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Presence of peritumoral edema on T2w MRI: a poor non-invasive prognostic marker in breast cancer patients

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Abstract

Background: The purpose of the study was to assess the correlation between peritumoral edema (PE) seen on magnetic resonance imaging (MRI) in breast cancer and the established pathological prognostic factors like tumor histology and molecular subtype, grade, Ki67 index, lymphovascular invasion (LVI) and nodal stage. The breast MRI and pathological data of post-surgery specimen of 126 breast cancer patients over a period of 18 months were retrospectively studied. Those who received neoadjuvant therapy, had non-invasive, locally advanced, inflammatory and bilateral breast cancers were excluded. Patients were divided into two groups based on finding of peritumoral edema on T2w MRI images: Group A with PE ($n=88$) and Group B without PE ($n=38$). Pathological results for the two groups were analyzed and compared using Chi square test. p values of $<.05$ were considered as significant.

Results: Statistically significant correlation was found between the PE and molecular subtype (p value of $<.01$), high grade (p value of .001) and High Ki-67 index (p value of .001). No significant correlation was present for the histological type and LVI pathological nodal stage (pN).

Conclusions: We concluded that presence of PE on MRI is associated with poor pathological prognostic factors in breast cancer. It can serve as an additional non-invasive marker to assess prognosis in breast cancer patients especially in those receiving neoadjuvant therapy where the whole tumor may not be available for pathological analysis post-therapy.

Keywords: Peritumoral edema, Breast cancer, Prognosis, Breast MRI

Background

Breast cancer is the most common cancer affecting females worldwide [1]. Breast cancer is a heterogeneous disease in terms of prognosis, treatment responsiveness, locoregional recurrence and distant disease-free survival [2]. Thus, it is important to have non-invasive prognostic markers in addition to clinical and pathological factors which will help to prognosticate the disease and individualize the treatment plan.

Till date, imaging features that have been found to correlate with prognosis have been based on the tumor morphology and enhancement characteristics. T2w images are important in standard breast MRI protocol as it not only improves specificity of the findings but also provides important information like the presence of edema. Edema in breast cancer patient may be categorized as peritumoral, pre-pectoral and subcutaneous, each carrying its own underlying mechanism and significance [3]. As in brain tumors, peritumoral edema (PE) is considered to be portending a poor prognosis, its presence in breast cancers may also serve as an additional prognostic marker [4–6].

There are well-established histopathological markers that portend a poor prognosis in breast cancer. These include triple negative and Her2neu positive tumors that have poor prognosis compared to the luminal ones.

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Similarly, patients with the same histological and molecular types may have different prognosis on the basis of higher grade, proliferation index (Ki67 index) and the presence of LVI and the nodal stage. But the fact is that all this information is available only once the tumor has been resected and the therapy regime has been decided.

There is an increasing need to identify or develop non-invasive prognostic markers as more and more patients, even those with early breast cancers, are being offered neoadjuvant chemotherapy and minimally invasive therapies, like cryoablation. The pathological results obtained from core biopsy samples may not be reliable and accurate in these clinical settings owing to intra-tumoral heterogeneity. Also, in case of responders to neoadjuvant chemotherapy, the whole tumor is never available for the pathological analysis. PE has been found to be associated with worse recurrence-free survival in patients with triple negative tumors [7]. However, this needs to be validated by studies. Till date and to the best of our knowledge, we found scarce data evaluating the role of PE as a marker of prognosis in breast cancer. Through this study, we aimed to assess if the PE on MRI can serve as a prognostic marker by correlating it with well-established histopathological prognostic markers.

Methods

Our study was retrospective and thus the requirement of informed consent was waived off by the institutional review board. A total of 215 patients with biopsy proven breast cancer over a period of one and half year (1st January 2019 to 31st May 2020) were identified from our breast center database. Only those patients who underwent both MRI and surgery at our institute were included in the study. A total of 126 patients were found eligible. Rest of the patients were excluded on the basis of MRI or surgery done elsewhere ($n=52$), who received neoadjuvant chemotherapy ($n=12$), had inflammatory breast cancer ($n=6$) or were locally advanced ($n=11$), had non-invasive ($n=5$) or bilateral breast cancers ($n=3$).

