

Accuracy of MRI for Prediction of Response to Neo-Adjuvant Chemotherapy in Triple Negative Breast Cancer Compared to Other Molecular Types

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Abstract

Purpose: The aim of this study was to compare the accuracy of MRI for prediction of response to Neo-adjuvant chemotherapy in Triple negative (TN) breast cancer, with respect to other molecular types.

Materials and methods: There were a total of 1610 breast cancers diagnosed between March 2009 and August 2014, out of which 82 patients underwent MRI before and after neo-adjuvant chemotherapy but just before surgery. Triple negative cancers were analysed with respect to others subtypes. Accuracy of MRI for prediction of pathological complete response was compared between different subtypes, by obtaining ROC curves. SPSS (version 21) was used for all data analysis with p value of 0.05 as statistically significant.

Results: Out of 82 patients, 29 were Luminal (HR+/HER2 -), 23 were triple negative (HR-, HER2-), 11 HER2 positive (HR-, HER2+) and 19 were of hybrid subtype (HR+/HER2+). Triple negative cancers presented as masses on the pre-chemotherapy MRI scan, were grade 3 on histopathology and show concentric shrinkage following chemotherapy. Triple negative cancers were more likely to have both imaging and pathological complete response following chemotherapy (p=0.055) in contrast to Luminal cancers, which show residual cancer. ROC curves were constructed for prediction of pCR by post chemotherapy MR. For the triple negative sub-group, MR had sensitivity of 0.745 and specificity of 0.700 (p=0.035), with an area under curve (AUC) of 0.745(95% CI 0.526-0.965), which was significantly better compared to other subtypes.

Conclusion: Triple negative breast cancers present as masses and show concentric shrinkage following chemotherapy. MRI is most sensitive and specific in predicting response to chemotherapy in the TN group, compared to others subtypes. MRI underestimates residual disease in Luminal cancers.

Keywords: Breast cancer; Magnetic resonance imaging; Neo-adjuvant chemotherapy; Residual tumour size

Introduction

Neo-adjuvant chemotherapy (NAC) has been used widely in clinical practice to downstage inoperable breast cancers and is increasingly used for operable cancers to achieve better outcomes in breast conserving surgery. Breast cancer is not a homogeneous entity and molecular subtypes behave differently, both in their imaging patterns and clinico-biological behaviour following neo-adjuvant chemotherapy [1,2]. Whilst traditional classification of breast cancer offers limited prognostic value novel molecular characterisation and biomarkers offers predictive categories of disease aggressiveness [3]. Tumour subtypes based on oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) status is now increasingly used for assessment of prognosis and treatment.

Patients with pathological complete response (pCR) following NAC have favourable prognosis [4-6]. Previous studies have demonstrated that triple negative (TN; ER-, PR-, HER2-) breast cancer is a distinct entity and behaves differently to other molecular subtypes of breast cancer, especially with respect to attainment of pathological complete

response (pCR) to NAC and imaging presentation on pre chemotherapy MRI [7-12]. The purpose of this study was to evaluate the accuracy of MRI for predicting response to chemotherapy in different molecular subtypes of breast cancer. The radiological and histopathological factors that influence the accuracy of MRI in predicting response to NAC were also evaluated such as histopathological grading of cancer, axillary status and baseline imaging size of the tumour. The strengths and weaknesses of MR for predicting residual cancer in different molecular subtypes of breast cancer were evaluated, enabling better surgical planning and prediction of prognosis. By combining clinico-pathological parameters with receptors, more informed decision about the use of neo-adjuvant treatment and optimal surgical planning can be made to achieve a tumour free margin. This can reduce the need for re-excision for involved margins and local recurrence rate.

