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Serial MRI scans help in assessing early response to neoadjuvant chemotherapy and tailoring breast cancer treatment

Introduction:

Breast cancer is the commonest cancer in women in the United Kingdom with 49,564 women diagnosed in 2010 [1]. The use of neoadjuvant chemotherapy (NAC) in breast cancer is becoming increasingly prevalent aiming to achieve tumour down-staging to facilitate breast-conserving surgery in patients who would otherwise have been candidates for mastectomy. There is convincing evidence that NAC results in similar overall survival rates to adjuvant chemotherapy [2-8]. Furthermore, NAC provides opportunities to assess in-vivo chemosensitivity by monitoring tumour response. Patients who achieve complete pathological response (pCR) have improved prognostic outcomes including both overall and disease-free survival [9]. The purpose of changing NAC when limited early response is observed is to improve tumour response using a second-line NAC. A meta-analysis of the association of breast cancer subtypes and pCR rates reports the odds of pCR to be significantly higher in hormone receptor negative/ HER2 positive (HR-/HER2+) tumours (38.9%) compared to triple negative tumours (31.1%). Furthermore, lower pCR rates were seen in the HER2+/HR+ (18.7%) and HER2-/HR+ (8.3%) tumours [10].

Dynamic contrast enhanced MRI (DCE-MRI) can detect changes in tumour microcirculation and uptake of contrast material as a result of increased permeability of new vessels formed in growing tumours. This allows an assessment of the pathophysiological response to NAC. MRI response evaluation is usually based on the change in tumour diameter, volume and/or tumour enhancement.

Clinical examination in combination with conventional imaging, such as mammography and ultrasound, were the gold standard method in monitoring response to NAC until MRI was proven to be significantly more accurate in predicting tumour response and its correlation with final pathology [11-14]. MRI is also more accurate in detecting lobular, multifocal and multicentric tumours. Beyond its diagnostic role, MRI is used to evaluate response to NAC at different stages of treatment and in the assessment of residual tumour extent at completion of NAC to allow for appropriate surgical planning [15, 16]. A meta-analysis by Marinovich et al. concluded good overall accuracy for MRI imaging post NAC. However, their summary accuracy estimates for MRI and USS showed no statistical difference in sensitivity rates in ten studies, but in 4 studies specificity rates were in favour of MRI. Given their subgroup analysis was based on fewer studies that directly compared MRI to USS the power in detecting differences in test accuracy is reduced [17].

The primary objective of this study was to evaluate the utility of MRI in assessing tumour response and correlation of the last imaging with final pathology in different tumour subtypes and its role in inflammatory tumours. A secondary objective was to assess whether serial MRI led to change of NAC regime and if this resulted in improved tumour response.

Materials and Methods:

Study design & data collection

This is a retrospective analysis of our standard practice at a large UK breast unit using electronic patient records over 5 years (2005-2009). Our inclusion criteria included all patients with operable invasive breast cancer who had an MRI scan at the start of treatment (baseline) and at least one subsequent MRI scan, including patients with inflammatory breast cancer. Most patients received anthracycline and cyclophosphamide chemotherapy (EC or FEC) unless they were part of the NEOTANGO trial (n=8) where some patients were started with taxane-based chemotherapy.

In our institution, MRI is used to assess both disease (unifocal or diffuse disease - multifocal/multicentric) and response patterns. Response to treatment was monitored using serial DCE-MRI scans: pre-treatment (baseline), after 2 and/or 4 cycles of treatment. Final MRI scan was performed towards the end of NAC as an aid to decision making regarding surgical options, but this was not done routinely following completion of NAC. NEOTANGO trial patients had their second imaging after completion of 4 cycles of NAC. Taxane-based chemotherapy was substituted for anthracycline and cyclophosphamide(AC) if MRI response was considered inadequate after 2 cycles of NAC. Tumours were defined as having drug resistant disease if they had inadequate response to AC and then progressed on taxane (T). Responding tumours received up to 6 cycles of AC and those switching received between 4 and 6 cycles of taxane in addition to the 2 cycles of AC. NEOTANGO trial patients were started on either 4 cycles of AC or T followed by 4 cycles of T or AC, subsequently. [18] Tumours showing response on MRI following 2 AC cycles were labelled 'early responders' whereas tumours showing response following switching chemotherapy to taxane were labelled 'late responders'. All responding patients planned for breast conservation had a radio-opaque marker clip inserted in the tumour to facilitate surgical excision.