MRI image acquisition and analysis

All patients underwent MRI on a 3T unit (Skyra, Siemens). The time gap between the biopsy and preoperative MRI was a minimum of two weeks. Surgery was done within three days of MRI in all the patients.

In our institution, multiparametric breast MRI is performed with acquisition primarily in the axial plane. Pre-contrast sequences include T2w STIR, (TR: 3040 ms, TE: 63 ms, Inversion recovery time: 230 ms), T1w gradient 3D without fat suppression (TR: 6 ms, TE: 2.6 ms), diffusion weighted imaging (DWI) at *b* values of 0 and 800. Dynamic post contrast data are acquired using 3D gradient T1w fat suppressed sequence, and subtracted images are generated for each post contrast series. T2w STIR images were retrieved for all the patients from picture archiving and communication systems (PACS) and read by two breast radiologists (with > 7 and > 10 years of experience) to reach a consensus for the PE for each case. Both the radiologists were blinded to the pathological results. PE was considered to be present only if there was a signal intensity surrounding the tumor as high as that of water. For multifocal tumors, the largest lesion was taken into consideration. Tumors were classified into group A or B based on the presence or absence of edema, respectively.

Pathological data collection and analysis

Histopathological data obtained on post-surgery specimens were considered as the gold standard, and the reports were retrieved from the hospital information database for each of the patients in both the groups. Tumors were classified as per the WHO classification and graded according to the Nottingham histological score. Molecular subtyping is done using immunostains for Estrogen receptor (ER), Progesterone receptor (PR) and Herceptin 2 (Her2). ER and PR are considered positive when the Allred scores are more than two [8]. Score of 0/1 for Her2 neu is considered negative, while score of 3 is positive. Her2 neu scores of 2 were equivocal and subjected to fluorescence in situ hybridization [9]. Average Her2 copy number > 6 or HER2/CEP17 ratio > 2 was considered positive. On the results of immunohistochemical (IHC) stains, these were further classified into Luminal A, Luminal B, Her2 positive and Triple Negatives as per 2013 St. Gallen international breast cancer conference classification [10].

The histological tumor type and grade, molecular subtype, Ki67 index, presence of lymphovascular invasion (LVI) and the pathological nodal stage (pN) were noted.

We classified the tumor type into invasive ductal carcinoma, invasive lobular carcinoma, and others. Tumors with mixed histology of both ductal and lobular carcinomas ($n=2$) were taken as the one which constituted the majority of the tumor. The grade was classified into 1, 2 or 3 as per the Nottingham score. Molecular subtype was divided into Luminal A, Luminal B, Her2 enriched and triple negative tumors based on IHC staining for the ER/PR/Her2. Ki-67 index was considered as low if </= 20% and high if > 20%. pN stage was classified as pN1/pN2/pN3 as per American Joint Committee on Cancer (AJCC) classification system [11].

Statistical analysis

The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables. Chi Square test was used to calculate the significance of differences in the two groups, and the probability value of less than .05 was considered as a significant level.

Results

A total of 126 patients were found eligible for the study out of which, 88 (69.8%) showed PE on MRI and constituted group A. Thirty-eight (30.2%) patients did not show PE and formed group B (Fig. 1). Patients in our study ranged from age group 33 to 83 years.

Pathological characteristics of tumors in two groups are summarized in Table 1.

Majority were T2 stage tumors with a total of 18 multifocal malignancies, 13 in group A and 5 in group B. Mean tumor size in our study was 2.9 cm with mean size of 3.1 cm in group A and 2.5 cm in group B patients.