Methods

Subjects and treatment

The University Health Board approved this retrospective study as a service evaluation project (Ref 8674, Reg Nov 2014). Requirement of informed consent and ethical approval was waived. Between March

2009 and August 2014, 1610 breast cancer patients were treated in this institution, out of which 89 patients with breast cancer underwent neo-adjuvant chemotherapy. Inclusion criteria included baseline MRI before start of neo-adjuvant treatment and a MRI scan after completion of NAC, but just before surgery (<30 days). Further inclusion was based on availability of core biopsy prior to the start of NAC to determine the histological diagnosis, hormone receptor status and Human epidermal growth factor receptor 2 (HER2) over

expression status, by using immunohisto-chemical (IHC) staining or fluorescence in situ hybridization (FISH). On IHC staining, a score of 3+ was considered positive for HER2+ positivity and scores of 0 and 1+ were considered negative. Scores of 2+ were further evaluated with FISH for HER2 gene amplification. Oestrogen and progesterone receptors positivity was based on >10% staining of tumour cells with immunoperoxidase staining. Patients were subdivided into four groups based on the receptor status as shown in Table 1.

	Triple -ve 23(28%)	Luminal 29(35.3%)	HER2+ 11(13.4%)	Hybrid 19(23.1%)
ER	-	+	-	+
PR	-	+/-	-	+/-
HER2+	-	-	+	+

Table 1: Intrinsic subtypes of breast cancer;ER- Oestrogen receptor, PgR- Progesterone receptor, HER2- Human epidermal Growth factor receptor 2.

Patients who were not able to have a pre and post treatment MRI scan or whose receptor status was not available or inadequately described or did not undergo surgery at our institute were excluded from the analysis. After all exclusions, there were a total of 82 patients, out of which 29 were Luminal (HR+/HER2 -), 23 were triple negative (HR-, HER2-), 11 were HER2 positive (HR-, HER2+) and 19 were Hybrid (HR+/HER2+).

The therapeutic treatment plan was explained to the patients, following which informed consent was obtained from all patients. The standard protocol was a combination of fluorouracil, cyclophosphamide and epirubicin (FEC75) for six cycles if nodes were negative, or FEC-T (addition of doxorubicin) for three cycles each if nodes were involved with cancer. Trastuzumab (Herceptin) was added for 12 weeks if HER2 was over-expressed in breast cancer tissue. Treatment protocol was chosen by the on-site oncologist after evaluating all available information for each patient.

Imaging and histology

MRI was performed with patient lying prone on a 1.5T magnet (GE HDxt 1.5 T, GE Health care, Tokyo, Japan), using an eight -channel phased array breast coil. Following a 3-plane localiser and axial 3D T1 (high resolution) sequences, multiphase VIBRANT dynamic post contrast axial 3D T1 fat suppressed high-resolution images were obtained. A dynamic study of both breasts was obtained after intravenous injection of gadopentetate dimeglumine (0.1m mol/kg body weight) and fat suppressed subtracted images were obtained in axial plane approximately every minute for 8 minutes. A three dimensional spoiled gradient recalled acquisition in the steady state sequence (TR/TE/TI 6/2.5/18 ms) with flip angle 10degrees, FOV 34 cms, section thickness 2 mm, matrix 512*256 and acquisition time 1 min and 5 seconds was used for post contrast images. MRI was performed in all patients both at baseline and following the end of chemotherapy, but just before surgery.

Radiologic tumour size was based on the largest two dimensions on the baseline axial MRI and post treatment axial MRI. In case of multi-focal tumours, the largest tumour focus was measured. Images were read by one of the radiologists (JB) with more than 5 years' experience of reading breast MR, blinded to both the receptor status and post-

surgical findings. In this study, 'concentric shrinkage' was defined as shrinkage in all planes simultaneously with no evidence of breaking of original lesion into multi-focal residual lesions on imaging. 'Non-Concentric' shrinkage was defined as breakage with multiple residual lesions/islands scattered in a large area. After treatment with NAC, all patients underwent surgery, either mastectomy or wide local excision (WLE). Post-surgical specimens were fixed with 10% neutral formaline and thin paraffin sections were evaluated by the on-site histopathologies after staining them with H and E for detailed histopathological examination. Pathological response following NAC was evaluated by estimating the maximum size of residual disease in two dimensions or by estimating residual tumour gross size and cellularity through the RCB (residual cancer burden) method [13]. The RCB method is considered ideal for estimating the residual tumour size in resected specimen, but it is not comparable with radiological tumour size. Therefore, maximum pathological residual tumour size in two dimensions was used in the majority of cases. For the purpose of this study, pathological complete response (pCR) was defined as absence of invasive malignancy within breast tissues on final pathology.

