surgery [37, 38].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v28.0 (IBM Corp).

Nonparametric statistical tests (Mann–Whitney U test for continuous variables and the χ^2/Fisher's exact test for categorical variables) compared clinical, radiologic, and pathologic features between pCR and RD groups. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables as frequencies and percentages (%).

Radiological response, categorized according to RECIST 1.1 criteria, was dichotomized for the primary analysis as complete response versus RD (including partial response, progressive disease, and stable disease). Sensitivity and negative predictive value (NPV) were selected as the primary endpoints due to their clinical relevance in identifying the presence of RD and safely excluding pathological

complete response in the neoadjuvant setting. Sensitivity and NPV were calculated for early-only, delayed-only, and combined CEM protocols and compared using the χ^2 test.

For completeness, diagnostic accuracy, specificity, positive predictive value (PPV), and receiver operating characteristic (ROC) curves with corresponding areas under the curve (AUC) were also calculated. ROC analysis was performed for descriptive purposes only; no formal statistical comparison between AUCs was conducted. True-positive (TP) cases were defined as RD detected on CEM and confirmed at histopathology, false-positive (FP) cases as RD detected on CEM with pCR at histology, true-negative (TN) cases as complete response on CEM confirmed at histology, and false-negative (FN) cases as complete response on CEM with RD at pathology. Performance metrics were compared with the χ^2 test. A two-sided p-value < 0.05 was considered statistically significant. Finally, Bland–Altman analysis assessed the agreement between the lesion size measured on early and delayed CEM images and pathology, the reference standard.

Results

Study population

After excluding 93 of 295 patients screened, 202 women (mean age, 54.7 ± 12.7) were included in the final analysis; pCR was achieved in 83 patients (41.1%), while 119 patients (58.9%) had RD. Among the demographic, radiological and pathologic characteristics shown in Table 1, molecular subtype was significantly associated with response: triple-negative and HER2-positive tumors showed higher pCR rates compared with luminal subtypes ($p \le 0.01$). Table 2 summarizes surgical and histopathologic data among RD patients. No adverse reaction to iodinated contrast medium occurred.

Table 1 Baseline clinicopathological and imaging characteristics of the study population according to pathological response after neoadjuvant chemotherapy (NAC)

Variable	All patients ($n = 202$)	pCR ($n = 83$)	RD ($n = 119$)	p-value
Age, years (median [IQR])	53.0 (46.0–61.0)	53.0 (46.0–59.5)	54.0 (47.0–65.0)	0.158
Breast density				0.581
A	25 (12.4%)	12 (14.5%)	13 (10.9%)	
B	73 (36.1%)	26 (31.3%)	47 (39.5%)	
C	66 (32.7%)	30 (36.1%)	36 (30.3%)	
D	38 (18.8%)	15 (18.1%)	23 (19.3%)	
BPE pre-NAC				0.667
Marked	16 (7.9%)	7 (8.4%)	9 (7.6%)	
Mild	62 (30.7%)	29 (34.9%)	33 (27.7%)	
Minimal	82 (40.6%)	30 (36.1%)	52 (43.7%)	
Moderate	42 (20.8%)	17 (20.5%)	25 (21.0%)	
BPE post-NAC				0.375
Marked	1 (0.5%)	0 (0.0%)	1 (0.8%)	
Mild	41 (20.3%)	16 (19.3%)	25 (21.0%)	
Minimal	153 (75.7%)	66 (79.5%)	87 (73.1%)	
Moderate	7 (3.5%)	1 (1.2%)	6 (5.0%)	
Size before NAC, mm (median [IQR])	32.0 [23.2–49.8]	30.0 [21.5–44.5]	35.0 [25.0–50.0]	0.047
Microcalcifications prior to NAC				0.544
No	111 (55.0%)	43 (51.8%)	68 (57.1%)	
Yes	91 (45.0%)	40 (48.2%)	51 (42.9%)	
Molecular subtype				< 0.001
HER2+	88 (43.6%)	52 (62.7%)	36 (30.3%)	
Luminal A	14 (6.9%)	4 (4.8%)	10 (8.4%)	
Luminal B	73 (36.1%)	13 (15.7%)	60 (50.4%)	
Triple negative	27 (13.4%)	14 (16.9%)	13 (10.9%)	