Invasive ductal cancers were the most common cancers in the study as well as in both the groups. Invasive lobular cancer was seen in five cases and rest were other subtypes that included mucinous, tubular, metaplastic, papillary and medullary varieties). No statistically significant correlation was found between the histological tumor type and the PE in two groups.

Luminal B were the most common molecular subtype as well as in both the groups separately followed by triple negatives, Her2 enriched and luminal A cancers. Majority of the triple negative tumors were associated with PE, while the majority of the luminal A subtypes did not show edema. There was statistically significant correlation present ($p < .05$) between the various molecular subtypes and the two groups.

Also, statistically significant correlation was found for the Ki 67 index ($p = .001$; p value $< .05$) and grade ($p = .001$; $p < .05$) in the two groups (Fig. 2). Group A tumors were of higher grade with high Ki 67 values as compared to the group B tumors that were lower grade and had low Ki 67 index.

No statistically significant difference (p values of .028; $p < .05$) was noted for LVI in the two groups.

pN0 was the most common nodal stage. Although no statistically significant difference was found between pathological nodal stages in the two groups, higher pN stage tumors were more often seen in group A tumors than group B tumors.

Discussion

Role of MRI is well established in locoregional staging of breast cancer, response assessment to neoadjuvant therapy and screening in high-risk patients. A standard MRI protocol involves both the T2w and DWI sequences along with pre- and post-contrast fat saturated T1w images with dynamic contrast study [12]. It is important to develop non-invasive imaging markers of prognosis to personalize and guide therapy. Till date, various imaging features have been found to correlate with pathological factors and are based on the lesion morphology, enhancement characteristics and diffusion coefficients.

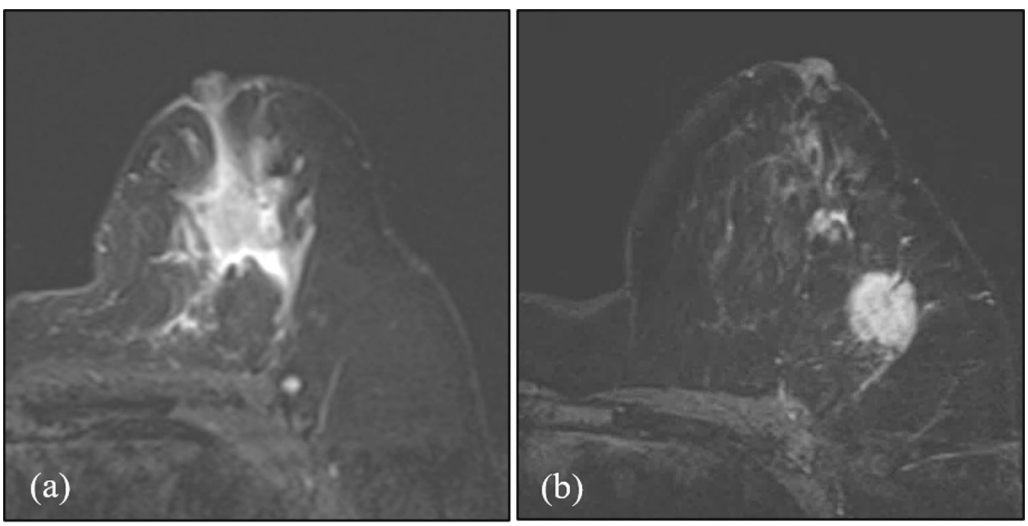

Fig. 1 Axial T2w STIR image of a patient in Group A (**a**) of size 2.7 cm with hyperintense peritumoral edema. It was grade 3 invasive ductal carcinoma, triple negative subtype, Ki67 of 88% and showed LVI. Axial T2w STIR image of a patient in Group B tumor (**b**) of size 3.1 cm with no peritumoral edema. It was a grade 1 invasive ductal carcinoma, luminal A subtype, Ki67 of 10% with no LVI