Chi square test and Mann-Whitney U was used for comparison of the groups, for comparison of nominal (categorical) variables and non-parametric scale variables respectively. SPSS (version 21) was used for all data analysis with p value of 0.05 as statistically significant. MRI as a predictor of pCR was evaluated with a Receiver operating characteristic (ROC) curve in different subgroups. The mean age of patients in this study was 48.6y (median 47y), ranging from 28- 70 years.

Results

The mean size of cancer on the initial MRI for the whole group was 53.5mm (median 46mm), ranging from 14-113 mm. There were 63 (76.9%) ductal, 12(14.1%) ducto-lobular, 3(3.8 %) DCIS, 2 (2.6 %) lobular and 2(2.6%) ductal with associated DCIS on the initial core biopsy histopathology. There were 43(53%) grade 2 cancers and 39(47%) grade 3 cancers. Fifty-six (68%) patients presented as 'mass' on the initial MRI and 26(32) % presented as 'non-mass like enhancement'. Sixty (73.7%) patients had proven axillary involvement with cancer on presentation. Twenty (24.3%) presented as multifocal

tumours, out of which 15 were multi-focal masses and 5 were multi-focal non-mass like enhancement.

Seventeen (21.1%) patients achieved radiological complete response and 22 patients (26.8 %) achieved pathological complete response (pCR) in this study. The mean difference between post treatment residual cancer on MRI and post-surgical size was 16mm (+/-10.1), ranging from 0- 80 mm.

Most triple negative cancers presented as mass on the initial MR (p=0.035), whereas non-mass like enhancement was associated with Luminal cancer (p=0.014) (Figure 1,2 Table 2). Triple negative cancers were predominantly pathological grade 3 at the time of presentation (p=0.006). Following NAC, Triple negative cancers demonstrated 'concentric' shrinkage (p=0.049), whereas 'non-concentric' shrinkage was more evident with Luminal cancer (p=0.004) (Table 3). There was no significant difference between the different subtypes with respect to axillary status or initial MR size at the time of presentation (p=0.192) (Table 4).

	Triple -ve N (%)	Luminal N (%)	HER2+ N (%)	Hybrid N (%)
Mass	20 (86.9%)	16 (55.1%)	7 (63.6%)	13 (68.4%)
Non mass	3 (13%)	13 (44.8%)	4 (36.3%)	6 (31.5%)
P value	0.035	0.014	0.672	0.829

Table 2: Baseline MRI presentation of the four different subtypes of breast cancer.

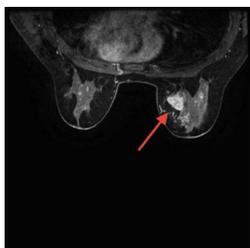


Figure 1a: Triple negative cancer presenting as mass within right breast.

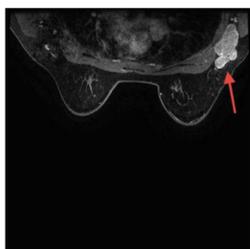


Figure 1b: Same patients as in Fig 1a, with right axillary lymphadenopathy at the time of presentation.

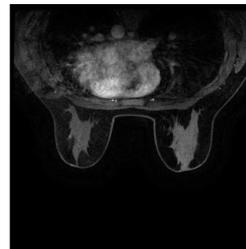


Figure 1c: Following neo-adjuvant chemotherapy (NAC), there is complete imaging response of the tumour within the breast.