Data are expressed as median [IQR] or number of patients (percentage). Comparisons were performed using the Mann–Whitney U test and χ^2 or Fisher's exact test, as appropriate

pCR pathological complete response, *RD* residual disease, *NAC* neoadjuvant chemotherapy, *BPE* background parenchymal enhancement

CEM diagnostic performance in predicting RD

Sensitivity for detecting RD was significantly higher for delayed-only (85.7%, 95% CI 78.1–91.5) and combined (86.6%, 95% CI 79.1–92.1) protocols compared with early-only acquisitions (68.1%, 95% CI 58.9–76.3) ($p < 0.0001$), with no significant difference between delayed-only and combined protocols ($p = 0.412$). A case-example is shown in Fig. 3. NPV was also significantly higher for delayed-only acquisitions (71.2%, 95% CI 60.3–80.1) than for early-only (58.2%, 95% CI 50.6–65.5) ($p = 0.0032$), with no significant difference between delayed-only and combined protocols (70.4%, 95% CI 58.7–79.9; $p = 0.847$). No statistically significant differences were observed among early-only, delayed-only, and combined protocols in terms of specificity ($\chi^2 = 2.98$, $p = 0.225$), PPV ($\chi^2 = 0.36$, $p = 0.837$), or diagnostic accuracy ($\chi^2 = 1.22$, $p = 0.543$). Diagnostic performance of early-only, delayed-only, and combined CEM protocols is detailed in Table 3 and ROC curves are shown in Fig. 4. Among discordant cases, 22/38 (57.9%) early FN were correctly reclassified as TP after delayed acquisitions, whereas 4/30 (13.3%) early FP were correctly identified as pCR adding delayed images. Conversely, 15/53 (28.3%) early TN became FP, and 1/81 (1.2%) TP case was misclassified as FN in delayed imaging.

Residual DCIS (ypTis) was found in 26.7%, 34.1% and 35.6% of FP cases of respectively early-only, delayed-only and complete protocol, and also in 22.6%, 38.1% and 10.5% of TN cases of respectively early-only, delayed-only and complete protocol, but remained undetected by imaging.

Table 2 Surgical and pathological outcomes in patients with residual disease (RD) after neoadjuvant chemotherapy

Variable	RD patients ($n = 119$)
Surgery	
Conservative surgery	51 (42.9%)
Mastectomy	68 (57.1%)
Hystotype	
IDC + ILC	3 (2.5%)
IDC NST	93 (78.2%)
ILC	11 (9.2%)
Microinvasive NST	3 (2.5%)
Other	9 (7.6%)
Associated DCIS	
No	85 (71.4%)
Yes	34 (28.6%)
Grade	
1	11 (9.2%)
2	56 (47.1%)
3	52 (43.7%)
Molecular subtype	
HER2+	33 (27.7%)
Luminal A	31 (26.1%)
Luminal B	35 (29.4%)
Triple negative	20 (16.8%)
Size, mm (median [IQR])	11.0 [6.0–20.0]
T stage	
ypT1	91 (76.5%)
ypT2	25 (21.0%)
ypT3	1 (0.8%)
ypT4	2 (1.7%)

Data are expressed as median [IQR] or number of patients (percentage)
RD residual disease, *DCIS* ductal carcinoma in situ, *ypT* pathological tumor stage

Size assessment

Bland–Altman analysis showed slightly better agreement between early images and histological specimens, indicating a more accurate size assessment compared with delayed acquisitions. The mean difference between imaging and histopathologic measurements was 5.74 mm for early images and 11.78 mm for delayed images (Fig. 5).

