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Value of Background Parenchymal Enhancement (BPE) On Breast Magnetic Resonance Imaging (MRI) As a Predictor for Assessing Pathological Tumor Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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Abstract

Objective: This study investigated whether Background Parenchymal Enhancement (BPE) on imaging is valuable in determining pathological tumour response to neoadjuvant chemotherapy (NAC) amongst breast cancer patients in a tertiary-care hospital Dubai, United Arab Emirates (UAE).

Methods: Retrospective data from 64 patients with invasive breast cancer who received neoadjuvant chemotherapy (NAC) between 2015 and 2020 were analysed. Each patient underwent a pre-NAC Magnetic Resonance Imaging (MRI) study which was used to assess BPE grading, and Ultrasound (US) imaging before and after the NAC treatment to assess patients that received a pathological complete response (pCR) to the treatment. Pre-NAC BPE was compared with achieving pCR to evaluate if there is an association between them. Subgroup analysis based on menopausal status and molecular subtype of breast cancer was also performed.

Results: 17 out of 64 patients received a pathological complete response (pCR). Chi squared test was performed to evaluate an association between pre-NAC BPE and pCR and p value was found to be 0.910. These results are not statistically significant. On subgroup analysis, pre-menopausal status was found to be associated with achieving pCR. On analysis based on molecular subtype of the breast cancer, there was no correlation with achieving pCR.

Conclusion: There is no association found between pre-treatment Background Parenchymal Enhancement on MRI and tumour response to neoadjuvant chemotherapy and hence it cannot be used as a biomarker to predict pathological tumor response to neoadjuvant chemotherapy.

Introduction

Background and rationale

Breast cancer is a major public health issue with 1,384,155 estimated new cases worldwide with nearly 459,000 related deaths and is the most frequently occurring cancer amongst women [1]. Neoadjuvant chemotherapy (NAC) is a potential therapeutic treatment in which patients receive systemic therapy before the surgical removal of the tumour with the objective of reducing the size of the tumour. This enables large tumours to be downstaged which eventually offer benefits to properly selected women, such as broadening surgical options and enhancing the likelihood of receiving a breast conserving surgery, rather than a mastectomy [2]. It is also well established that patients who show a pathological complete response (pCR) to NAC have a better prognosis, hence response to NAC provides valuable information regarding patient prognosis [3]. Due to the advantages of NAC, it is widely used for treatment in breast cancer patients. However, only 10-20% of patients who undergo NAC achieve pCR [4]. Therefore, utilizing a biomarker that can predict tumour response to NAC may improve patient outcome and promote personalized treatment by preventing its unnecessary use for patients who are not likely to benefit from such therapy.

Predictive factors like the degree of expression of oestrogen receptor (ER) and progesterone receptor (PR) as well as HER2 positivity in predicting tumour response to NAC have been reported [5]. In addition, identification of multi-gene classifiers for prediction of pCR based on DNA microarray analysis has also been recognized [6,7]. However, they are still not satisfactory and hence, more clinically accurate predictive biomarkers need to be developed.

Dynamic contrast enhanced (DCE) Magnetic Resonance Imaging (MRI) is widely used for the diagnosis of breast cancer. The amount of contrast agent on intravenous administration that can reach the normal fibro-glandular tissue, captured on breast MRI, is an indicator of blood perfusion to the normal tissue and is referred to as background parenchymal enhancement (BPE) [8]. BPE may vary in degree and distribution in different patients as well as in the same patient over time. It usually presents in a bilateral, symmetrical distribution [9]. Normal BPE is classified according to the Breast Imaging Reporting and Data System (BIRADS) lexicon classification system into four categories which are defined by the visually estimated enhancement of the fibro glandular tissue of the breast as minimal (<25% of glandular tissue demonstrating enhancement), mild (25%-50% enhancement), moderate (50%-75% enhancement), or marked (>75% enhancement) [10]. This is illustrated in Figure 1.

