Journal of Clinical Imaging Science

Editor-in-Chief: Vikram S. Dogra, MD
Department of Imaging Sciences, University of Rochester Medical Center, Rochester, USA

OPEN ACCESS
HTML format

For entire Editorial Board visit : www.clinicalimagingscience.org/editorialboard.asp

www.clinicalimagingscience.org

ORIGINAL ARTICLE

Effects of Neoadjuvant Chemotherapy on Benign Breast Lesions Compared to Cancers: Should an Additional Lesion on Magnetic Resonance Imaging Responding Similar to Cancer after Neoadjuvant Chemotherapy be Viewed with Suspicion?

Rebecca Leddy, Abid Irshad, Lara Hewett, Heather Collins, Frank Vento, Susan Ackerman, Madelene Lewis

Department of Radiology, Medical University of South Carolina, Charleston, SC 29425, USA

Address for correspondence:
Dr. Rebecca Leddy,
Department of Radiology, Medical University of South Carolina, 96 Jonathan Lucas Street, Charleston, SC 29425, USA.
E-mail: leddyr@musc.edu

Received : 13-07-2016
Accepted : 17-08-2016
Published : 20-09-2016

ABSTRACT

Purpose: Determining the effects of neoadjuvant chemotherapy (NAC) on benign breast lesions and to evaluate their response in comparison to breast cancers. **Methods:** A retrospective analysis performed on breast cancer patients between 2008 and 2014 to identify patients who had a pre- and post-NAC magnetic resonance imaging (MRI) and biopsy-proven benign lesions. Pre- and post-NAC size and intensity of enhancement of benign lesions and cancers were measured. Breast glandularity and background enhancement were graded. A 2 × 2 repeated measures ANOVAs and Sidak *post hoc* tests were conducted for multiple comparisons. Paired *t*-tests were conducted to examine changes over time, and two-tailed *P* values were reported. **Results:** The effects of NAC in 38 cancers were compared to the effects of NAC in 47 benign lesions in these patients. From pre- to post-NAC, the mean size (cm) of malignant lesions on MRI decreased from 4.09 (±standard deviation [SD] 2.51) to 1.54 (±SD 2.32), ($P < 0.001$); the mean size (cm) of benign lesions decreased from 0.83 (±SD 0.54 cm) to 0.28 (±SD 0.51), ($P < 0.001$). Both benign and malignant lesions decreased in size after NAC, the size reduction in malignant lesions was significantly greater than benign lesions. From pre- to post-NAC, the mean lesion enhancement of the malignant lesions (scale 1–4) decreased from 3.43 (±SD 0.80) to 1.02 (±SD 1.34); the mean lesion enhancement of benign lesions decreased from 2.96 (±SD 1.04) to 0.98 (±SD 1.51). For both benign and malignant

Access this article online

Quick Response Code:

Website: www.clinicalimagingscience.org

DOI: 10.4103/2156-7514.190899

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Leddy R, Irshad A, Hewett L, Collins H, Vento F, Ackerman S, *et al*. Effects of Neoadjuvant Chemotherapy on Benign Breast Lesions Compared to Cancers: Should an Additional Lesion on Magnetic Resonance Imaging Responding Similar to Cancer after Neoadjuvant Chemotherapy be Viewed with Suspicion?. J Clin Imaging Sci 2016;6:39. Available FREE in open access from: http://www.clinicalimagingscience.org/text.asp?2016/6/1/39/190899

lesions, there was a significant overall reduction in enhancement after NAC from moderate at pre-NAC to minimal at post-NAC, $P < 0.001$. There was no overall difference in the enhancement of cancers (mean = 2.22, SD = 0.79) versus benign lesions (mean = 1.97, SD = 1.08), ($P = 0.23$). There was no significant change in glandularity from pretherapy (mean = 3.11, SD = 0.84) to posttherapy (mean = 3.13, SD = 0.82), $P < 0.001$. **Conclusion:** Similar to cancers, benign breast lesions also show a significant decrease in size and enhancement after NAC; however, the decrease in size is less compared to cancers.