Discussion

Evidence on the optimal use of CEM for response assessment after NAC remains limited, with few available studies and heterogeneous acquisition protocols reported in the literature. This retrospective study demonstrated that adding delayed acquisitions to CEM improves diagnostic sensitivity from 68.1 to 85.7% (delayed-only) and 86.6% (combined protocol) ($p < 0.0001$) and NPV from 58.2% to 71.2% (delayed-only) and 70.4% (complete protocol) ($p = 0.0032$) for detecting RD after NAC, without compromising overall diagnostic accuracy. Specificity and PPV were slightly higher for early images (63.9% and 72.9% vs. 60.6% and 71.3% for delayed images), but differences were not significant, indicating a comparable ability to correctly identify complete responders across protocols. Diagnostic accuracy and AUC values were marginally higher for delayed and complete acquisitions than early images (71.3% and 69.8% vs. 66.3%; 0.682 and 0.662 vs. 0.66), supporting the added value of incorporating delayed imaging. Early images provided a better tumor size estimation (mean difference 5.74 mm vs. 11.78 mm for delayed images), suggesting complementary roles for both acquisitions.

The observed differences between early and delayed CEM acquisitions can be explained by treatment-related changes in tumor vascularity after neoadjuvant chemotherapy. Delayed imaging may improve detection of RD by allowing progressive contrast accumulation in areas of persistent neoangiogenesis or low-perfusion tumor components, thereby increasing sensitivity and NPV. Conversely, early acquisitions may better reflect the viable tumor core and tumor margins, which may explain the more accurate estimation of residual tumor size observed in our Bland–Altman analysis.

In this study, we evaluated the diagnostic performance of CEM in assessing response to neoadjuvant chemotherapy, focusing on the detection of RD rather than the prediction pCR. The apparent difference compared with the pooled sensitivity of 93% reported in the recent meta-analysis by Kaiyin et al [39] and of 83% (95% CI, 0.66–0.93) in a previous meta-analysis by Tang et al [40], likely reflects the inverse definition of the diagnostic target—our endpoint being RD detection rather than pCR prediction—as well as methodological differences, including single-center design, variable CEM protocols, and heterogeneous definitions of pCR. Most studies included in the Kaiyin et al meta-analysis considered DCIS as non-pCR [25, 41–43], while in our study, pCR was defined as the absence of invasive components. Similarly, the pooled specificity reported in that meta-analysis (68%; $I^2 = 20\%$) [39] conceptually aligns with our 68.1% early-image sensitivity for RD and is lower than the 85.7% observed with delayed acquisitions.

Consistent with our results, Hogan et al reported a CEM sensitivity of 64% for RD detection among 83 patients, comparable to our early-image sensitivity (68.1%) in our cohort of 119 patients with RD [41]. Barra et al found 76% sensitivity and 53.8% NPV in detecting RD after NAC on 33 women [44], using a slightly different image acquisition order [45], which may account for our lower early-image sensitivity (68.1%). Nevertheless, our delayed CEM showed higher sensitivity (85.7%) and NPV (71.2%), confirming the diagnostic gain of delayed imaging.