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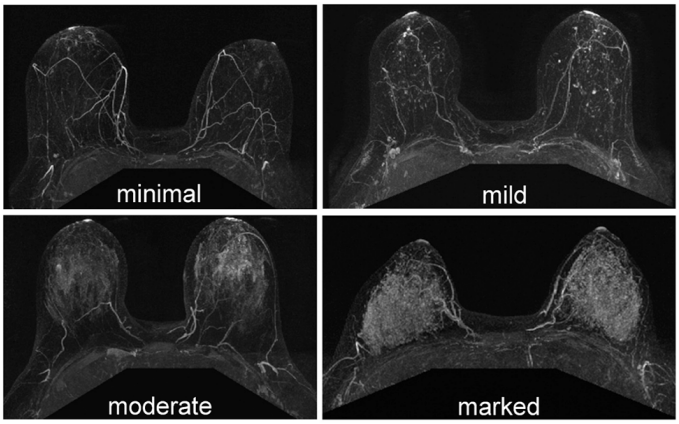

Figure 1: Examples from the Breast Imaging-Reporting and Data System (BI-RADS) lexicon for contrast-enhanced MRI, showing the different degrees of background parenchymal enhancement (BPE) in the breast: minimum, mild, moderate, and marked enhancement.

BPE is established to be affected by age, physiological hormonal status, and hormone therapy [11]. It was noted that BPE fluctuates depending on the menopausal status as well as the phase of the menstrual cycle in premenopausal women [9]. Multiple studies have shown that elevated BPE levels are associated with a greater risk of developing breast cancer [12-14] hence understanding a patient's BPE can be useful in understanding the breast physiology and can in turn, improve patient care. Our study aims to assess whether we can evaluate pathological tumor response to neoadjuvant chemotherapy by analyzing a patient's BPE grading, ultimately improving patient outcome.

Objectives

1. Determine the relation between the degree of BPE on pre-NAC MRI and degree of response to neo-adjuvant chemotherapy, if any.

2. Determine the relation between menopausal status and molecular subtype of cancer and degree of response to neo-adjuvant chemotherapy, if any.

Methods

Study design

The following study is a retrospective cohort study analysing patient data related to BPE parameters on MRI and tumour response to neoadjuvant chemotherapy

Study setting

The study was conducted in a Tertiary Care Hospital, Dubai, United Arab Emirates (UAE) and includes a time frame sample of all patients diagnosed with invasive breast cancer that qualify for NAC from January 2015 to January 2020.

Participants

All included patients must have had undergone a pre-NAC MRI to assess baseline BPE Grading, pre-NAC US to extract tumor size before treatment and post-NAC pre-surgery US to extract tumor size after treatment to assess tumor response to NAC. 3 patients included in the study were imaged pre-NAC externally but were reviewed and followed treatment at our institution.

Variables

The MRI reports or second read reports (in the instance of external imaging) of the qualifying patients that fell under our inclusion criteria were reviewed to assess the documented grade of Background Parenchymal Enhancement (BPE) reported as minimal, mild, moderate or marked according to the BIRADS lexicon classification system [10].

The size of the tumor pre-NAC and post-NAC was analyzed on US to confirm the documented imaging response and categorized into pCR and non-pCR. The data being collected and analyzed is primarily qualitative. Other variables like patients, menopausal status and hormonal status of the tumor were also collected and analyzed.

Data sources/measurement

The pre-NAC MRI report/review was collected from hospital records and the BPE grading was documented as was recorded visually by the reporting radiologist and grouped into minimal, mild, moderate and marked. Both pre-NAC and post-NAC imaging US reports were also obtained from hospital records and tumor measurements of the largest primary tumor was captured and compared.

The pathologic response was determined based on the examination of surgical specimen after completing NAC. The final radiology report was extracted from hospital records and assessed for documented tumor response and classified into complete pathological response (pCR) and incomplete pathological response (non-pCR). pCR was defined as the absence of residual tumor cells on hematoxylin and eosin evaluation of the complete resected breast specimen and all regional lymph nodes following the completion of NAC and non-pCR was defined as presence of any tumor cells even after treatment [15].

Patients' menopausal status was collected and categorized as pre-menopause and post-menopause. Hormonal status of the breast cancer was analyzed by looking at estrogen receptor positivity, progesterone receptor positivity, and HER2 receptor expression on the tumor as well as Ki-67 protein, which was collected from patient's lab reports. Then, they were categorized into 4 major molecular subtypes-Luminal A (ER+/PR+/HER2-/lowKi-67); Luminal B (ER+/PR+/HER2-/+/high Ki-67); HER2-overexpression (ER-/PR-/HER2+) and triple negative breast cancers (TNBC) (ER-/PR-/HER2-) according to the St. Gallen Consensus 2011 [16].

