Received:
11 June 2015

Revised:
15 October 2015

Accepted:
22 October 2015

doi: 10.1259/bjr.20150479

Cite this article as:

Mistry KA, Thakur MH, Kembhavi SA. The effect of chemotherapy on the mammographic appearance of breast cancer and correlation with histopathology. *Br J Radiol* 2016; **89**: 20150479.

FULL PAPER

The effect of chemotherapy on the mammographic appearance of breast cancer and correlation with histopathology

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Objective: To document the mammographic changes after neoadjuvant chemotherapy with histopathological correlation, to calculate the accuracy of mammography (MG) in predicting residual tumour size and to measure the interobserver agreement in reading mammograms.

Methods: In 446 consecutive cases, the pre- and post-chemotherapy mammograms were retrospectively evaluated by two blinded observers, and consensus findings were compared with reference standard of surgical specimen. The accuracy of MG in predicting residual tumour size was calculated. Kappa statistics were calculated for measuring the interobserver agreement for reading mammograms. The sensitivity, specificity, positive-predictive value and negative-predictive value for the prediction of residual disease were calculated.

Results: The most common primary abnormalities were mass lesions without and with microcalcifications. After chemotherapy, there was decrease in size of most (95.1%)

of the measurable masses, with decrease in the mean tumour size from 4.1 to 2.5 cm. The density of the tumour decreased in 66.6% (241/362) cases with residual disease. There was almost perfect interobserver agreement for describing the primary abnormality in the pre- as well as post-chemotherapy mammograms ($k = 0.87$ and 0.81 , respectively) with substantial agreement for measurement of the mass lesions before and after chemotherapy ($k = 0.69$ and 0.68 , respectively). MG showed accuracy of 60.0%, sensitivity of 94.4%, specificity of 50.0%, positive-predictive value of 91.3% and negative-predictive value of 61.8%.

Conclusion: MG remains a highly sensitive and reproducible investigation for the assessment of residual disease after chemotherapy.

Advances in knowledge: There is substantial interobserver agreement in characterizing and measuring breast tumours on mammograms.

INTRODUCTION

Breast cancer is the leading cause of cancer-related deaths in females worldwide.¹ Its treatment depends upon multiple factors such as the tumour size, chest wall and/or skin invasion, nodal and/or systemic metastases. Neoadjuvant chemotherapy (NACT) was introduced more than four decades ago for the treatment of locally advanced breast cancer (LABC). It refers to the administration of systemic chemotherapy prior to the definitive surgical treatment. It is currently employed in the treatment of tumours >5 cm in size (*i.e.* T3), LABC and inflammatory breast cancers (IBCs). Its main role in the management of LABC is to enable adequate local control of the disease. It has permitted more patients with large operable breast cancers and LABC to undergo breast-conserving surgeries than radical mastectomies by pre-operatively decreasing the tumour size.²⁻⁴ Administration of NACT allows earlier treatment of systemic micrometastasis.⁵ It is also postulated

that the chemotherapeutic agents may be better able to reach the tumour and surrounding tissues when administered pre-operatively owing to the tumour neoangiogenesis which, thus, increases the efficacy of chemotherapy.⁶ Patients with LABC and IBC have improved outcome when treated with the combination of surgery and chemotherapy compared with only locoregional therapy.⁷ There is, however, no significant difference in the overall survival, progression-free survival and time to locoregional recurrence of patients treated with NACT and surgery *vs* those undergoing surgery followed by adjuvant chemotherapy.⁸ NACT also allows for *in vivo* evaluation of the efficacy of chemotherapy and thus helps in selection of appropriate adjuvant chemotherapeutic agents.⁹

Accurate assessment of the residual disease after NACT is important for further surgical management. This can be achieved by physical examination, mammography (MG),

ultrasonography (USG) and/or MRI. At our institute (Tata Memorial Hospital, Mumbai, India), post-chemotherapy evaluation is performed by physical examination and MG. USG is used in selected patients, where MG is inconclusive (*e.g.* dense breasts) or not feasible (*e.g.* extensive skin involvement). MRI is not routinely employed in our setup.

We undertook this retrospective study to document the mammographic changes after chemotherapy and correlate them with histopathology, to calculate the accuracy of MG in predicting the size of the residual disease and to measure the interobserver variability in reading mammograms.