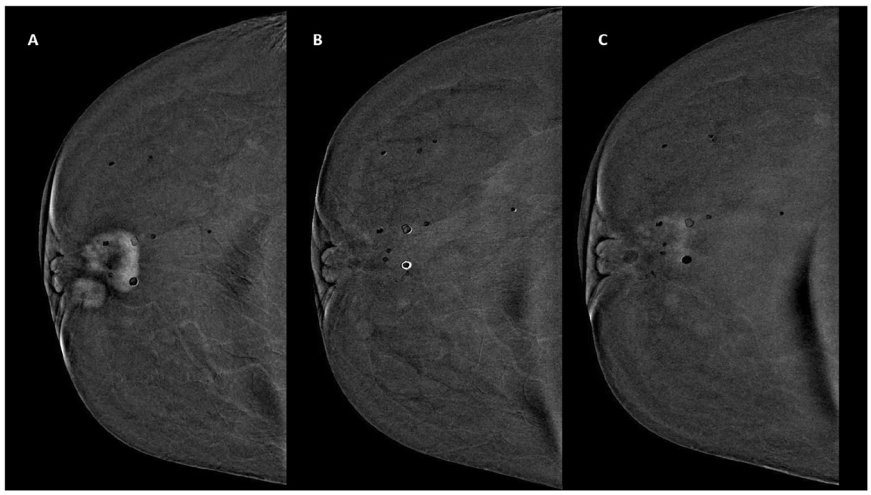


Fig. 3 A 61-year-old woman with a 35-mm right retroareolar invasive ductal carcinoma (luminal A subtype) and biopsy-proven metastatic axillary lymph nodes underwent contrast-enhanced mammography (CEM) before and after neoadjuvant chemotherapy (NAC). **A** Pre-treatment recombined CEM image shows the retroareolar enhancing mass with nipple–areolar complex involvement. **B** Early post-NAC recombined CEM demonstrates no residual enhancement, and the examination was interpreted as a radiological complete response. **C** Delayed post-NAC recombined CEM reveals a persistently enhancing 2-cm mass, consistent with residual disease. Final pathology after mastectomy showed invasive ductal carcinoma NST, grade 2, measuring 15 mm, ER 100%, PgR 90%, HER2-negative, Ki-67 5% (luminal A), staged ypT1c

Table 3 Diagnostic performance of early-only, delayed-only, and combined CEM protocols for detecting residual disease after NAC

	Early	Delayed	Combined
Sensitivity (%)	68.1 [58.90–76.31]	85.7 [78.12–91.45]	86.6 [79.09–92.12]
Specificity (%)	63.9 [52.57–74.12]	60.6 [39.40–61.76]	45.8 [34.79–57.08]
PPV (%)	72.9 [66.42–78.66]	71.3 [66.41–75.79]	69.6 [64.98–73.85]
NPV (%)	58.2 [50.61–65.50]	71.2 [60.25–80.11]	70.4 [58.72–79.86]
Accuracy (%)	66.3 [59.37–72.82]	71.3 [64.52–77.42]	69.8 [62.96–76.05]

Data in brackets are 95% confidence intervals
CEM contrast-enhanced mammography, *NAC* neoadjuvant chemotherapy, *PPV* positive predictive value, *NPV* negative predictive value

In the meta-analysis by Lobbes et al, MRI sensitivity and specificity for predicting pCR were 42% (range 25–92%) and 89% (range 50–97%), respectively, with PPV and NPV of 64% (50–73%) and 87% (71–96%) [3]. In that analysis, sensitivity referred to the ability of MRI to correctly identify patients with pCR—that is, cases showing no residual enhancement—while specificity represented the proportion of patients with residual disease correctly identified as non-responders. When considered from this inverse perspective, their specificity (89%) parallels our RD sensitivity of 85.7% for delayed images. Conversely, their reported sensitivity (42%) for detecting pCR equates to the specificity in our analysis, which was higher at 60%. These comparisons suggest that, despite differences in definition and imaging modality, delayed CEM demonstrates diagnostic performance broadly comparable to MRI for response assessment after NAC.

As also reflected by the wide variability in reported sensitivity and specificity across studies mentioned above in the meta-analysis [3], these metrics are strongly influenced by differences in imaging protocols and, importantly, by the definition of pCR itself, since studies including the residual DCIS within the pCR category typically report lower sensitivity in predicting complete response [4].