Her-2 positive tumours had their treatment switched from AC to T following 4 cycles, even if responsive to treatment, to include Trastuzumab that is proven to increase rates of pCR.[19] This switch in regimen was performed earlier for tumours non-responsive to two cycles of AC. In tumours with small tissue on core biopsy to assess for HR(n=3) or HER2(n=6) receptors, decision for planning chemotherapy was based on alternative factors including patient age, tumour size and lymph node status.

Imaging data:

MRI tumour size, extent, and tumour response to treatment were recorded. Response to NAC was measured using the Leeds response evaluation criteria in solid tumours (modified-RECIST). Tumours showing minimal, no response or disease progression on MRI were considered to have inadequate response and the recommendation was to switch treatment. Size measurements included maximal tumour diameter for focal tumours and summed maximal diameters for multifocal tumours.

Modified RECIST criteria

Almost complete response(ACR) Disappearance of all lesions

PR 50% reduction in diameter of the main tumour mass or 25%-50% reduction in main tumour size and improved enhancement curve

Minimal response 25-50% reduction in tumour size with no improvement in enhancement curve

No response No change

Progression New disease or 25% increase in tumour size

Pathological response:

pCR was defined as the absence of residual invasive carcinoma in the breast with or without the presence of in-situ carcinoma in the surgical specimen as previously described [20-22]

PR: residual tumour with histological evidence of tumour regression

No response: No evidence of regression

Statistics:

Data analysis was performed using IBM SPSS statistics version 22. Chi-squared(χ^2) test was calculated to determine the association between final MRI and pathology. Sensitivity and specificity tests were calculated, and Kappa analysis was calculated to measure the agreement between final MRI and pathological response. Predictive factors for response were tested for statistical significance by univariate and multivariate analysis using the Cox proportional hazards regression model. P value of ≤ 0.05 was considered statistically significant.

Results:

Patient characteristics

162 breast cancer patients with 166 tumours were treated with NAC. Median age was 47 years (IQR 41–54) (Table 1). On clinical presentation, 18.7% of the breast tumours were inflammatory and 31.3% were triple negative. 44.6% tumours were T2 on baseline MRI and 50% were T3 compared to 36% and 21% following NAC. pCR was reported in 22.3% of tumours on histopathology. 8 patients received NAC as part of the NEOTANGO trial.

Tumour subtypes:

MRI was assessed against tumour subtypes: HR-/HER2+ (n=13), HR-/HER2- (n=53), HR+/HER2+ (n=29) and HR+/HER2- (n=63). In addition, we evaluated MRI's role in inflammatory tumours (n=31) and compared them to non-inflammatory tumours to assess whether they behave differently.

Imaging data:

MRI was performed on all patients in the cohort (162 patients with 166 tumours). Contralateral invasive BC was incidentally diagnosed in 4 patients. Disease pattern and extent on baseline MRI were available for all 166 tumours. In 3 cases baseline MRI was performed in other centres but the disease pattern was accepted as described and was consistent with the pattern mentioned in subsequent scans. In total, patients had 2(n=22), 3(n=101), 4(n=40), 5(n=2) or 6(n=1) MRI scans. Tumour size was available for all tumours on baseline MRI with a mean size of 52 cm (range 8-120cm). Final MRI was available for 147 tumours with mean size of 31.4cm (range 0-120cm) with an average percentage reduction in tumour size of 45.3%(range 0-100%). On analysing tumour subtypes, the highest percentage reduction in tumour size was observed in HR-/HER2+ tumours (71.9%) followed by HR+/HER2+ tumours (47%). Comparable percentage reduction was seen between HR-/HER2- (40.9%) and HR+/HER2- (42.2%) tumours.

MRI accuracy:

To investigate the accuracy of MRI in predicting pathological response to NAC (table 2) final MRI response was assessed against tumour response on final pathology. Final MRI scan(n=144) was performed towards the end of NAC but not always after completion of treatment, as this was not deemed necessary for surgical decision making. The remaining tumours(n=22) had a single MRI scan after 2 cycles; one patient opted for surgery instead of switching NAC and another refused a final scan.

