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FULL PAPER

Predicting the response to neoadjuvant chemotherapy. Can the addition of tomosynthesis improve the accuracy of contrast-enhanced spectral mammography? A comparison with breast MRI

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Objectives Image monitoring is essential to monitor response to neoadjuvant chemotherapy (NACT). Whilst breast MRI is the gold-standard technique, evidence suggests contrast-enhanced spectral mammography (CESM) is comparable. We investigate whether the addition of digital breast tomosynthesis (DBT) to CESM increases the accuracy of response prediction.
Methods Women receiving NACT for breast cancer were included. Imaging with CESM+DBT and MRI was performed post-NACT. Imaging appearance was compared with pathological specimens. Accuracy for predicting pathological complete response (pCR) and concordance with size of residual disease was calculated.
Results Sixteen cancers in 14 patients were included, 10 demonstrated pCR. Greatest accuracy for predicting pCR was with CESM enhancement (accuracy: 81.3%, sensitivity: 100%, specificity: 57.1%), followed by MRI (accuracy: 62.5%, sensitivity: 44.4%, specificity: 85.7%). Concordance with invasive tumour size was greater for CESM enhancement than MRI, concordance-coefficients 0.70 *vs* 0.66 respectively. MRI demonstrated greatest concordance with whole tumour size followed by CESM+microcalcification, concordance coefficients 0.86 *vs* 0.69. DBT did not improve accuracy for prediction of pCR or residual disease size. CESM+DBT underestimated size of residual disease, MRI overestimated but no significant differences were seen (p>0.05).
Conclusions CESM is similar to MRI for predicting residual disease post-NACT. Size of enhancement alone demonstrates best concordance with invasive disease. Inclusion of residual microcalcification improves concordance with ductal carcinoma in situ. The addition of DBT to CESM does not improve accuracy.
Advances in knowledge The addition ofDBT to CESM does not improve NACT response prediction.
CESM enhancement has greatest accuracy for residual invasive disease, CESM+calcification has greater accuracy for residual in situ disease.

INTRODUCTION

With developments in oncological treatment, increasing numbers of females with breast cancer are receiving pre-surgical neoadjuvant chemotherapy (NACT), to downstage inoperable locally advanced disease, and to reduce the extent of surgery in both breast and axilla in females with operable disease.[1] For certain cancer subtypes, such as triple negative or HER2+ tumours, chemotherapy may be given in the neoadjuvant setting to allow *in vivo* assessment of chemosensitivity, regardless of tumour size.

Imaging monitoring of treatment response is necessary during NACT to assess chemosensitivity and aid surgical decision-making. Currently, contrast-enhanced MRI is considered the gold-standard technique for predicting both residual tumour size and pathological complete response (pCR).[2–4] Unfortunately, it is an expensive and time-consuming technique that may be hard to access due to service pressures. Furthermore, for some patients, it is either contraindicated or poorly tolerated.[5–7] Whilst MRI consistently surpasses the standard imaging techniques of mammography and greyscale ultrasound for response

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prediction,[2] an increasing body of evidence suggests that the advanced mammographic technique of contrast-enhanced mammography (CEM) may have comparable accuracy.[8–10] Whilst digital breast tomosynthesis (DBT) also has greater accuracy than conventional imaging, there is only limited evidence comparing it to MRI.[11]

CEM is a functional imaging technique which produces both low energy mammograms, equivalent to full field digital mammography, and a reconstructed image which demonstrates the vascularity of breast lesions through dual energy subtraction. DBT is a pseudo-3D mammographic technique, which eliminates overlapping breast tissue and improves visibility of malignant structural features, particularly spiculation, with increased cancer detection rates, especially in dense breasts, when compared with 2D mammograms.[12] Recent technological developments allow a DBT acquisition during the same breast compression as a CEM study.

In this novel pilot study, we hypothesised that the addition of CEM to DBT may improve accuracy by combining the functional data of CEM with the morphological information derived from DBT. Unlike in previous research, the step-wise additional benefit of the low-energy mammogram, DBT and subtracted CEM image are considered in comparison with MRI for prediction of response to NACT.

METHODS AND MATERIALS

This was an ethically approved prospective, paired imaging comparison study: CONtrast enhanced Digital breast tomosynthesis for monitoring Of Response to neoadjuvant chemotherapy,CONDOR (researchregistry5895). Females aged over 18 years with invasive cancers undergoing NACT were eligible for inclusion. Exclusion criteria were contraindication to iodinated contrast, contraindication to MRI, history of previous breast cancer surgery or implants, and current pregnancy or lactation. Study participants were imaged using CEM+ DBT alongside standard-of-care MRI prior to NACT and at the end of NACT. Our standard protocol consisted of six cycles of FEC-T [fluorouracil (5FU), epirubicin, cyclophosphamide and docetaxel]. Chemotherapy regimens were modified in cases of co-morbidity/frailty and drug reactions.