In our series, an in situ component (ypTis) was found in a substantial proportion of discordant cases, including 26.7%, 34.1%, and 35.6% of FP cases in the early-only, delayed-only, and complete protocols, respectively, and in 22.6%, 38.1%, and 10.5% of TN cases, remaining undetected by imaging. This may be explained by the variable enhancement patterns of DCIS, which can show minimal or absent enhancement in low-grade lesions but more conspicuous enhancement in high-grade forms [46]. As a

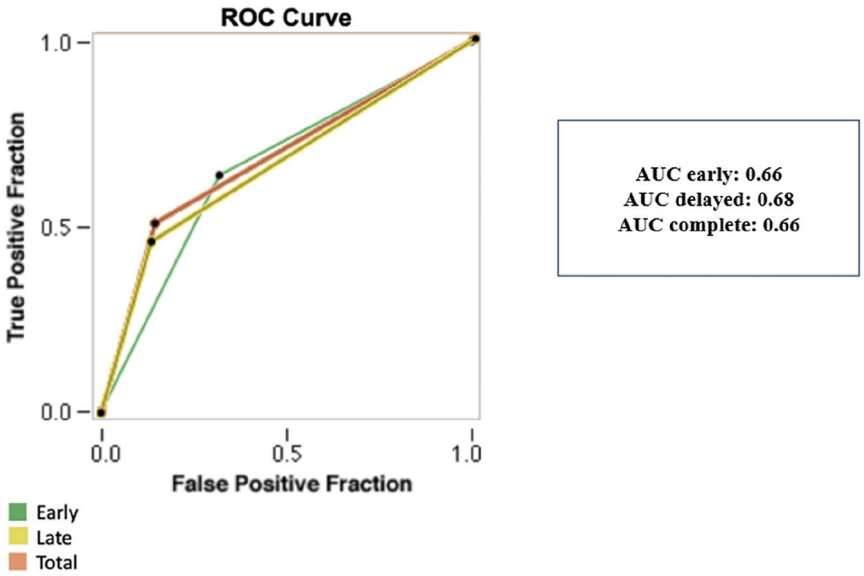


Fig. 4 Receiver operating curve (ROC) analysis of the three CEM protocols

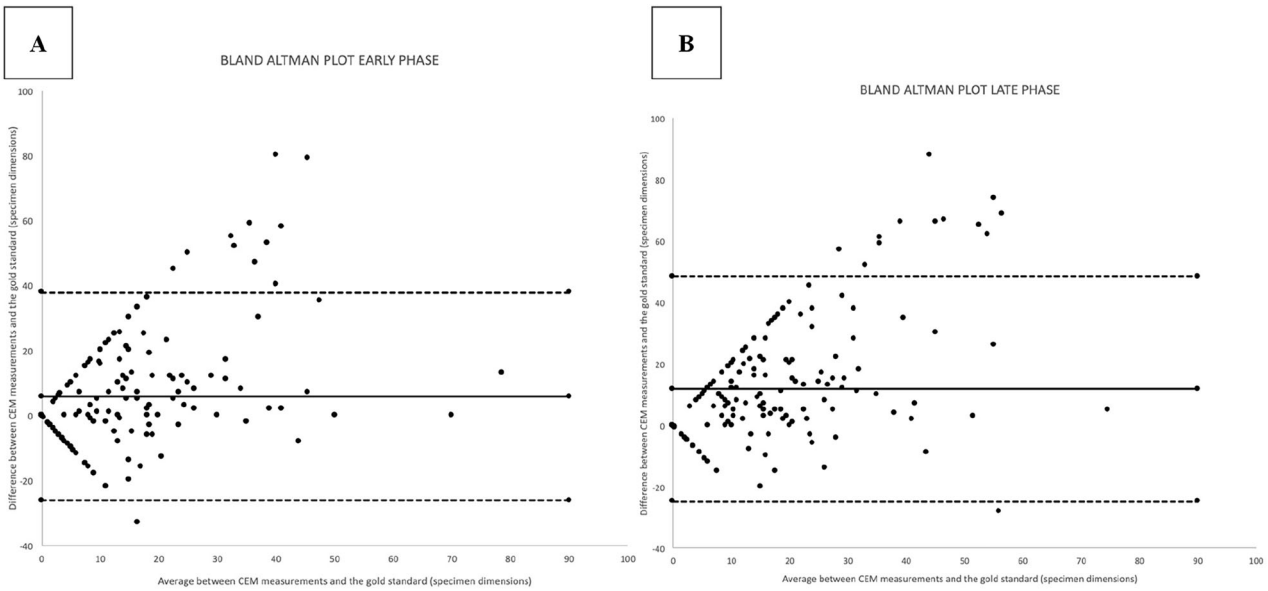


Fig. 5 Bland–Altman plots comparing lesion size estimated on early (**A**) and delayed (**B**) contrast-enhanced mammography images with the final histopathologic size