Table 1 Pathological characteristics of tumors in two groups

Pathological characteristics	Group A $n=88$ (69.8%)	Group B $n=38$ (30.1%)	*p* value
Tumor size			$p=.012$
pT1	10 (11.3%)	12 (31.5%)	
pT2	76 (86.3%)	24 (63.1%)	
pT3	2 (2.2%)	2 (5.2%)	
Histological type			$p=.025$
IDC	76 (86.4%)	27 (71.1%)	
ILC	1 (1.1%)	4 (10.5%)	
Others	11 (12.5%)	7 (18.4%)	
Molecular subtype			$p=.007$
Luminal A	7 (8%)	10 (26.3%)	
Luminal B	36 (40.9%)	16 (42.1%)	
Her 2 enriched	19 (21.6%)	9 (23.7%)	
Triple negative	26 (29.5%)	3 (7.9%)	
Tumor grade			$p<.001$
G1	8 (9.1%)	11 (28.9%)	
G2	25 (28.4%)	22 (57.9%)	
G3	55 (62.5%)	5 (13.2%)	
Ki 67 index			$p<.001$
Low (</= 14%)	8 (9.1%)	13 (34.2%)	
High (> 14%)	80 (9.9%)	25 (65.8%)	
LVI			$p=.028$
Present	64 (72.7%)	20 (52.6%)	
Absent	24 (27.3%)	18 (47.4%)	
Nodal stage			$p=.123$
pN0	38 (43.1%)	26 (68.4%)	
pN1	35 (39.7%)	9 (23.6%)	
pN2	7 (7.9%)	2 (5.2%)	
pN3	8 (9%)	1 (2.6%)	

T2w STIR images have been used to increase the specificity of MRI. Lesions can be differentiated as benign or malignant based on their T2w signal intensity as breast cancers are known to have low signals owing to their increased cellularity and low water content, few exceptions being mucinous & metaplastic variants of invasive ductal carcinomas [13]. Also, presence of edema around the lesion favors malignancy [14].

Underlying reason for PE has been attributed to various underlying mechanisms. An important reason postulated is the neo-angiogenesis associated with malignant process. These vessels are leaky and thus lead to exudation of fluid [15]. Second reason is the altered microenvironment of the surrounding peritumoral tissue. It has been found that the levels of polysaccharide hyaluronan are increased that leads to increased T2 relaxation times [15, 16]. Another basis for the PE is the lymphovascular invasion. Presence of LVI portends a poor prognosis as this implies that the tumor cells have already seeded the lymphovascular space and thus the likelihood of positive nodal disease and the disease recurrence [17, 18].

We did not find a statistically significant correlation between the PE and LVI and this may be attributed to the fact that other factors also play role in causing PE. These results match those by Mori et al. and are supported by Uematsu et al. who reported that it is pre-pectoral edema that is found to be more commonly associated with LVI rather than the PE [3, 19]. Cheon et al. also found no statistically significant results [20]. However, in another study done by the same authors where they evaluated MRI imaging features to predict LVI in node negative patients after appropriately matched controls and the exclusion of in situ disease associated malignancies, they found statistically significant correlation between the presence of LVI and the edema [17]. The difference may be in that we did not exclude the in situ component from our study that might also cause increased perilesional signals on T2w images [21].

Recently, PE on T2w images has been found to be a useful finding that can act as an important prognostic factor in breast cancer. PE has been included in the imaging lexicon by The Cancer Genome Atlas research study group in breast cancer [22].

The prognostic significance of PE on T2w STIR images in patients of breast cancer has been evaluated by few recent studies.

In our study, we found that there existed no correlation between PE and the histological tumor type. These results are similar to those of Cheon et al. and Panizironi et al. [20, 23]. Out of the total five cases of invasive lobular cancers, PE was found in only one case (Fig. 3). Low propensity of invasive lobular cancers to have edema is probably due to their growth pattern as single sheets of cells along the normal tissue planes [18, 24]. We need more numbers of lobular carcinoma in the study group to obtain statistical significance.