Bias

Since the data collected in this study was collected from 1 tertiary care hospital only, it is not representative of the entire population and hence could lead to a selection bias. Additionally, this study is a retrospective cohort study and existing records were used during data collection. Missing information could have also caused information bias.

Statistical analysis

Several statistical tests including Chi square test, Logistic Regression and ROC Curve were conducted to investigate the correlation between BPE grading and tumour response to neoadjuvant chemotherapy and assess whether pCR rates were higher under a particular BPE grading. This was performed on IBM SPSS Statistics (Statistical Package for the Social Sciences).

Results

Participants

A total of 64 patients met the criteria for inclusion. Out of 64 patients, the pathological tumor response after NAC was a pCR in 17 (26.56%) non-pCR in 47 (73.43%). 3 patients had luminal-A breast

cancer, 37 patients had luminal-B breast cancer, 17 had triple negative breast cancer (TNBC) and 7 had HER2 receptor positive breast cancer. According to BPE grading, 33 patients had mild enhancement, 16 patients had moderate enhancement, 9 had minimal enhancement, and 6 had marked enhancement. Clinicopathological information of BPE, menopausal status, molecular subtype of breast cancer and age compared to tumour response to NAC is shown in Table 1.

BPE, background parenchymal enhancement; NAC, neoadjuvant chemotherapy; pCR, pathological complete response.

Chi-square test was applied to estimate an association. A p value ≤0.05 was considered for statistical significance.

Main Results

As seen in Table 1, a large number of patients with a mild pre-treatment BPE achieved a pCR whereas; only 1 patient with a marked pre-treatment BPE grading achieved the same. Chi squared test was performed to evaluate an association between pre-NAC BPE and pCR. The p value is larger than 0.05 (p value=0.910). This indicates that there is no statistical significance.

While comparing menopausal status and achieving pCR, it is observed that all patients that achieved pCR were pre-menopausal. The p value of 0.026 illustrates that these results are significant.

On assessment of molecular subtype of breast cancer with pCR groups, it is noted that a large number of patients had a luminal-B subtype of breast cancer. The p value of 0.367 shows us that there is no statistical significance while comparing molecular subtype with achieving pCR.

Logistic regression and ROC Curve analysis was also done to re-establish the findings and results were not statistically significant indicating that there is no association between the groups as stated above.

Discussion

Summary of major findings

In this study, we measured pre-treatment BPE grading on MRI and compared it to tumour response to NAC which is displayed in Table 1. Firstly, it is observed that the pCR group is much less in number as compared to the non-pCR group. This is in agreement with previous studies which have proved that pCR rates are lower than non-pCR rates. (4) On comparing pre-NAC BPE grading and pCR, the results are not statistically significant (p-value=0.910) indicating that BPE grading cannot be used to predict tumour response to NAC.

Table 1: Descriptive data of breast cancer patients who received neoadjuvant chemotherapy in a tertiary care hospital, Dubai, United Arab Emirates, 2015-2020 compared to pathological tumour response.

Variables	pCR (N=17)	Non-pCR (N=47)	p-value
Mean age	38.76	42.74	
BPE grading			0.910
Minimal	3	6	
Mild	9	24	
Moderate	4	12	
Marked	1	5	
Menopausal status			0.026
Pre-menopause	17	35	
Post-menopause	0	12	
Molecular subtype of cancer			0.367
Luminal-a	0	3	
Luminal-b	8	29	
TNBC	6	11	
Her2-positive	3	4	

This is in contrary to the expectation we had before started the study. Since a high BPE is reflective of higher vascularity in a patient's breast, ensuring more vascular delivery of the IV chemotherapeutic agent to the site of the tumour, we expected a large number of patients with a moderate or marked BPE to achieve pCR as compared to those patients with a minimal or mild BPE grading. A likely cause of the unexpected results could be because; a higher BPE is known to be associated with a higher risk of developing malignant breast lesions. This has been confirmed in several studies [13,14,17]. This could be a possible reason why only 1 patient with a marked BPE grading received pCR whereas 9 patients with a mild BPE grading achieved the same.

Another possible reason could be because a large number of patients were pre-menopausal. Hence the timing of the MRI taken to evaluate BPE could have been impacted by the patient's hormonal surges at ovulation or menstruation. Existing literature proves that BPE is affected by menstruation [9,18]. It has also been recorded that BPE decreases after menopause [19]. Hence it is likely that hormonal status of the patient variably impacts BPE, making it unreliable as a predictor for assessing tumour response to NAC.