Key words: Benign breast lesions on magnetic resonance imaging, breast cancer, breast magnetic resonance imaging, neoadjuvant chemotherapy

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has evolved in its role in therapy of both inoperable and operable breast cancer.[1-3] Potential advantages of NAC include improved outcomes in breast conservation therapy, reduction in size of inoperable cancers rendering them operable, decrease in mastectomy rates in patients with large cancers, decrease in the size of involved axillary nodes, and early treatment of micrometastatic disease.[1,3-8] The early assessment of tumor response to NAC also allows for a potential modification in the treatment plan and may affect long-term outcome.[6]

NAC has been reported to significantly change tumor morphology, grade, and receptor expression.[9] Reported findings include the loss of support in the tumor vasculature due to direct effects on endothelial cell function; lobular morphologic change due to decreased cellularity and increased fibrosis;[10] increased nuclear grade; changes in tubule formation and mitotic count; tumor cell enlargement; and altered inflammatory reaction.[5,10,11] In addition to its effects on the pathologic tumor, NAC also leads to morphologic changes in the surrounding normal breast tissue as evidenced on histologic analysis.[5] The histologic changes induced by NAC in nonneoplastic breast tissue include fibrosis, diffuse lobular atrophy, intralobular fibrosis, and drug-induced mild epithelial atypia.[5,8]

Contrast-enhanced breast magnetic resonance imaging (MRI) has shown to accurately assess pathologic response to NAC.[12-19] Contrast-enhanced breast MRI is valuable before, during, and/or after NAC to assess treatment response and the extent of residual disease before surgery.[20] Pre- and post-NAC contrast-enhanced MRI not only provides morphologic details of the tumor but also helps in assessing the enhancement characteristics based on the uptake of contrast agent into the tumor. It has been reported in some studies that tumors with a higher degree of pretreatment enhancement tend to have a better response to treatment.[19,21,22] It is hypothesized that increased angiogenesis in these cases may favor accessibility of the chemotherapy within the tumor leading to an improved response.[19]

Background parenchymal enhancement (BPE) on MRI is a recognized phenomenon in which the breast parenchyma physiologically enhances after intravenous contrast administration. The degree of BPE can be variable and depends on the patient age, menopausal status,[23-25] lactational status,[26-28] phase of the menstrual cycle,[23,29,30] and use of hormone replacement therapy.[30-32] Other exogenous/technical factors that can affect apparent BPE include the type of MRI sequences and type of contrast agent used.[33] BPE can also be affected by treatment with NAC, radiation therapy, and endocrine therapies.

Although the effects of NAC (as seen on MRI) on breast cancers and BPE have been well studied in the previous literature, the effects of NAC on benign breast lesions have not been evaluated to the best of our knowledge. The lack of such data may lead to management dilemmas in certain clinical situations. In routine clinical practice, many times the patients with newly diagnosed breast cancer may show on MRI, additional benign appearing (Breast Imaging Reporting and Data System [BI-RADS] 2 or 3) lesions in the ipsilateral or contralateral breast that are not biopsied.[34] One may face a management dilemma when such a lesion responds to NAC in a similar fashion as known cancer. Since there is no data available, some radiologists or surgeons may prefer the excision of those lesions as well due to the suspicion of cancer-based on their similar response. Our study may be considered as a baseline study in this regard that will show how benign lesions respond to NAC treatment, and this may help in making appropriate management decisions.

METHODS

Study population

The study was approved by the Institutional Review Board for human investigation. The mammography database was reviewed for patients diagnosed with breast cancer who underwent NAC from 2008 to 2014, and a total of 195 patients were found. From these, 82 patients were excluded because they did not have a complete set of pre- and post-NAC breast MRI imaging available. The charts of the remaining 113 patients who have had both pre- and post-NAC MRI were evaluated for a history of any additional previous benign biopsy performed before the start of NAC treatment. Among these 113 newly diagnosed breast cancer patients, 38 patients were found to have undergone additional benign biopsies for 47 ipsilateral or contralateral lesions either before their breast cancer diagnosis or before receiving NAC. The biopsy-proven benign lesions were identified on the pre-NAC MRI by their enhancement and by the location of the postbiopsy clip markers in place. These 47 biopsy-proven benign lesions formed the cohort for our study. The demographic information including age, race, and gender was noted for each patient.