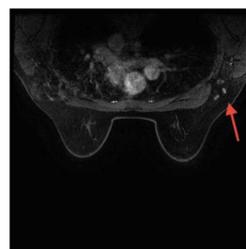


Figure 1d: Following neo-adjuvant chemotherapy (NAC), right axillary lymph nodes appear normal.

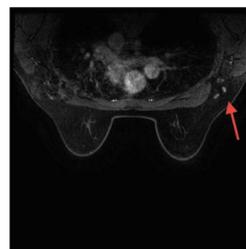


Figure 2a: Luminal cancer presenting as non-mass like enhancement within left breast.

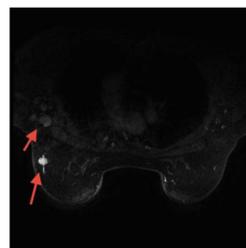


Figure 2b: Same patient as 2a, showing left intra mammary node and left axillary lymphadenopathy at the time of presentation.

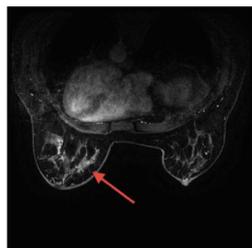


Figure 2c: Following neo-adjuvant chemotherapy (NAC), subtle enhancement persists at the site of known cancer within left breast.

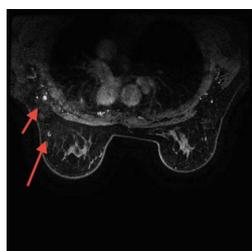


Figure 2d: Following NAC, there is partial response of the nodes within the left axilla and of the intra-mammary lymph node within left breast.

Most triple negative cancers demonstrated both radiological and pathological complete response following NAC ($p=0.006$) (Table 5). Luminal cancers showed residual cancer following NAC ($p=0.004$), both on imaging and on histology. Mann-Whitney U test was used to calculate significant difference between the sub-groups with respect to residual imaging size on MRI and post-surgical pathological invasive size. The difference between post chemotherapy MR size of residual tumour and post-surgical pathological size was least for triple negative cancer, when compared to other subtypes ($p=0.051$; 95%CI 0.047-0.055) (Table 6).

ROC curves were constructed for prediction of pCR by post chemotherapy MR. At a post chemotherapy size difference of 5mm between post chemotherapy MR and post-surgical pathology, for the triple negative group, MR had a sensitivity of 0.745 and specificity of 0.700 ($p=0.035$), with an area under curve (AUC) of 0.745(95% CI 0.526-0.965) (Figure 3). For Luminal, HER-2 positive cancers and Hybrid cancers, results were not statistically significant ($p=0.908$ $p=0.317$ and $p=0.230$ respectively). MRI underestimated disease in 17 (58.6%) Luminal cancers.

Overall, increased likelihood of pCR was associated with Grade 3($p=0.014$) and Triple negative cancers ($p=0.055$). Luminal cancers most commonly demonstrated residual tumour ($p=0.014$). No significant association was found between pCR and other factors.

	Triple -ve N (%)	Luminal N (%)	HER2+ N (%)	Hybrid N (%)
Concentric	21 (91.3%)	17 (58.6%)	10 (90.9%)	15 (78.9%)
Non concentric	2 (8.6%)	12 (41.3%)	1 (9%)	4 (21%)
P value	0.049	0.004	0.145	0.611

Table 3: Pattern of response following NAC of the subtypes of breast cancer.

	Triple -ve N (%)	Luminal N (%)	HER2+ N (%)	Hybrid N (%)
Present	15 (65.2%)	24 (82.7%)	9 (81.8%)	12 (63.1%)
Absent	8 (34.7%)	5 (21.7%)	2 (18.1%)	7 (36.8%)
P value	0.192	0.241	0.990	0.733

Table 4: Baseline axillary involvement for different subtypes of breast cancer.