METHODS AND MATERIALS

Study population and recruitment

Institutional ethics board approval with waiver of informed consent was obtained for this retrospective study. Consecutive cases of newly diagnosed breast cancers that were treated with NACT followed by surgery in Tata Memorial Hospital, Mumbai, India from 1 January 2007 to 31 December 2011 were screened for eligibility. The patients who had a pair of baseline mammograms and post-NACT mammography followed by surgery and a histopathology report were enrolled in the study. Patients without pre- or post-chemotherapy mammograms at Tata Memorial Hospital, Mumbai, India, patients who underwent excision biopsy prior to starting chemotherapy and those patients who did not undergo surgical excision of the tumour within 30 days of the post-chemotherapy mammograms were excluded from the study.

Mammographic data collection

All the mammograms were obtained on Senographe DS® (GE Healthcare, Milwaukee, WI). They were retrieved from picture archiving and communication system (Centricity 3.0™, GE Healthcare) and independently reviewed on dedicated high-resolution (5 megapixels) workstation by two radiologists with special interest and 20 and 10 years' experience in breast imaging, respectively. Both observers were blinded to the findings of the other observer and the final histopathological reports.

The baseline mammograms were assessed for the type of breast parenchyma according to the breast imaging reporting and data system classification, the type of primary abnormality and its distribution, single longest dimension if mass was present, presence of microcalcifications, distribution of microcalcifications, presence of skin thickening and/or nipple retraction.

The post-chemotherapy mammograms were assessed for the type of residual abnormality. The size of the residual mass using the single longest dimension, the density of the residual mass as compared with that of the pre-chemotherapy lesion with the density of the pectoralis major muscle acting as an internal control, the presence of microcalcifications and their prominence as compared with the pre-chemotherapy mammograms and the presence of skin thickening and/or nipple retraction were noted.

The primary abnormality in the baseline mammograms was classified as mass without microcalcification, mass with microcalcification (defined as the presence of a mass with associated microcalcification in the same region of the breast), mass and

microcalcification (defined as the presence of a mass and microcalcification in different regions of the same breast), only microcalcification, architectural distortion, asymmetric density, IBC-like lesion (defined as dense breast without obvious mass and with associated skin thickening), architectural distortion and microcalcification (defined as the presence of architectural distortion and microcalcification in different regions of the same breast), and asymmetric density and microcalcification (defined as the presence of asymmetric density and microcalcification in different regions of the same breast).

The distribution of masses was described as single, multifocal (more than one mass in same quadrant within 5 cm apart) or multicentric (more than one mass in different quadrants or lying >5 cm apart).

The distribution of microcalcification was classified as within the mass only, within and around the mass, focal (a focal cluster of microcalcification in a different quadrant than that of the mass), regional (microcalcifications diffusely involving a single quadrant), extending to adjacent quadrant and diffuse.

The residual abnormality after chemotherapy was described using the same terminology as that of the baseline mammographic abnormality with an additional description of no measurable mass.

Discordant findings between two observers were resolved by consensus, prior to comparison with reference standard—for example, the presence of residual disease on mammography. When the difference between sizes of the residual mass lesions measured by the two observers was within 1 cm, the arithmetic mean of the sizes measured by the observers was calculated and compared with the reference standard. For size difference >1 cm between the two observers, a consensus measurement was made by the observers and the same was used for comparison with the reference standard.

Reference standard

The histopathological details of the surgical specimens were obtained from the electronic medical records and were used as the reference standard.

Statistical analysis

The accuracy of MG to predict the residual tumour size to within 1 cm of the histopathological tumour size was calculated.

Cohen's kappa statistics were calculated on IBM® SPSS® Statistics software v. 19.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for measuring the interobserver agreement in assessment of the primary abnormality, the post-chemotherapy abnormality and in the measurement of the pre- and post-chemotherapy mass lesions. The strength of interobserver agreement for the kappa coefficients were interpreted as follows: <0 = poor, 0.01–0.2 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81–1.0 = almost perfect.¹⁰

The sensitivity, specificity, positive-predictive value and negative-predictive value of MG for detection of the residual disease were calculated.

Table 1. Distribution of the primary abnormality in pre- and post-NACT mammograms

Baseline abnormality	Post-NACT abnormality										
	Mass without microcal	Mass with microcal	Only microcal	AD	Asymmetric density	IBC-like	Mass and microcal	AD and microcal	Asymmetric density and microcal	No measurable mass	Total
Mass without microcal	184	1		44	3					50	282
Mass with microcal		85	19					13	1		118
Only microcal			7								7
AD				6						2	8
Asymmetric density					8					3	11
IBC-like				1		5					6
Mass and microcal							5				5
AD1 and microcal								6			6
Asymmetric density and microcal			3								3
Total	184	86	29	51	11	5	5	19	1	55	446

AD, architectural distortion; IBC, inflammatory breast cancer; microcal, microcalcification, NACT, neoadjuvant chemotherapy.