result, CEM may misclassify some DCIS as residual invasive disease, potentially reducing specificity. The present study was not designed to formally assess the specific impact of residual DCIS on CEM diagnostic performance. Dedicated analyses focusing on the imaging behavior and clinical implications of DCIS after NAC are warranted and will be the subject of future investigations. In this context, combined interpretation of RC and LE, particularly in cases without residual enhancement, could improve DCIS detection and assist presurgical planning [18]. Our mean lesion size differences (5.74 mm early, 11.78 mm delayed) align with Barra et al, who found 8 mm for CEM and 18 mm for MRI [44]. However, considerable variability has been reported across studies regarding tumor size assessment after NAC, with reports of both over- and underestimation [41, 43].

When comparing early and delayed CEM images, our findings are also consistent with those of Bernardi et al, who first evaluated delayed CEM acquisitions for assessing response to neoadjuvant therapy [25]. They reported larger lesion size and higher specificity for delayed CEM in assessing pCR, findings echoed in our results. Taken together, the complete CEM protocol offers the optimal balance between sensitivity, NPV, and dimensional accuracy.

Some concerns could be raised regarding the radiation dose of the combined CEM protocol. In our experience, the median average glandular dose (AGD) was 4.5 mGy for single-phase acquisitions (either early-only or delayed-only) and 8.4 mGy for the complete dual-phase protocol, in line with previous data from our group [47]. Importantly, the AGD for each projection remained below the 3-mGy action level specified by the Mammography Quality Standards Act, consistent with published literature and confirming the feasibility of this technique in daily clinical practice [48, 49]. The increase in radiation dose associated with the complete protocol can be justified by the significant improvement in sensitivity and NPV through the addition of delayed acquisitions. Moreover, this consideration is particularly relevant in the context of clinical breast imaging, where patients are symptomatic or undergoing treatment rather than participating in population screening programs.

This study has some limitations that should be acknowledged. First, its retrospective design may have introduced selection bias, as only patients with complete CEM and histopathologic data were included. Second, image analysis was performed by two experienced breast radiologists in consensus, and interreader agreement was not assessed; therefore, reproducibility of the findings across readers with different levels of expertise remains to be determined. Third, CEM acquisitions were performed on a single system and within a single institution, which may limit the generalizability of the results to other settings or imaging platforms. Despite these limitations, the consistency of the findings with existing literature and the robust sample size strengthen the reliability of the observed trends.

In conclusion, integrating delayed acquisitions into standard CEM protocols after NAC significantly improves sensitivity and NPV for RD detection (up to 86.6% and 70.4%), while maintaining acceptable dimensional accuracy and radiation exposure. The complete CEM protocol represents a reliable, accessible, and cost-effective alternative to MRI for post-NAC assessment and surgical planning in breast cancer patients.

Abbreviations

CEM	Contrast-enhanced mammography
DCIS	Ductal carcinoma in situ
NAC	Neoadjuvant chemotherapy
NPV	Negative predictive value
pCR	Pathological complete response
PPV	Positive predictive value
RD	Residual disease
ypT	Pathological tumor stage

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Compliance with ethical standards

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Conflict of interest
The authors of this manuscript declare no relevant relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry
Francesco Amato kindly provided statistical advice for this manuscript.

Informed consent
Written informed consent was waived by the Institutional Review Board.

Ethical approval
Institutional Review Board approval was obtained.

Study subjects or cohorts overlap
103 study subjects have been previously reported in a previously published paper (https://doi.org/10.3390/cancers16152694).

Methodology

- Retrospective
- Diagnostic study/observational
- Performed at one institution

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