CEM+DBT protocol

CEM+DBT images were acquired using the Selenia Dimensions system (Hologic™, MA). Imaging was commenced 3 min after initiation of intravenous administration of 1.5 mg/kg iodinated contrast agent (Omnipaque 300, GE Healthcare™, Buckinghamshire, UK), at a rate of 2–3 ml/s. Imaging consisted of bilateral craniocaudal and oblique views prior to NACT acquired in the following order: index MLO, index CC, contralateral MLO, contralateral CC. Two views of the index breast, MLO followed by CC were acquired at the end of treatment. For each view, CEM (low energy and high energy images) followed by DBT were acquired during one compression.

MRI protocol

Breast MRI was performed on a Siemens 3T Prisma Fit scanner (Siemens Healthineers, Erlangen, Germany), using a dynamic contrast-enhanced protocol. The sequences included T1 2D axial high resolution, T2 axial turbo spin echo, diffusion sequences, T1 3D dynamic sequences (two pre-contrast and seven post-contrast) and a delayed T1 axial high-resolution sequence, with a total scan time of approximately 40 min.

Histopathology

Histology data were recorded from the diagnostic core biopsy and surgical excision specimen. Grade, tumour type and receptor status were assessed on the core biopsy specimen while residual whole tumour size (WTS) and invasive tumour size (ITS) were assessed on the resection specimen. Pathological complete response was defined as the absence of residual invasive disease within the breast (ypT0/is).[13]

Measurement of response

All imaging assessment by readers was blinded to pathological outcomes. Patients with matched CEM+DBT and MRI end-of-treatment imaging were included, and maximum suspicious disease dimensions were recorded in each affected breast. All components of CEM+DBT were read in sequence—low energy (LE) mammogram followed by DBT then CEM—therefore, the LE mammogram was read with no prior imaging while the CEM was read knowing what the mammogram and DBT had shown. The size and location of lesion(s), and total suspicious disease extent was recorded for each. CEM+DBT images were reported by a breast radiologist blinded to the MRI findings.

Similarly, MRI scans were read by an experienced radiologist blinded to CEM+DBT findings but aware of the LE mammogram findings. Lesion position, size and total disease extent was documented.

Resolution of mass or malignant microcalcification was considered a complete imaging response on LE mammogram and DBT. No enhancement above background was considered a complete response on CEM and MRI. To assess the additive benefit of the CEM+DBT study, two further components were considered; CEM+calc—the maximum dimension of enhancement and/or mammographic microcalcification, and CE-DBT—the maximum area of enhancement, mammographic microcalcification and/or DBT abnormality.

Pathological results, ITS and WTS were considered the 'ground truth'. Analysis was conducted at lesion level. In cases of pathological multifocality, the size of individual lesions was considered separately. Concordance of residual WTS and ITS with size of residual disease as predicted by each imaging modality was assessed. Both the signed difference—where a negative value indicates an imaging underestimate of pathological size and a positive value indicates an overestimate, and the absolute difference were recorded. For prediction of pCR, analysis was conducted at 'breast level'. For patients with bilateral cancers the response in each breast was considered separately.

Statistical analysis

Sensitivity was defined as the proportion of lesions demonstrating pCR at surgical excision with a corresponding imaging

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complete response; and specificity the proportion of lesions with residual invasive disease (non-pCR) with an incomplete response on imaging.[2] Concordance of residual WTS and ITS with size of residual disease as predicted on each imaging modality was calculated using Lin's concordance coefficient.[14] Difference between MRI size and pathology size *vs* components of CEM+DBT and pathology was calculated using the Student's *t*-test for dependent means, $p < 0.05$ was taken as the limit of statistical significance.

Statistical analyses were performed using SPSS (SPSS for Windows. 2017, v 25. Armonk. NY: IBM Corp) and MedCalc (MedCalc for Windows, v. 20.011). Ostend, Belgium: MedCalc Software). Software was chosen according to availability of required functionality.