Table 2. Distribution of breast density in the primary abnormality in pre-NACT mammograms

Primary abnormality	Breast density			
	1	2	3	4
Mass without microcalcification	52	90	87	53
Mass with microcalcification	10	42	42	24
Only microcalcification	0	1	1	5
Architectural distortion	0	2	5	1
Asymmetric density	0	4	3	4
IBC-like	0	1	2	3
Mass and microcalcification	1	1	1	2
Architectural distortion and microcalcification	0	1	4	1
Asymmetric density and microcalcification	0	0	2	1
Total	63	142	147	94

IBC, inflammatory breast cancer; NACT, neoadjuvant chemotherapy.

RESULTS

446 patients were found eligible for the study and all of them were included in the final analysis. The age range for the study participants was 27–73 years with a mean of 49 years.

225 patients received a combination chemotherapy of cyclophosphamide, epirubicin and 5-fluorouracil; 184 patients received cyclophosphamide, doxorubicin and 5-fluorouracil; 27 patients received only paclitaxel; 6 patients received

Figure 1. Pre-chemotherapy mammogram (a) of the left breast, mediolateral oblique view, reveals multiple masses of varying sizes in the upper quadrants (white arrows), classified as multifocal disease; which showed complete regression after chemotherapy (b).

Figure 2. Baseline mammogram (a) of the left breast, mediolateral oblique view, shows two mass lesions in upper (black arrow) and lower (white arrow) quadrants, respectively, classified as multicentric disease. Skin thickening (white arrowhead) and nipple retraction (white asterisk) is also seen. Post-neoadjuvant chemotherapy mammogram (b) reveals decrease in size of the mass lesions (black and white arrows). The skin thickening (white arrowhead) and nipple retraction (white asterisk) persist.

docetaxel, doxorubicin and cyclophosphamide; 3 patients received paclitaxel and carboplatin; and 1 patient received cyclophosphamide, doxorubicin, 5-fluorouracil and paclitaxel.

The type of primary abnormality detected in the baseline mammograms and its appearance after chemotherapy has been cross-tabulated in Table 1. The breast density was assessed using ACRBI-RADS® Atlas 4th Edition categories, and 63, 142, 147 and 94 females had type 1, 2, 3 and 4 parenchyma, respectively (Table 2).

The kappa coefficient for interobserver variability for assessing the primary abnormality in the pre-NACT mammograms was calculated to be 0.87, whereas that in the post-NACT mammogram was 0.81. There was discordance in 10 (2.2%) cases between the two observers with regards to the presence of residual disease in the post-chemotherapy mammograms.

Out of the 405 cases with mass lesions in the baseline mammograms, 394 (97.3%) cases had single lesions, 10 (2.5%) cases showed multifocal lesions (Figure 1) and 1 (0.2%) case had multicentric lesions (Figure 2). The mean size of the mass lesions in the baseline mammograms was 4.1 cm [range: 0.9–12.6 cm, standard deviation (SD): 1.5 cm]. This decreased to 2.5 cm (range: 0.5–9.4 cm, SD: 1.2 cm) after chemotherapy in the residual mass lesions. The kappa values for the interobserver agreement in

measurement of the mass lesions were 0.69 in pre-chemotherapy mammograms and 0.68 in the post-chemotherapy mammograms.

On histopathological analysis, 434 (97.3%) cases had infiltrating ductal carcinoma, 3 (0.7%) cases had infiltrating lobular carcinoma, 2 (0.4%) cases showed invasive micropapillary carcinoma, 2 (0.4%) cases had invasive cribriform carcinoma, and 1 case each (*i.e.* 5 cases) showed invasive papillary carcinoma, infiltrating pleomorphic lobular carcinoma, infiltrating solid variant of papillary carcinoma, infiltrating ductal carcinoma with squamous differentiation and poorly differentiated carcinoma. The mean size of the residual tumour in surgical specimens was 3.0 cm (range: 0.3–13 cm, SD: 1.7 cm).

Out of 405 cases with mass lesions, only 13 cases (3.2%) showed increase in mass size after chemotherapy while stable size was noted in 7 cases (1.7%).