These unexpected findings were initially thought to be due to the small number of subjects that were included in the study, but the particularly high p-value establishes that it is highly likely that there truly is no association between the two variables. Hence it cannot be used as a predictive biomarker to assess tumour response.

On sub-group analysis of menopausal status amongst pCR and non-pCR groups, it is observed that all patients who received pCR were pre-menopausal. All post-menopausal patients did not achieve pCR. There is a positive association between menopausal status and pCR groups since p value is less than 0.05 (p value=0.026). This was an expected finding. This implies that pre-menopausal women are more likely to achieve pCR with NAC treatment as compared to post-menopausal women.

The molecular subtype of the breast cancer and pCR groups were also analysed and concluded to have no associated significance (p-value=0.367).

Comparison with previous studies

It has been shown in existing literature that there is positive correlation between change in BPE with NAC treatment and tumour response. Changes in BPE after NAC were significantly greater in the pathological complete response (pCR) group than in the non-pCR group [20]. However, there are no studies done that are solely focused on establishing a relationship between BPE on pre-NAC MRI and tumour response, as we have. Former studies have performed subgroup analyses evaluating whether there is an association between BPE on pre-NAC MRI and tumour response to NAC and suggest that there is no association [8,20]. These findings are similar to ours which state that BPE grading cannot be used as a predictor for tumour response to neoadjuvant chemotherapy.

While looking at the association between menopausal status and tumour response to NAC, a positive association was found. This is in agreement with other studies which have proved a positive association between the two. There is sufficient evidence that show that pre-menopausal women undergoing NAC for their breast cancer have a

higher chance of achieving pCR as compared to post-menopausal women [21,22].

The negative association between molecular subtype of breast cancer and pCR differs from former studies that have demonstrated that triple negative and HER2+ subtypes of breast cancer are more sensitive to NAC and hence these subtypes are more likely to achieve pCR. The difference in findings observed in our study could be due to the small sample size of only 64 patients. Future studies should include a larger sample size to ensure that their results are more dependable while looking molecular subtype of breast cancer.

Implications for public health practitioners/clinicians

This paper provides evidence on the relationship between BPE grading on imaging and pathological tumour response to NAC. This information can be used by future researchers to discover other biomarkers which can be used as a predictor for tumour response to NAC. With such advances, we could promote patient centred care and personalized therapy.

Strengths, limitations, and generalisability

To our knowledge, this is the first study that has assessed the value of BPE for evaluating pathological tumor response to NAC in the UAE. However, this study has several limitations: 1) data has been extracted from a single hospital in UAE and thus is not representative of the entire population; 2) the number of subjects included in this study was small. This small sample size was because of limitations that occurred during data collection due to insufficient details in the hospital records. Hence these patients had to be excluded from study; 3) we did not collect information on factors such as reproductive history or co-morbidities which could be possible factors that affect BPE grading or likelihood of achieving pCR with NAC treatment.

It would also have been noteworthy to know if a change in BPE was seen before and after receiving NAC but because of cost limitations, a fair number of patients did not get a final review MRI to assess post-NAC BPE.

This paper contains the first data in the UAE on the assessment of BPE as a clinically valuable biomarker for predicting response to neoadjuvant chemotherapy. However, as mentioned in the limitations, the data has been collected from a single hospital in the UAE with a small sample size. While this study provides novel and original data, the results are not generalisable and additional studies with a larger number of subjects must be conducted.

Areas for future research

Our study was limited by the lack of detailed information required to further our understanding of the factors associated with tumour response to neoadjuvant chemotherapy and the reason why only 10-20% of patients who undergo this treatment achieve the ideal pathological complete response (pCR). In view of this limitation, future studies may want to consider collecting and reporting data on factors that may affect the chances of success of the neoadjuvant chemotherapy regimen.

Since this study proves no association between pre-treatment BPE and tumour response to NAC, it would be ideal if future studies assess other biomarkers as possible predictors since establishing one would have great implications for improving patient care.

Conclusion

This study is the first to show that BPE grading on pre-treatment MRI cannot be used as a predictive biomarker to assess tumour response to neoadjuvant chemotherapy amongst breast cancer patients.

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