Imaging and image interpretation

All imaging was performed at an American College of Radiology (ACR) certified "Breast center of excellence" under the ACR guidelines.[35]

Breast MRI with a dedicated phase array breast coil (Siemens Healthcare, Erlangen, Germany) was performed with patients in the prone position. The standard sequences were obtained using the ACR breast MR accreditation guidelines.[36] Axial T1- and T2-weighted precontrast MRI followed by five postcontrast T1-weighted dynamic sequences at 90 s intervals were obtained. Reconstructed sagittal T1-weighted postcontrast images were generated from the axial T1-weighted postcontrast images. The breast glandularity was noted based on the amount of fibroglandular tissue using the noncontrast axial fat-suppressed T1-weighted images on both the pre- and post-NAC MRI. Using the ACR BI-RADS MRI lexicon, the amount of background glandularity was visually assessed by 2 fellowship-trained breast radiologists and categorized by consensus into 1 through 4 using the ACR BI-RADS categories with category 1: almost entirely fatty, category 2: scattered fibroglandular tissue, category 3: heterogeneous fibroglandular tissue, and category 4: extreme fibroglandular tissue.[34] The BPE was recorded using the axial first postcontrast subtracted T1-weighted images obtained at 90 s on both the pre- and post-NAC MRI. Using the ACR BI-RADS MRI lexicon, BPE was also visually assessed by 2 fellowship-trained breast radiologists and categorized by consensus into 1 through 4 with category 1: minimal, category 2: mild, category 3: moderate, and category 4: marked enhancement.[34] The size of breast cancer and the biopsy-proven benign lesion was measured in centimeters (cm) on the first postcontrast axial and sagittal fat-suppressed subtracted T1-weighted images for the maximum dimension on the pre- and post-NAC MRI. In only one patient, cancer and the benign lesion were not well seen on the first postcontrast sequence, and the second postcontrast sequence was used for the measurement. The enhancement of breast cancer and the benign lesion was assessed by 2 fellowship-trained breast radiologists and categorized by consensus as 1 through 4 based on the enhancement characteristics above background glandular enhancement using the first postcontrast axial fat-suppressed subtracted T1-weighted image for both the pre- and post-NAC MRI. The enhancement was categorized as follows (1) minimal enhancement, (2) mild enhancement, (3) moderate enhancement, and (4) marked enhancement with the enhancing aorta as a visual reference for marked enhancement.

Pathology

A pathologic review of the tumor was performed for tumor type, grade, and tumor markers. Based on the classification proposed by Dupont and Page,[37,38] the benign pathology was divided into nonproliferative lesions and proliferative lesions.

Statistical analysis

A 2 (intervention: Pre, post) ×2 (tumor type: cancer, benign) repeated measures ANOVA was conducted on the size and enhancement characteristics of benign lesions and cancers. *Post hoc* tests were conducted using the Sidak method for multiple comparisons. A repeated measures *t*-test was conducted to examine changes in background breast glandularity and background enhancement over time, and two-tailed *P* values are reported. The analysis by independent *t*-tests was preformed to evaluate for any potential differences between the proliferative (p) and nonproliferative (np) groups with respect to changes in benign lesion size, benign lesion enhancement, cancer size, cancer enhancement, and background glandularity and enhancement with two-tailed *P* values are reported. All analyses were considered statistically significant at the $P < 0.05$ threshold.