We found that edema was more often associated with non-luminal tumors especially the triple negative subtype, while luminal A cancers were rarely associated with PE as found by other authors in their studies [20, 23, 25] (Fig. 3). This is explained by the fact that triple negative cancers are high-grade tumors with high proliferation index. Bae et al. in their study on response to neoadjuvant therapy in triple negative tumors found that the presence of PE was associated with worse distant metastasis-free survival [7].

We found that tumors with PE tend to be of higher grade with a high Ki-67 index. In our study, 62.5% of the tumors with peritumoral edema on MRI were grade 3 in line with studies by Cheon et al. (56%) and Panizorini et al. (63%) [20, 23]. They also found that these tumors

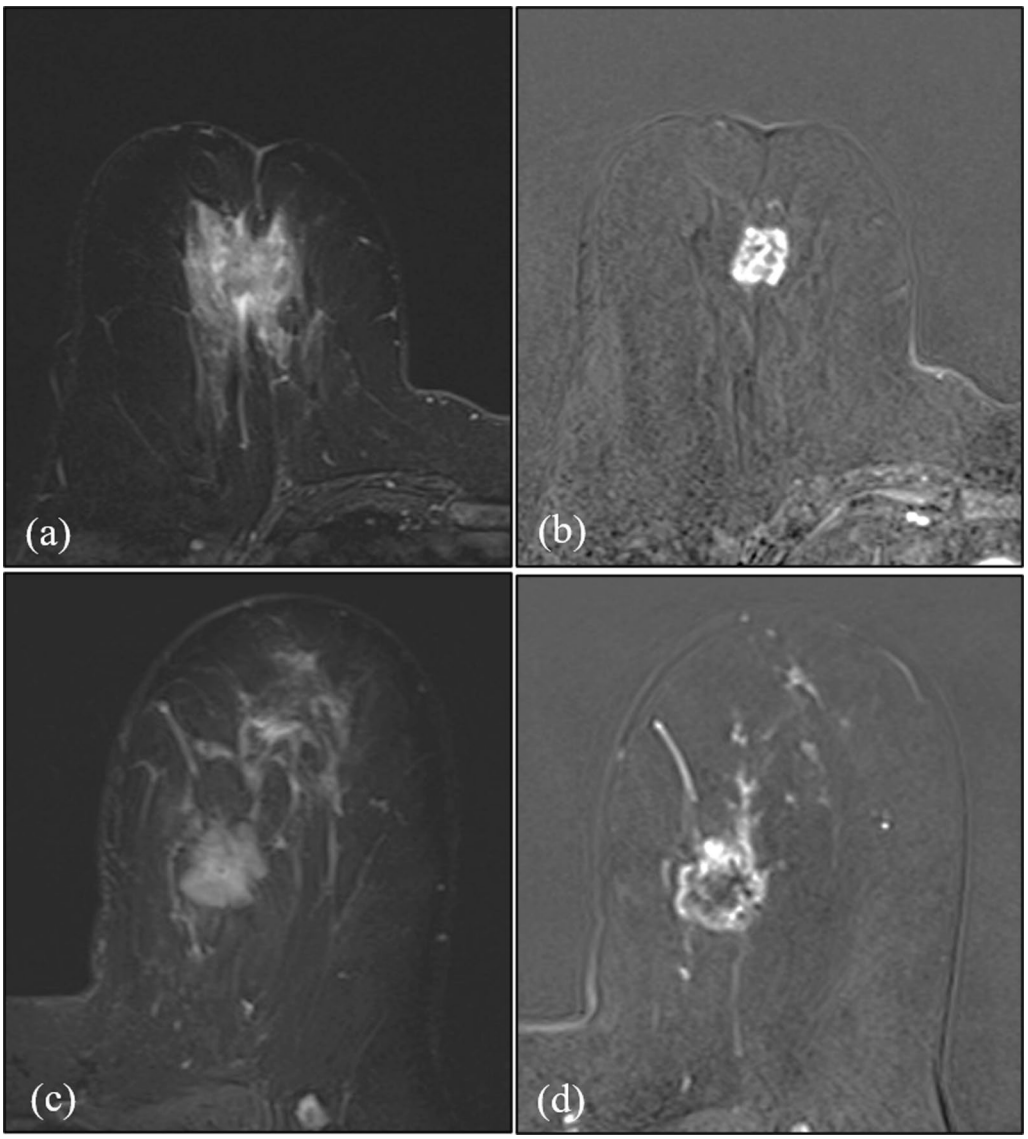

Fig. 2 Images from two different patients with grade 2 invasive ductal carcinoma Her2 enriched subtype with one having high Ki-67 of 63% (**a**, **b**) showing peritumoral edema (**a**) on T2w STIR image and heterogeneous enhancement (**b**) on subtracted post-contrast image and the other with lower Ki-67 index of 12% (**c**, **d**) shows no peritumoral edema (**c**) and rim enhancement (**d**)

were of high proliferation index as by Song et al. [20, 23, 26].

Although no statistical significant correlation existed between the PE and the pN stage, it was found that these patients tend to have higher nodal stage as opposed to those without edema. These results are similar to those obtained in previous studies [20].

Limitations

Ours was a retrospective single institution study thus results cannot be generalized. Long-term outcomes like locoregional recurrence and distant disease-free survival need to be assessed with larger sample size before the peritumoral edema can be validated as a prognostic marker.

Conclusions

It is concluded from our study that PE on T2w MRI images is associated with all the aggressive pathological markers (poor prognostic molecular subtype, high Ki-67, higher grade) and thus can serve as a non-invasive marker portending a poor prognosis in breast cancer patients.