RESULTS

Patient cohort

Eighteen of 31 (58%) eligible patients were recruited. Three patients could not be recruited due to logistical issues regarding availability of pre-treatment CEM+DBT after the decision to treat with NACT and the first chemotherapy cycle. Average participant age was 52.7 years (range 32–72 years). 14 patients received FEC-T chemotherapy, two patients FEC-only chemotherapy (six cycles) and two, taxane-only chemotherapy (four cycles) due to comorbidities.

Histopathology

Multifocal disease was present in five cases. Three females had unilateral multifocal disease (two tumours), two had bilateral disease. One of the females with bilateral disease had three distinct tumours. In total, there were 24 invasive carcinomas. One was a mammographically occult invasive lobular cancer (ILC), in a patient with bilateral invasive ductal carcinoma (IDC), the remainder were IDC. With respect to invasive tumour grade, 14 (58.3%) were Grade 3, 9 (37.5%) Grade 2 and 1 (4.2%) Grade 1. Regarding receptor status, 11 (45.8%) were ER/PR+ve HER-ve, 10 (41.7%) were HER2+ve and 3 (12.5%) were triple negative.

Imaging pathway

There were no significant adverse events. One patient withdrew at mid-treatment because of difficult intravenous access. One patient developed bone metastases and treatment became palliative. The two patients who had four cycles of taxane-only chemotherapy did not have end-of-treatment MRI as per local hospital guidelines. Therefore, 14 patients (16 breasts) had both CEM+DBT and MRI at end-of-treatment. There was no significant difference in the mean interval between imaging and surgery; 25.71 days, (range:13–42) and 25.79 days (range:19–38) for CEM+DBT and MRI respectively, $p = 0.711$.

Prediction of pCR on post-chemotherapy images

Of the 16 breasts with cancer, 9 (56.3%) demonstrated a complete pathological response (pCR). The diagnostic accuracy of each imaging modality for predicting pCR is illustrated in Table 1.

The greatest accuracy for predicting pCR, 81.25%, was seen with CEM (corresponding accuracy for MRI was only 62.50%). All

Table 1. Accuracy for predicting pCR according to imaging technique

Modality	Imaging response	Pathological response		Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy
		pCR	Non-pCR					
LE mammo	CR	5	3	55.6 (21.20–86.30)	57.1 (18.41–90.10)	62.5 (37.17–82.44)	50.0 (27.44–72.56)	56.3 (29.88–80.25)
	Non-CR	4	4					
DBT	CR	5	2	55.6 (21.20–86.30)	71.4 (29.04–96.33)	71.4 (40.31–90.25)	55.6 (34.42–74.86)	62.5 (35.43–84.80)
	Non-CR	4	5					
CESM (CE)	CR	9	3	100.0 (66.37–100.00)	57.1 (18.41–90.10)	75.0 (56.05–87.59)	100.0	81.3 (54.35–95.95)
	Non-CR	0	4					
CESM (CE+calc)	CR	5	3	55.6 (21.20–86.30)	57.1 (18.41–90.10)	62.5 (37.78–82.06)	50.0 (27.44–72.56)	56.3 (29.88–80.25)
	Non-CR	4	4					
CE-DBT	CR	5	2	55.6 (21.20–86.30)	71.4 (29.04–96.33)	71.4 (40.31–90.25)	55.6 (34.42–74.86)	62.5 (35.43–84.80)
	Non-CR	4	5					
MRI	CR	4	1	44.4 (13.70–78.80)	85.7 (42.13–99.64)	80.0 (36.13–96.59)	54.6 (38.33–69.85)	62.5 (35.43–84.80)
	Non-CR	5	6					

CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis; pCR, pathological complete response.

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Table 2. Lin's concordance coefficient for predicting whole tumour size according to imaging modality

	Mean lesion size (mm)	Lin's concordance coefficient	95% confidence interval	
			Lower	Upper
WTS				
LE mammogram	19.1	0.68	0.33	0.86
DBT	19.3	0.64	0.27	0.85
CEM (CE)	11.2	0.52	0.12	0.78
CEM (CE+calc)	18.5	0.69	0.36	0.87
CE-DBT	21.5	0.65	0.29	0.85
MRI	22.8	0.86	0.67	0.95

CEM, contrast-enhanced mammography; DBT, digital breast tomosynthesis; LE, low energy; WTS, whole tumour size.

nine patients with pCR were identified on CEM. However, three patients were incorrectly classified as complete responders due to absence of residual enhancement. In two of these breasts, the foci of residual invasive disease measured 6 mm or less. In the third case, whilst there was 'marked and almost pathological complete response to neoadjuvant chemotherapy… more than 90% loss of tumour cellularity', microscopic foci of invasive disease persisted over an area of 72 mm. The same residual disease was also occult on DBT in two cases, and for all three with mammography. Sensitivity for pCR was lower for mammography and DBT. The combined measure of CEM+calc resulted in lowered sensitivity with no improvement in specificity. CE-DBT demonstrated an incremental increase in specificity but larger drop in sensitivity compared to CEM.