RESULTS

The mean patient age was 53 years; all were females, 55.4% were African-American, 40.4% were Caucasian,

and 4.2% were hispanic. Of the 38 breast cancer patients who underwent NAC, pre- and post-NAC MRI and had an ipsilateral or contralateral benign breast biopsy, 37 (97%) had invasive ductal carcinoma and one patient (3%) had invasive lobular carcinoma. Among the 47 benign lesions, 27 (57.4%) lesions were classified as nonproliferative and 20 (42.6%) as proliferative. The effects of NAC in 38 cancers were compared to the effects of NAC in 47 benign lesions in these 38 patients.

Neoadjuvant chemotherapy effects on lesion size

Both cancers and the benign lesions showed a significant decrease in size ($P < 0.001$) after NAC (Figure 1 and Table 1). The mean cancer size decreased from 4.09 cm (±standard deviation [SD] =2.51 cm) on pre-NAC MRI to 1.54 cm (±SD = 2.32 cm) on the post-NAC MRI. The benign masses also showed a significant decrease in size from the mean size of 0.83 cm (±SD = 0.51 cm) on pre-NAC MRI to 0.28 cm (±SD = 0.51 cm) on post-NAC MRI (Figure 1 and Table 1). Although both benign and malignant lesions decreased in size after NAC, the size reduction in malignant lesions was significantly greater than in benign lesions [$F (1, 46) = 42.36$, $P < 0.001$].

Neoadjuvant chemotherapy effects on lesion enhancement (scale 1–4)

Cancers showed a decrease from a moderate enhancement value ($M = 3.43$; ±SD = 0.80) on pre-NAC MRI to a mild enhancement value ($M = 1.02$; ±SD = 1.34) on post-NAC MRI ($P < 0.001$) (Figure 1 and Table 1). The benign lesions also showed a decrease from moderate enhancement value ($M = 2.96$; ±SD = 1.04) to a mild enhancement value ($M = 0.98$; ±SD = 1.51). There was a significant overall decrease in the enhancement for both benign and malignant lesions after NAC and both types of lesions showed a similar decrease in enhancement without a significant difference in the enhancement patterns ($P = 0.23$).

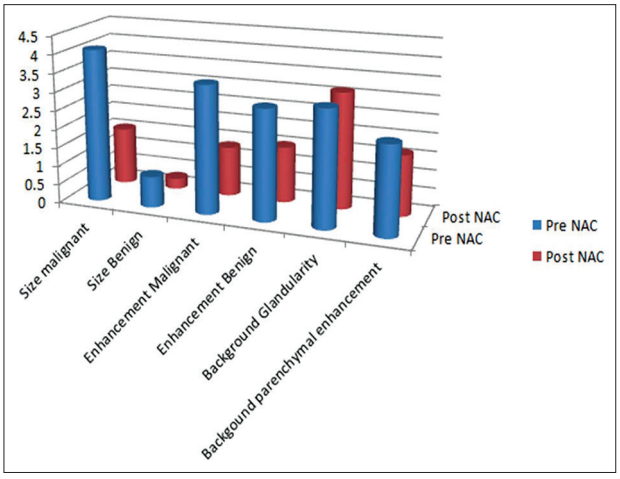

Figure 1: Effects of neoadjuvant chemotherapy on the size and enhancement of malignant and benign lesions, background breast glandularity, and background parenchymal enhancement.

Breast glandularity (scale 1–4)

There was no change in the breast glandularity from pre-NAC ($M = 3.11$; SD = 0.84) to post-NAC treatment ($M = 3.13$, SD = 0.82); $t (46) = 0.44$, ($P = 0.66$) (Figure 1).

Breast background parenchymal enhancement (scale 1–4)

There was a significant decrease in BPE from pre-NAC MRI ($M = 2.38$, SD = 0.97) to post-NAC MRI ($M = 1.64$, SD = 0.70); $t (46) = 4.95$, ($P < 0.001$).

Proliferative versus nonproliferative benign lesions

The size reduction from pre-NAC to post-NAC in nonproliferative lesions versus proliferative lesions was not significantly different ($M = 0.53$ cm, SD = 0.37 cm vs. $M = 0.59$ cm, SD = 0.32 cm; $P = 0.60$) (Table 2). There was also no significant difference between the enhancement patterns ($P = 0.27$).