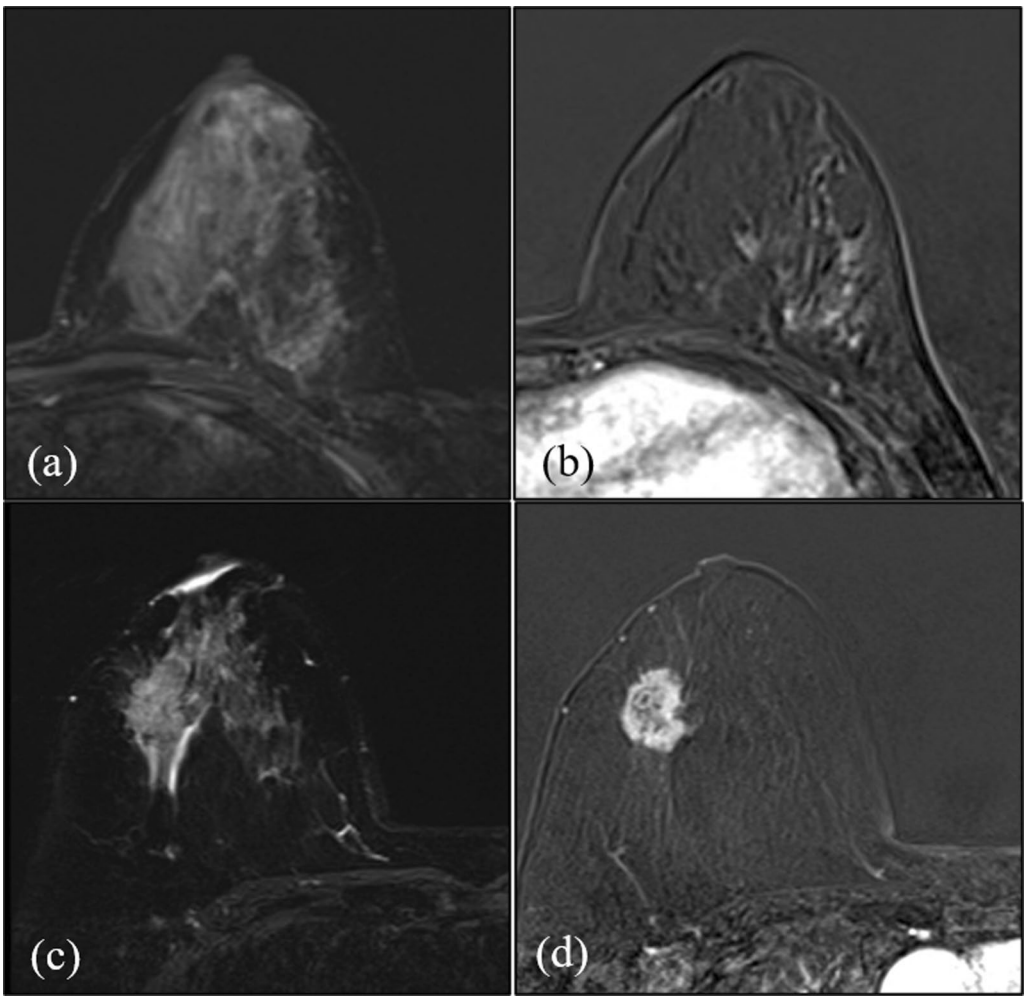

Fig. 3 Images of a patient with invasive lobular carcinoma (**a**, **b**) of size 3.7 cm with no peritumoral edema on T2w STIR (**a**) and segmental clumped NME on subtracted postcontrast sequences (**b**). Images of separate patient with invasive ductal carcinoma of size 3.6 cm showing peritumoral edema on T2w STIR (**c**) and heterogeneous enhancement on subtracted postcontrast sequences (**d**)

Abbreviations
PE: Peritumoral edema; MRI: Magnetic resonance imaging; LVI: Lymphovascular invasion; pN: Pathological nodal stage; STIR: Short-Tau-inversion recovery; TR: Repetition time; TE: Echo time; PACS: Picture Archiving and Communications System; WHO: World Health Organization; ER: Estrogen receptor; PR: Progesterone receptor; HER 2: Herceptin 2; IHC: Immunohistochemistry; AJCC: American Joint Committee on Cancer; DWI: Diffusion weighted imaging.

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Author contributions
All the authors have contributed in conceptualizing and designing the study, retrieval, analysis and interpretation of data. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously. The contents of this manuscript are not now under consideration for publication elsewhere. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere, while acceptance by the Journal is under consideration. There are no directly related manuscripts or abstracts, published or unpublished, by any authors of this paper. Both authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available for maintaining the anonymity but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was taken from the institutional KMCH ethics committee, Kovai Medical Center and Hospital limited, (EC/AP/866/11/2021). As ours is a retrospective observational study, informed consent was waived off by the review board of Kovai Medical Center and Hospital limited.

Consent for publication
We have used images maintaining the anonymity of the participants.

Competing interests
The authors declare that they have no competing interests.