MRI had the highest specificity (85.7%) with only one case considered a complete response on imaging but with residual disease at surgery—a 6 mm focus of invasive disease. However, MRI only correctly identified five patients with pCR, resulting in a lower sensitivity (44.4%) and lower overall accuracy for pCR.

Prediction of residual tumour size on post-chemotherapy imaging

Results of size prediction for whole tumour size and invasive tumour size are displayed in Tables 2 and 3 respectively. MRI demonstrated the strongest concordance, 0.86 (CI: 0.67,0.95) with WTS. The individual components of CE-DBT demonstrated similar reliability for predicting WTS, with concordance coefficients for mammography, DBT and CEM of 0.68 (CI:0.33–0.86), 0.64 (CI: 0.27–0.85) and 0.52 (0.12–0.78) respectively. The combined assessment CEM+calc increased concordance to 0.69 (CI:0.36–0.87). No benefit was seen when combining with DBT, with an overall CE-DBT concordance of 0.65 (CI:0.29–0.85).

By comparison, CEM and MRI had similar concordance for predicting ITS, with CEM demonstrating greater reliability than MRI, concordance coefficients 0.70 (CI: 0.39–0.88) and 0.66 (CI: 0.34–0.85) respectively. The combined assessment of CEM+calc and CE-DBT lowered the concordance.

Both signed and absolute difference between imaging size and pathology are displayed in Table 4. The signed differences indicate that all components of CEM+DBT tend to underestimate WTS with CEM demonstrating a mean underestimation of 10.7 mm which is reduced to 3.4 mm and 0.4 mm when combined with the presence of residual microcalcification and DBT findings. By comparison, MRI overestimates WTS by an average of 1 mm. However, when the absolute difference is considered, CEM+calc demonstrates the closest estimation of 10.8 mm, with a mean difference of 16.3 mm for MRI.

Table 3. Lin's concordance co-efficient for predicting invasive tumour size according to imaging modality

	Mean lesion size (mm)	Lin's concordance coefficient	95% Confidence Interval	
			Lower	Upper
ITS				
LE mammogram	18.1	0.43	<0.01	0.73
DBT	18.2	0.43	<0.01	0.73
CEM (CE)	10.6	0.70	0.39	0.88
CEM (CE+calc)	17.4	0.46	<0.01	0.74
CE-DBT	20.3	0.43	0.02	0.72
MRI	21.6	0.66	0.34	0.85

CEM, contrast-enhanced mammography; DBT, digital breast tomosynthesis; ITS, invasive tumour size; LE, low energy.

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Table 4. Signed and absolute difference between imaging size and pathological size

	Whole tumour size (mm)		Invasive tumour size (mm)	
	Signed difference (mean)	Absolute difference (mean)	Signed difference (mean)	Absolute difference (mean)
Mammogram	−2.8	15.1	6.1	15.3
DBT	−2.6	15.8	6.3	15.7
CESM	−10.7	16.2	−1.3	8.0
CESM+calc	−3.4	10.8	5.5	14.8
CE-DBT	−0.4	14.8	8.3	17.0
MRI	1.0	16.3	9.7	11.9

CESM, contrast-enhanced spectral mammography; DBT, digital breast tomosynthesis.

For ITS, the signed mean indicates an underestimation of only 1.3 mm for CEM, with an absolute difference of 8 mm. By comparison, MRI tends to overestimate invasive disease extent by an average of 9.7 mm (signed difference) and 11.9 mm (absolute difference). No significant difference was seen between MRI and all other modalities for signed or absolute differences, $p > 0.05$.

DISCUSSION

We have demonstrated that the use of CEM+DBT for monitoring response to NACT is feasible within the workflow of the breast imaging unit. Of those patients meeting inclusion criteria, 58% were recruited. This may have increased to 68% had it been possible to offer timely pre-treatment CEM+DBT to an additional three patients. With regard to a future multicentre trial, it is likely that enrolment would be higher in centres using CEM at time of diagnosis. There were no adverse outcomes reported during the trial, one patient withdrawing at mid-treatment because of poor intravenous access. Of note, the challenges around recruitment would not apply if this modality were introduced as routine clinical practice. Although not the focus of this study, we demonstrated through patient feedback questionnaires, a high acceptance of CEM+DBT as an imaging technique and a preference for it compared with CE-MRI.[15] This further supports the feasibility of CEM+DBT as a treatment monitoring modality.