DISCUSSION

Breast MRI is considered helpful to determine the extent of disease in patients with known breast cancer, evaluate

Table 1: Pre- and post-neoadjuvant chemotherapy magnetic resonance imaging measurements of size (cm) and enhancement of cancer and biopsied benign lesions

	Mean (SD)		*P*
	Pre-NAC	Post-NAC	
Size			
Cancer	4.09 (2.51)	1.54 (2.32)	<0.001
Benign	0.83 (0.54)	0.28 (0.51)	<0.001
Enhancement			
Cancer	3.43 (0.80)	1.02 (1.34)	<0.001
Benign	2.96 (1.04)	2.96 (1.04)	<0.001

The enhancement was categorized (in numerical values) into 1-4 as (1) minimal, (2) mild, (3) moderate, and (4) marked enhancement. SD: Standard deviation, NAC: Neoadjuvant chemotherapy

Table 2: Comparison between the patient groups showing benign nonproliferative and benign proliferative pathology

	Mean (SD)		*P*
	Nonproliferative (*n* = 27)	Proliferative (*n* = 20)	
Change in lesion size (cm) after NAC	0.53 (0.37)	0.59 (0.32)	0.60
Change in enhancement after NAC	1.78 (1.55)	2.25 (1.25)	0.27
Change in glandularity	−0.07 (0.38)	0.05 (0.22)	0.21
Change in background enhancement	0.93 (1.07)	0.50 (0.95)	0.16

The changes in lesion size and enhancement after neoadjuvant chemotherapy. SD: Standard deviation, NAC: Neoadjuvant chemotherapy

for occult malignancy, and assess response in breast cancer patients treated with NAC. MRI can detect occult disease in the ipsilateral breast in about 12–27% of patients and in the contralateral breast in about 4% of patients.[20] In evaluating the response to chemotherapy, breast MRI is better than the clinical examination or mammography.[12,13,15,16]

In patients with newly diagnosed breast cancer who receive an MRI, further management not only depends on the extent of known cancer but also on discovery of additional ipsilateral and/or contralateral lesions. Many times, additional work-up with targeted ultrasound and/or additional biopsies is recommended before either any definitive surgical treatment is provided or treatment with NAC is started. In general, an additional lesion having suspicious morphology/dynamic characteristics will be biopsied before the treatment to rule out additional malignancy if an additional cancer diagnosis will change the further management decision. However, the additional lesions having benign or probably benign morphology are frequently left unbiopsied, and many of these patients will proceed to NAC treatment for their cancers. A management dilemma may arise when such a lesion responds to the NAC in a similar fashion as the patient's known cancer responds. This may raise the radiologist's or clinician's level of suspicion about these unbiopsied lesions for possible additional cancer foci.

The results of our study demonstrate that NAC affects benign lesions in a similar fashion as it affects cancers [Figure 2]. Although the size reduction happens to a lesser degree compared to cancers, there is no significant difference in the degree of decrease in the lesion enhancement. The response of benign lesion to NAC can be explained based on the previous work of Yeh et al., and Moll and Chumas.[5,8] They showed histologic changes such as lobular atrophy, decreased cellularity, and increased fibrosis occurring in normal glandular tissue after NAC treatment. It can be postulated that the same processes can probably happen in benign lesions as well leading to a decrease in size. Since cancers are generally excessively cellular, their size reduction can be expected to be more than the benign lesions. In addition, NAC affects the endothelial lining of the vessels leading to loss of vascular support. Similar changes may be expected to be seen in benign lesions leading to decreased enhancement. Protopapa et al., reported a positive correlation between the degree of tumor angiogenesis and the efficacy of chemotherapy.[39] They proposed increased angiogenesis in a cancer leads to a better delivery of the chemotherapeutic agent within the tumor increasing its chemosensitivity. One may intuitively think that the proliferative benign lesions would be expected to respond more than the nonproliferative