	Triple -ve N (%)	Luminal N (%)	HER2+ N (%)	Hybrid N (%)
Present	9 (39.1%)	1 (3.4%)	3 (27.2%)	4 (21%)
Absent	14 (60.8%)	28 (96.5%)	8 (63.6%)	15 (78.9%)

P value	0.006	0.004	0.758	0.952
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Table 5: Radiological complete response following NAC for the subtypes.

Triple -ve N (%)	Luminal N (%)	HER2+ N (%)	Hybrid N (%)
10.5 (+/-8.1)(0-33)	19.9 (+/-18.5);(3-80)	10.8 (+/-7.3);(3-35)	19.5 (+/-15.2);(0-77)

Table 6: Difference between post NAC MRI size and post -surgical size for subtypes.

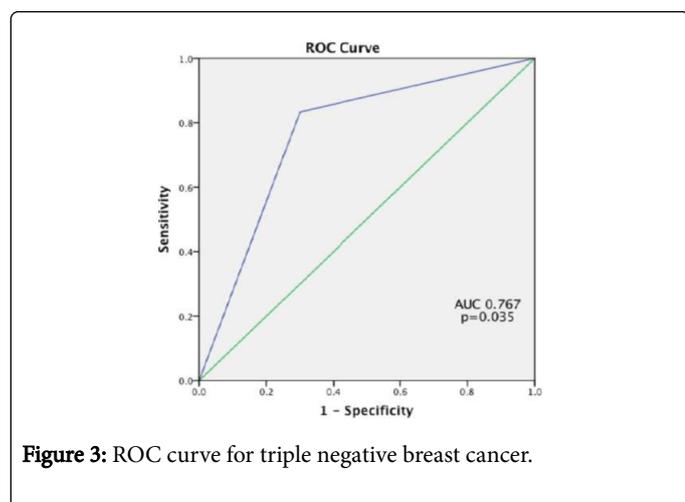


Figure 3: ROC curve for triple negative breast cancer.

Discussion

‘Cancer radiogenomics’ is recently coined term that correlates the imaging features of cancer with molecular/genetic features. This can be helpful in ‘personalised’ diagnosis, treatment and prognosis [14]. This field is rapidly expanding with the use of various imaging modalities like CT, MRI or PET scan. Besides, breast cancer is a heterogeneous group and can be divided into different subgroups by gene expression analysis [15]. Moreover, in routine clinical setting therapeutic plans are formed based on each intrinsic subtype.

There are certain strengths of this study. Whilst in some previous studies diagnostic performance of MRI was reported as true positive, true negative, false positive and false negative, it did not reflect the accuracy of MRI for prediction of post NAC tumour size or the extent of disease for surgical planning [16]. In the present study, the size discrepancy between the post NAC residual MRI tumour size and post-surgical size has been used, similar to Chen et al. [17] allowing better evaluation of extent of disease for surgical planning. Second, all imaging, histopathology and treatment were performed ‘in-house’, following standard protocols with no variation in individual management of subjects. Third, all patients had their second MRI performed after finishing NAC treatment and less than 30 days before surgery. Fourth, our definition of pCR did not include axilla and DCIS. The focus of this study was to evaluate the response of the breast tissue to NAC. Response of axillary nodes to chemotherapy may not correlate with response of breast tissue and this could be the focus for further study. Detection of DCIS by MRI is likely to improve in future and can become a regular indication of post NAC MRI but further studies are needed to assess MRI efficacy in assessing DCIS after NAC [18].