MG accurately predicted the residual tumour size to within a centimetre of the histopathological size in 165 out of 275 (60.0%) cases with measurable mass lesions on the post-chemotherapy mammograms. It overestimated the tumour size in 45 (16.4%) cases and underestimated in 65 (23.6%) cases.

In the 362 cases showing residual lesions (including the measurable masses, asymmetric densities, architectural distortions

Figure 3. Pre-chemotherapy mammogram (a) of the left breast, craniocaudal view, reveals dense breast parenchyma (black arrow) with generalized skin thickening (white arrow), classified as inflammatory breast cancer-like lesion. Post-chemotherapy mammogram (b) reveals decrease in the breast density. The skin thickening persists (white arrow).

and IBC-like lesions and excluding the “no measurable mass” and “only microcalcifications” categories), there was decrease in density of the residual lesion in 241 (66.6%) cases (Figure 3). In 115 (31.8%) cases, the density remained unchanged, whereas density of the residual lesion was increased in 6 (1.6%) cases.

139 (31.2%) patients showed the presence of microcalcifications in the pre-chemotherapy mammograms (Table 3), out of which 134 (96.4%) appeared malignant, 3 (2.2%) appeared indeterminate and 2 (1.4%) appeared benign. After chemotherapy, residual microcalcifications were seen in all of the 139 cases and appeared more prominent in 71 (51.1%), remained unchanged in 63 (45.3%) and appeared less prominent in 5 (3.6%) cases. New microcalcifications were seen after chemotherapy in one patient (Figure 4). On histopathological examination, out of the 140 cases showing residual microcalcifications on mammography, 56 (40.0%) cases showed no evidence of ductal carcinoma *in situ* (DCIS). In the 306 cases without microcalcifications on post-therapy images, 104 (34.0%) cases showed the presence of DCIS in the surgical specimen.

By consensus of the two observers, there were mammographic features of residual disease in 391 (87.7%) cases post chemotherapy, of which 357 (91.3%) cases had residual disease on reference standard.

Out of the 55 cases showing mammographic complete response (Figure 1), residual viable disease was observed in 21 (38.2%) cases on histopathological examination. 68 cases showed no residual disease on histopathology, out of which 34 (50.0%) cases showed imaging features suggestive of residual disease on post-chemotherapy mammograms. Out of these 34 false-positive cases, 24 cases showed a measurable mass, 9 cases showed architectural distortion and 1 case showed IBC-like features on the post-chemotherapy mammograms.

Table 3. Distribution of microcalcifications in baseline mammograms

Distribution	Frequency	Percent
Within the mass only	67	48.2
Within and around the mass	45	32.4
Regional	13	9.4
Diffuse	1	0.7
Extending to adjacent quadrant	2	1.4
Focal	11	7.9
Total	139	100

Figure 4. Baseline mammogram (a) of the right breast, mediolateral view, reveals a mass lesion (white arrow) without microcalcifications in the central region. An axillary node is also seen (black asterisk). Post-neoadjuvant chemotherapy mammogram (b) reveals decrease in size of the mass (white arrow) with presence of new microcalcifications (black arrows) within and around the mass. The axillary node is not visualized in the post-therapy mammogram.

MG showed sensitivity of 94.4%, specificity of 50.0%, positive-predictive value of 91.3% and negative-predictive value of 61.8% for the prediction of residual disease (Table 4).

Out of the 68 patients with pathologic complete response, 46 (67.6%) patients had triple-negative breast cancers.

DISCUSSION

In our analysis of 446 patients treated with NACT, the most common primary abnormalities were mass lesions without microcalcifications followed by mass lesions with microcalcifications. After chemotherapy, there was reduction in size of most of the measurable masses (95.1% of mass lesions), with decrease in the mean tumour size. Also, the density of the tumour decreased in 66.6% of cases in patients with residual disease in the post-therapy mammogram. Vinnicombe et al¹¹

observed decrease in the size and/or density of the primary tumour in 82.0% of the cases after chemotherapy, while Helvie et al¹² reported mammographic response in 96.0% of the cases.