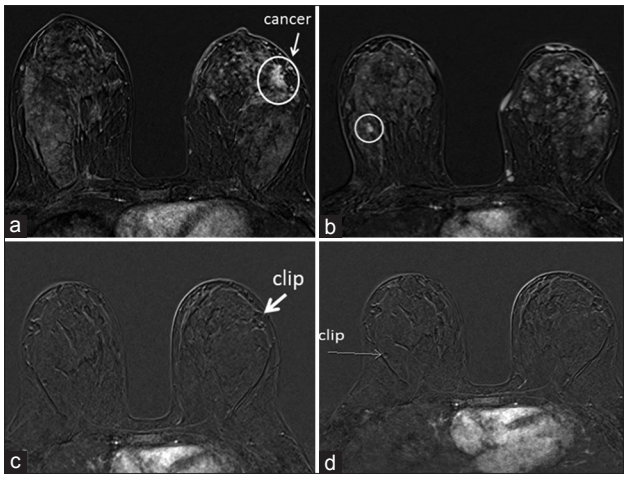

Figure 2: A 44-year-old female with a history of newly diagnosed left breast cancer at 3 o'clock position (a). Subtraction T1-axial images from the first dynamic sequence of bilateral contrast-enhanced breast magnetic resonance imaging before neoadjuvant chemotherapy (a and b) and after neoadjuvant chemotherapy (c and d) are shown. Another enhancing mass in the right breast (circled image b) was found to be a fibroadenoma on subsequent biopsy. Images c and d from the respective slices after neoadjuvant chemotherapy show disappearance of enhancement in cancer as well as benign lesion (fibroadenoma).

benign lesions because they tend have more cellularity and/or microvasculature. However, our study did not show any difference in response between proliferative and nonproliferative lesions. This could be due to a small sample size or a number of other factors in the tumor microenvironment that may affect the response to NAC.

Our study showed a significant decrease in BPE after NAC treatment [Figure 2a and c] which is consistent with the results reported in several previous studies.[40-43] Li et al., reported a decrease in BPE in both the treated and the untreated breast.[40] Due to the changes of lobular atrophy and fibrosis that occurs after the NAC, one may also expect an overall decrease in breast glandularity after NAC treatment. A decrease in breast glandularity after NAC was demonstrated by Chen et al.,[44] when they measured it by quantitative MRI technique. They showed a 10–16% decrease in amount of the glandular tissue after the NAC treatment. Our study did not show any significant decrease in glandularity which could be due to the fact that it was only visually assessed.

The limitations of our study include a small sample size and retrospective nature of the study. The other limitation was that the mean size of the benign lesions was smaller than the mean size of the malignant lesions which could have impacted on some of our results. A future larger study including larger benign lesions may give better comparative results.

CONCLUSION

Benign breast lesions also decrease in size and enhancement after NAC; however, the size reduction is to a lesser degree