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References

1. Ferlay J, Colombet M, Soerjomataram I et al (2019) Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144:1941–1953. https://doi.org/10.1002/ijc.31937
2. Perou CM, Sorlie T, Eisen MB et al (2000) Molecular portraits of human breast tumours. Nature 406:747–752. https://doi.org/10.1038/35021093
3. Uematsu T (2015) Focal breast edema associated with malignancy on T2-weighted images of breast MRI: peritumoral edema, prepectoral edema, and subcutaneous edema. Breast Cancer 22:66–70. https://doi.org/10.1007/s12282-014-0572-9
4. Wu CX, Lin GS, Lin ZX et al (2015) Peritumoral edema on magnetic resonance imaging predicts a poor clinical outcome in malignant glioma. Oncol Lett 10:2769–2776
5. Abe T, Black PM, Ojemann RG et al (1994) Cerebral edema in intracranial meningiomas: evidence for local and diffuse patterns and factors associated with its occurrence. Surg Neurol 42:471–475
6. Schoenegger K, Oberndorfer S, Wuschitz B et al (2009) Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma? Eur J Neurol 16:874–878
7. Bae MS, Shin SU, Ryu HS et al (2016) Pretreatment MR imaging features of triple-negative breast cancer: association with response to neoadjuvant chemotherapy and recurrence-free survival. Radiology 281:392–400
8. Allred DC, Harvey JM, Berardo M et al (1998) Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 11:155–168
9. Wolff AC, Hammond ME, Hicks DG et al (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31:3997–4013
10. Goldhirsch A, Winer EP, Coates AS et al (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24:2206–2223
11. Gabriel NH, James LC, Carl JD et al (2017) Breast. In: Mahul BA (ed) American Joint Committee on Cancer (AJCC). AJCC cancer staging manual, 8th edn. Springer, New York, pp 589–628
12. Newell MS, Giess CS, Argus AD et al (2018) ACR practice parameter for the performance of contrast enhanced magnetic resonance imaging (MRI) of the breast. American College of Radiology, Reston
13. Mann RM, Cho N, Moy L (2019) Breast MRI: state of the art. Radiology 292:520–536
14. Baltzer PA, Yang F, Dietzel M et al (2010) Sensitivity and specificity of unilateral edema on T2w-TSE sequences in MR-mammography considering 974 histologically verified lesions. Breast J 16:233–239
15. Auvinen P, Tammi R, Parkkinen J et al (2000) Hyaluronan in peritumoral stroma and malignant cells associates with breast cancer spreading and predicts survival. Am J Pathol 156:529–536
16. Koyama H, Kobayashi N, Harada M et al (2008) Significance of tumor-associated stroma in promotion of intratumoral lymphangiogenesis: pivotal role of a hyaluronan-rich tumor microenvironment. Am J Pathol 172:179–193
17. Cheon H, Kim HJ, Lee SM et al (2017) Preoperative MRI features associated with lymphovascular invasion in node-negative invasive breast cancer: a propensity-matched analysis. J Magn Reson Imaging 46:1037–1044
18. Uematsu T, Kasami M, Watanabe J (2014) Is evaluation of the presence of prepectoral edema on T2-weighted with fat-suppression 3 T breast MRI a simple and readily available noninvasive technique for estimation of prognosis in patients with breast cancer? Breast Cancer 21:684–692
19. Mori N, Mugikura S, Takasawa C et al (2016) Peritumoral apparent diffusion coefficients for prediction of lymphovascular invasion in clinically node-negative invasive breast cancer. Eur Radiol 26:331–339
20. Cheon H, Kim HJ, Kim TH et al (2018) Invasive breast cancer: prognostic value of peritumoral edema identified at preoperative MR imaging. Radiology 287:68–75
21. Van Goethem M, Schelfout K, Kersschot E et al (2004) Enhancing area surrounding breast carcinoma on MR mammography: comparison with pathological examination. Eur Radiol 14:1363–1370
22. Rao A, Net J, Brandt K et al (2015) Identification of associations between radiologist-annotated imaging features and genomic alterations in breast invasive carcinoma, a TCGA phenotype research group study. Med Phys 42:3603–3604
23. Panzironi G, Moffa G, Galati F et al (2020) Peritumoral edema as a biomarker of the aggressiveness of breast cancer: results of a retrospective study on a 3 T scanner. Breast Cancer Res Treat 181:53–60
24. Dietzel M, Baltzer PA, Vag T et al (2010) Magnetic resonance mammography of invasive lobular versus ductal carcinoma: systematic comparison of 811 patients reveals high diagnostic accuracy irrespective of typing. J Comput Assist Tomogr 34:587–595
25. Costantini M, Belli P (2012) Distefano D et al Magnetic resonance imaging features in triple-negative breast cancer: comparison with luminal and HER2-overexpressing tumors. Clin Breast Cancer 12:331–339
26. Song SE, Shin SU (2017) Moon HG et al MR imaging features associated with distant metastasis-free survival of patients with invasive breast cancer: a case–control study. Breast Cancer Res Treat 162:559–569

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