None of the patients showed complete resolution of microcalcification after chemotherapy. However, on histopathological examination, 40.0% of cases with residual microcalcifications showed no evidence of DCIS. Also, 34.0% of cases without microcalcification on mammograms showed the presence of DCIS in the final surgical specimen. Thus, the presence of microcalcifications after chemotherapy does not necessarily imply presence of DCIS. Conversely, DCIS can be present despite the absence of microcalcifications. Vinnicombe et al,¹¹ Helvie et al¹² and Segel et al¹³ have also arrived at similar conclusions regarding the presence of microcalcifications and DCIS in post-NACT mammograms. The increased conspicuity

Table 4. Correlation between mammography and histopathology for the presence of residual disease

Mammography	Histopathology		Total
	Residual disease present	Residual disease absent	
Residual disease present	357	34	391
Residual disease absent	21	34	55
Total	378	68	446

of the microcalcifications after chemotherapy could be due to decrease in the size and/or density of the primary tumour and consolidated appearance of the microcalcifications due to tumour shrinkage.

We found almost perfect interobserver agreement for describing the primary abnormality in the pre- as well as post-NACT mammograms ($k = 0.87$ and 0.81 , respectively) and substantial interobserver agreement for measurement of the mass lesions before and after chemotherapy ($k = 0.69$ and 0.68 , respectively).

The accuracy of MG in measuring the residual tumour to within 1 cm of the histopathological size was 60.0% in our study, which is similar to that calculated by Atkins et al¹⁴ (56.0%) but higher than that found by Keune et al¹⁵ (31.7%) and lower than that found by Chagpar et al¹⁶ (70.0%).

Also, MG showed high sensitivity (94.4%) and moderate specificity (50.0%) for prediction of residual disease in our study. Atkins et al¹⁴ found lower sensitivity (87.0%) and specificity (28.0%) of mammography. The majority of the cases showing pathologic complete response in our study had triple-negative breast cancers.

There is no clear consensus regarding the best modality for measurement of residual tumour after NACT. Segel et al,¹³ Coconi et al¹⁷ and Dershaw et al¹⁸ compared physical examination and MG for the assessment of the residual tumour post NACT and came to similar conclusions that both physical examination and MG provided information complementary to each other and both were important for the assessment of the residual disease. Helvie et al¹² found that MG was more sensitive whereas physical examination was more specific for measurement of the residual disease. On comparing physical examination, MG and USG with the pathologic specimen, Herrada et al¹⁹ found physical examination by an experienced oncosurgeon to have best correlation with the pathologic size of the primary tumour, whereas the size of the axillary lymph nodes was most accurately predicted by USG. They further suggested using a combination of physical examination and MG for evaluation of the primary tumour, and physical examination and USG for assessing the regional lymph nodes. Loehberg et al²⁰ similarly concluded that MG and physical examination were the best non-invasive methods for assessing the residual tumour size, and USG was best for evaluation of axillary lymph nodes. Chapgar et al¹⁶ found only moderate correlation

between physical examination, MG and USG with the pathologic size for the assessment of residual tumour. Keune et al¹⁵ revealed USG to be more accurate than MG in estimating residual tumour size. There was, however, little difference in the ability of either of these modalities to predict pathologic complete response. Recent studies have shown higher accuracy of MRI for assessing the residual disease.^{14,21,22} However, no modality was found to be superior to the rest for prediction of pathologic complete response.¹⁴

The strength of our study was the large cohort of patients that we were able to include and analyse in our study. Also, to our knowledge, ours was the only study to objectively calculate the interobserver variation in reading mammograms with respect to classification of the primary abnormality and measurement of the mass lesions. MG has a distinct advantage as compared with other modalities for the detection and characterization of microcalcifications. We could thus correlate the presence of microcalcifications with the presence of DCIS in the surgical specimen.

The main limitation of our study was the inability to compare mammography, physical examination, USG and MRI for the assessment of residual disease after NACT. The size of residual tumours on physical examination was available in the patient records. However, they were only approximate measurements and not made with clinical measurement calipers. Thus, these data were not analysed as it would lead to erroneous results. USG was not performed in most of the cases after chemotherapy and, being an operator-dependent modality, there were doubts regarding the available images actually representing the longest dimension of the residual tumour. Hence, USG data were also not included in final analysis. MRI is not a part of the routine post-NACT assessment protocol in our institute and hence not included in our study. Also, the statistical correlation between the mammographic tumour size and histopathological tumour size was not performed since we did not intend to compare MG with other imaging modalities or physical examination findings; a fair-to-moderate correlation between the two would, anyway, be expected since both measure the same physical object, i.e. the residual tumour.

CONCLUSION

We thus conclude that MG remains a highly sensitive and reproducible investigation for the assessment of the residual disease after chemotherapy, with a high positive-predictive value for residual disease but limited negative-predictive value.

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