than breast cancers. Therefore, additional ipsilateral or contralateral lesions seen on preoperative MRI that respond to NAC similar to the patient's known cancer may not be assumed to be cancers. The management decisions should still rely on the initial level of suspicion.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672-85.
2. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-804.
3. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001;30:96-102.
4. Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, et al. Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. J Clin Oncol 2002;20:1456-66.
5. Moll UM, Chumas J. Morphologic effects of neoadjuvant chemotherapy in locally advanced breast cancer. Pathol Res Pract 1997;193:187-96.
6. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012;48:3342-54.
7. Volders JH, Haloua MH, Krekel NM, Negenborn VL, Barbé E, Sietses C, et al. Neoadjuvant chemotherapy in breast-conserving surgery – Consequences on margin status and excision volumes: A nationwide pathology study. Eur J Surg Oncol 2016;42:986-93.
8. Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, et al. Prospective comparison of mammography, sonography, and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. AJR Am J Roentgenol 2005;184:868-77.
9. Gahlaut R, Bennett A, Fatayer H, Dall BJ, Sharma N, Velikova G, et al. Effect of neoadjuvant chemotherapy on breast cancer phenotype, ER/PR and HER2 expression – Implications for the practising oncologist. Eur J Cancer 2016;60:40-8.
10. Carder P. Typing breast cancer following primary chemotherapy. Histopathology 1999;35:584-5.
11. Close PM, Tiltman AJ, Hacking EA. The effect of chemotherapy on the morphology of human breast carcinoma. S Afr Med J 1987;72:103-6.
12. Abraham DC, Jones RC, Jones SE, Cheek JH, Peters GN, Knox SM, et al. Evaluation of neoadjuvant chemotherapeutic response of locally advanced breast cancer by magnetic resonance imaging. Cancer 1996;78:91-100.
13. Hylton NM, Blume JD, Bernreuter WK, Pisano ED, Rosen MA, Morris EA, et al. Locally advanced breast cancer: MR imaging for prediction of response to neoadjuvant chemotherapy – results from ACRIN 6657/I-SPY TRIAL. Radiology 2012;263:663-72.
14. Rosen EL, Blackwell KL, Baker JA, Soo MS, Bentley RC, Yu D, et al. Accuracy of MRI in the detection of residual breast cancer after neoadjuvant chemotherapy. AJR Am J Roentgenol 2003;181:1275-82.
15. Chen JH, Feig B, Agrawal G, Yu H, Carpenter PM, Mehta RS, et al. MRI evaluation of pathologically complete response and residual tumors in breast cancer after neoadjuvant chemotherapy. Cancer 2008;112:17-26.
16. Chen JH, Feig BA, Hsiang DJ, Butler JA, Mehta RS, Bahri S, et al. Impact of MRI-evaluated neoadjuvant chemotherapy response on change of surgical recommendation in breast cancer. Ann Surg 2009;249:448-54.
17. Marinovich ML, Houssami N, Macaskill P, Sardanelli F, Irwig L, Mamounas EP, et al. Meta-analysis of magnetic resonance imaging in detecting residual breast cancer after neoadjuvant therapy. J Natl Cancer Inst 2013;105:321-33.
18. Marinovich ML, Sardanelli F, Ciatto S, Mamounas E, Brennan M, Macaskill P, et al. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: Systematic review of the accuracy of MRI. Breast 2012;21:669-77.
19. Nagashima T, Sakakibara M, Nakamura R, Arai M, Kadowaki M, Kazama T, et al. Dynamic enhanced MRI predicts chemosensitivity in breast cancer patients. Eur J Radiol 2006;60:270-4.
20. ACR Practice Parameter for the Performance of Contrast-Enhanced Magnetic Resonance Imaging (MRI) of the Breast. Available from: http://www.acr.org/guidelines/Breast.MRI. [Last accessed on 2016 Jun 14].
21. Chen JH, Yu HJ, Hsu C, Mehta RS, Carpenter PM, Su MY. Background parenchymal enhancement of the contralateral normal breast: Association with tumor response in breast cancer patients receiving neoadjuvant chemotherapy. Transl Oncol 2015;8:204-9.
22. Ah-See ML, Makris A, Taylor NJ, Harrison M, Richman PI, Burcombe RJ, et al. Early changes in functional dynamic magnetic resonance imaging predict forpathologic response to neoadjuvant chemotherapy in primary breast cancer. Clin Cancer Res 2008;14:6580-9.
23. Kuhl CK, Bieling HB, Gieseke J, Kreft BP, Sommer T, Lutterbey G, et al. Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: Normal contrast medium enhancement and cyclical-phase dependency. Radiology 1997;203:137-44.
24. DeMartini WB, Liu F, Peacock S, Eby PR, Gutierrez RL, Lehman CD. Background parenchymal enhancement on breast MRI: Impact on diagnostic performance. AJR Am J Roentgenol 2012;198:W373-80.
25. King V, Gu Y, Kaplan JB, Brooks JD, Pike MC, Morris EA. Impact of menopausal status on background parenchymal enhancement and fibroglandular tissue on breast MRI. Eur Radiol 2012;22:2641-7.
26. Talele AC, Slanetz PJ, Edmister WB, Yeh ED, Kopans DB. The lactating breast: MRI findings and literature review. Breast J 2003;9:237-40.
27. Giess CS, Yeh ED, Raza S, Birdwell RL. Background parenchymal enhancement at breast MR imaging: Normal patterns, diagnostic challenges, and potential for false-positive and false-negative interpretation. Radiographics 2014;34:234-47.
28. Espinosa LA, Daniel BL, Vidarsson L, Zakhour M, Ikeda DM, Herfkens RJ. The lactating breast: Contrast-enhanced MR imaging of normal tissue and cancer. Radiology 2005;237:429-36.
29. Müller-Schimpfle M, Ohmenhaüser K, Stoll P, Dietz K, Claussen CD. Menstrual cycle and age: Influence on parenchymal contrast medium enhancement in MR imaging of the breast. Radiology 1997;203:145-9.
30. Delille JP, Slanetz PJ, Yeh ED, Kopans DB, Garrido L. Physiological changes in breast magnetic resonsnce imaging during the menstrual cycle: Perfusion imaging, signal enhancement, and influence of the T1 relaxation time of breast tissue. Breast J 2005;11:236-41.
31. Delille JP, Slanetz PJ, Yeh ED, Kopans DB, Halpern EF, Garrido L. Hormonal replacement therapy in postmenopausal women: Breast tissue perfusion determined with MR imaging-initial observations. Radiology 2005;235:36-41.
32. Reichenbach JR, Przetak C, Klinger G, Kaiser WA. Assessment of breast tissue changes on hormonal replacement therapy using MRI: A pilot study. J Comput Assist Tomogr 1999;23:407-13.
33. Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology 2007;244:356-78.