Consistent with previous studies we have shown that CEM has greater accuracy at predicting pCR than mammography.[8,16–19] With respect to DBT, our results are similar to two studies which compared DBT to mammography and ultrasound, reporting a sensitivity of 44.7–50% and specificity of 91–97.6% for predicting pCR.[11,20] However, this is the first study to consider the combined use of CEM and DBT in the context of NACT. We have demonstrated lower accuracy for DBT than CEM and suggest there is no additive value in combining DBT with CEM for predicting pCR, nor residual WTS or ITS. Thus, although our study numbers are small our findings do not support the combined use of CEM+DBT as a modality for detection of pCR, especially when the increased radiation dose is taken into consideration.

With regard to MRI, whilst we demonstrate a similar specificity and accuracy to previous studies comparing CEM and MRI, our sensitivity is lower.[9,10,16] This may be related to variation of pCR definition. Indeed, meta-analysis of MRI studies demonstrated that those that permitted residual ductal carcinoma in situ in the definition of pCR—such as our study – tended to demonstrate lower accuracy, AUC 0.83 *vs* 0.88.[19]

In addition to predicting pCR pre-operatively, it is important to quantify the size of residual disease to guide surgery—whether breast conserving surgery is feasible, to improve surgical margins and reduce surgical re-excision rates. Whilst presence of residual *in situ* disease in the absence of invasive disease does not affect survival or local recurrence rate,[13] it is important for surgical decision-making. Therefore, we considered both residual WTS for surgical decision-making, as well as ITS for prognostication.

In our study, CEM enhancement demonstrated the greatest accuracy for predicting residual ITS, the greatest concordance occurring with CEM enhancement alone, followed by MRI. Regarding WTS, MRI demonstrated the greatest concordance with promising results seen for CEM, especially when microcalcification was considered in addition to residual enhancement. No significant difference was seen between the accuracy of MRI and CEM+DBT.

Our results are consistent with published data on CEM for the prediction of residual disease, with concordance coefficients ranging from moderate to good, 0.7–0.81.[9,10,16] Our findings concur with those of Iotti et al who report that the addition of a measurement of microcalcification to the diameter of residual enhancement increases sensitivity for detection and accurate measurement of residual disease, though it reduces specificity.[21] Furthermore, it is accepted that the presence of residual mammographic microcalcifications is not consistently related to residual disease, and that even with loss of MRI enhancement, it is not possible to predict absence of residual disease with sufficient accuracy to avoid complete excision of tumour bed calcifications.[22–24] We suggest that this finding is also true for persistent microcalcifications in the absence of CEM enhancement.

Our results for DBT and residual tumour size assessment are consistent with the limited published literature. Park et al reported an intraclass correlation coefficient of 0.63, with mean difference between DBT and pathology of 16.6 mm.[11]

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This is a novel exploratory study and thus, was not powered to detect significant differences in the performance of CE+DBT and MRI. However, our findings suggest no benefit from incorporating DBT to produce a full CE-DBT score for predicting either WTS or ITS.

The main limitation of this study is the small numbers of patients. Although this is partially mitigated by the fact that it is a prospective study allowing direct comparison of two imaging techniques, it is acknowledged that this limits the weight that can be given to the statistical analysis. No assessment of inter-reader reproducibility was possible as the CEM+DBT and MRI studies were each interpreted by single but independent readers. However, we have demonstrated comparable accuracy for CEM+DBT studies interpreted by a relatively inexperienced reader, compared to MRI studies reported by an expert with extensive MRI experience. The small numbers preclude evaluation of performance by imaging phenotype and tumour subtype. Whilst the findings of this study do not support the addition of DBT to CEM for treatment monitoring, a fully powered multicentre study is required to confirm the comparative accuracy of CEM *vs* MRI. Additionally, further research would allow performance evaluation by tumour subgroup and analysis of the relative importance of findings on low energy and enhancement on recombined images.

CONCLUSIONS

The findings of this pilot study do not support the addition of DBT to CEM for detecting pCR or size of residual disease following NACT. We suggest CEM is similar to MRI for predicting pCR and residual invasive tumour size. We recommend that the residual contrast enhancement on recombined CEM images is reported in parallel with residual microcalcifications on the low energy mammograms to improve accuracy of predicting residual *in situ* disease.

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