In this study, Triple negative cancers commonly present as a mass on baseline MR and were grade 3, whilst non-mass like enhancement was more common in Luminal cancers. Previous studies [16,7,11] have evaluated imaging characteristics of different subtypes, but few characteristics have been revealed, apart from Triple negative cancers. Dent et al [7] evaluated 1601 women, out of which 180 were triple negative. They demonstrated that triple negative cancers were larger at the time of presentation, involved lymph nodes more frequently and were high-grade tumours. Several studies have demonstrated TN cancers present as unifocal mass on mammography and US 8-10. Uematsu et al [11] was the first to describe MR features of TN cancers. He evaluated 59 TN cancers and demonstrated that they are more likely to be unifocal mass. Absence of non-mass like enhancement correlated with absence/rarity of DCIS with TN cancers [11]. This is similar to the present study, where non-mass like enhancement was associated with Luminal cancers, in keeping with higher incidence of DCIS associated with them. However, difference in the lymph node positivity rate or initial MR size between different subtypes was not observed in the present study.

NAC is increasingly being offered to women with breast cancers, as it offers an opportunity of tumour shrinkage and breast conserving surgery. Previous investigators have demonstrated that the accuracy of MR varies with different subtypes of breast cancer. Loo et al [4] demonstrated residual disease in 93% Luminal cancers compared to 66% TN cancers. In their study, TN cancers had a typical concentric shrinkage pattern following NAC, similar to the present study.

In the present study, pCR was defined as the absence of invasive malignancy in the breast tissues, without consideration of the axillary involvement. Focus of this study was on NAC response of the breast tissue, with respect to different subtypes of breast cancer. Moreover, previous studies have shown that triple negative cancers do not show a linear correlation between tumour size and likelihood of lymph node involvement [19,20]. Some authors even demonstrated a propensity for node negative, but direct systemic progression in the triple negative group [21]. The presence of ductal carcinoma in situ (DCIS) in the surgical specimen for the definition of pCR was not taken into account as there is no evidence that residual in situ carcinoma alone increased the risk of future distant relapse [22].

Whilst the definition of pCR varies in different studies, investigators have shown that accuracy of MRI for predicting pCR varies with different subtypes [5,6,23]. Loo et al. [4] found excellent correlation between residual tumour size on MRI and post treatment surgical size for TN and HER2+ subtypes, but not for Luminal cancers. However, MR was performed during the NAC treatment, but not after the completion of chemotherapy in their study. Luminal cancers’ heterogeneous appearance on MRI and areas of non-mass like

enhancement with low rate of pCR contributed to these findings, similar to the present study. A good response to NAC in HER2+ subgroup was not observed in our study. This may be due to small number of HER+ cancers in our group. Our results are in agreement with a study by De Los Santos [23], who evaluated 475 Luminal cancers, 150 TN cancers and 101 HER2+ cancers. They found highest negative predictive value (the ability to predict pCR) with TN and HER2+ cancers. Hayashi et al [5] evaluated 264 breast cancers and found highest discrepancy between imaging and pathology for Luminal cancers and cautioned when interpreting MR images in Luminal cancers, with underestimation of disease in two-thirds of them. In our study, MR underestimated disease in 17 (58.6%) Luminal cancers. The clinical significance of this underestimation remains to be seen as the radiotherapy following surgery could wipe out the residual cells, even if surgery misses it. Moreover, one may argue that although these cells are present, they could have already lost their ability to grow.

There are a few limitations of this study. Firstly, this is a retrospective single centre study with small number of patients in each subgroup. Despite the small numbers, we thoroughly examined the different subtypes of cancer and indeed our results were consistent with other reports in literature. Another potential limitation is that we did not calculate the tumour volume on MRI. Hylton et al [24] used tumour volume of residual tumour on MR in ISPY-1 and found it was significantly more accurate. However, tumour volume is still not used widely as a parameter of response monitoring in breast cancer patients due to lack of large multi-centre studies to validate its superiority. Lastly, HER2+ group had small number of patients, which may not be representative of the entire population.

Conclusion

In conclusion, the molecular classification of breast cancers is clinically relevant and supports treatment choices. This study demonstrates that MRI is more accurate in predicting the size of residual cancer in Triple negative cancers as compared to Luminal cancers, where there is high incidence of underestimation of residual disease. Refining our understanding of the different subtypes of cancers will lead to more personalised management and lesser rates of re-excisions.

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