34. Morris EA, Comstock CE, Lee C, Lehman CD, Ikeda DB, Newstand GM, et al. ACR BI-RADS® magnetic resonance imaging. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.
35. American College of Radiology Mammography Accreditation Requirements. Available from: http://www.acr.org/~/media/ACR/Documents/Accreditation/Mammography/Requirements.pdf. [Last accessed on 2016 Jun 14].
36. American College of Radiology Breast MR Accreditation Guidelines. Available from: http://www.acr.org/~/media/ACR/Documents/Accreditation/MRI/Requirements.pdf. [Last accessed on 2016 Jun 14].
37. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146-51.
38. Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA, et al. Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. Cancer 1993;71:1258-65.
39. Protopapa E, Delides GS, Révész L. Vascular density and the response of breast carcinomas to mastectomy and adjuvant chemotherapy. Eur J Cancer 1993;29A: 1391-3.
40. Li J, Dershaw DD, Lee CH, Joo S, Morris EA. Breast MRI after conservation therapy: Usual findings in routine follow-up examinations. AJR Am J Roentgenol 2010;195:799-807.
41. Chen JH, Yu H, Lin M, Mehta RS, Su MY. Background parenchymal enhancement in the contralateral normal breast of patients undergoing neoadjuvant chemotherapy measured by DCE-MRI. Magn Reson Imaging 2013;31:1465-71.
42. Schrading S, Kuhl CK. Breast cancer: Influence of taxanes on response assessment with dynamic contrast-enhanced MR imaging. Radiology 2015;277:687-96.
43. Preibsch H, Wanner L, Bahrs SD, Wietek BM, Siegmann-Luz KC, Oberlecher E, et al. Background parenchymal enhancement in breast MRI before and after neoadjuvant chemotherapy: Correlation with tumour response. Eur Radiol 2016;26:1590-6.
44. Chen JH, Nie K, Bahri S, Hsu CC, Hsu FT, Shih HN, et al. Decrease in breast density in the contralateral normal breast of patients receiving neoadjuvant chemotherapy: MR imaging evaluation. Radiology 2010;255:44-52.