Significant correlation was seen between final MRI and pathology with complete agreements observed in 85 tumours (59%): the majority of agreements were observed for PR (80%, Chi Square test showing a significant relationship $X^2 = 12.1$, $p < 0.001$). In a small group of tumours there was a trend for final MRI to underestimate (9.7%) or overestimate (9%) response compared to final pathology. 14 tumours were reported to show PR on final MRI but had pCR on final pathology and 13 tumours had minimal or PR on final MRI but no pathological evidence of response to treatment. There were two cases showing progressive disease on final MRI from initial PR on previous imaging, these were found to have minimal response on pathology. pCR (n=29) was correctly diagnosed on final MRI in 15 (40.5%) cases. Pathological response was predicted with

93.1% sensitivity and 30.8% specificity using MRI. Weighed Kappa analysis shows fair agreement ($K = 0.31$, 95% CI 0.17-0.44). On analysing the correlation in different tumour subtypes and tumour grades (table 2), significant agreement was observed between final MRI response and pathology in all subgroups except for HR-/HER2+ tumours. MRI was more accurate in the triple negative, HR+/HER2+ and high-grade tumours than in HR+/HER2- and low-grade tumours. No difference was seen in MRI performance on comparing inflammatory to non-inflammatory tumours.

Early responders vs. late responders on MRI:

Tumour response was categorised into Responders (partial or complete) or Non-Responders (minimal or none). We examined pCR rates in all tumours (n=166) after 2 cycles of chemotherapy (Early responders) and after 2 further cycles (late responders) of chemotherapy (table 3). 86 (51.8%) tumours showed early response; 30 (34.9%) of the early responders showed pCR on post-surgical specimens compared to 7 (13.2%) of the late responders (n=53) following change in chemotherapy. Of the patients without early response (n=80), 53 (66.3%) showed late response on MRI. Most of these patients (except for 5) had their treatment switched as suggested by imaging. On analysing response per tumour subtype, highest rates of response on second MRI were seen in triple negative tumours (62.3%), with more than half achieving pCR, followed by HR+/HER2+ (58.6%) and HR+/HER2- (46%) tumours. In the HR-/HER2+ group, 38.4% showed early MRI response, whereas 53% showed late MRI response with 71.4% achieving pCR. In inflammatory tumours (n=31), 40% of the early responders achieved pCR and 60% achieved PR to first-line chemotherapy. Majority of the tumours that showed no response to first-line NAC responded to second-line NAC achieving pCR rates of 25% and 75% of PR.

pCR rates in different tumour subtypes:

Higher pCR rates were seen amongst HR-/HER2+ (46.2%) tumours followed by triple negative tumours (35.8%). Lower pCR rates were seen in the HR+/HER2+ (24.1%) and HR+/HER2- (7.9%) tumours. pCR rates in inflammatory tumours were as high as 40.9%. Sensitivity analysis showed that ER negative, PR negative, high-grade tumours and early responders to be best predictors of pCR. Logistic regression using all four highly sensitive variables confirmed early response to be a significant predictor of pCR (OR=5.65, $\beta=1.732$, SE=0.486, $p<0.001$) (Table 4).

Role of MRI in tailoring NAC:

For this assessment we excluded the NEOTANGO trial patients as their treatment was pre-planned. We included tumours that showed minimal response on second MRI scan (n=72) following 2 NAC cycles and divided them into two groups: inflammatory (n=16) and non-inflammatory (n=56) groups (Figure 1). For the majority of tumours in both groups treatment was switched after 2 NAC cycles (81.3% and 87.5%, respectively). In the inflammatory group, majority of the tumours 10/13 (76.9%) responded to change in treatment and showed PR (n=9) and ACR (n=1) on final MRI scan. Only 2/13 (15.4%) tumours continued to show minimal response despite switching treatment with 1 showing disease progression. In the non-inflammatory group, response was seen in 37/49 (75.5%) tumours; PR (n=34) and ACR (n=3). 10/49 (20.4%) continued to show minimal response and 1 (2%) showed disease progression. Final MRI was not repeated in

1 case (2%) that showed PR final pathology. In total 10 tumours with inadequate initial MRI response did not undergo switching of NAC regime, 3 inflammatory and 7 non-inflammatory tumours. One patient underwent surgery before completion of NAC, and the remaining 9 patients continued with AC chemotherapy, as tailoring of treatment was not routinely practised in the initial study period.

We also looked at the surgical procedure performed on tumours that achieved PR or ACR on final MRI. In the non-inflammatory group, 6/34 (17.6%) tumours achieved sufficient down staging to facilitate breast conservation surgery. Whereas the remaining 28 (82.4%) tumours underwent a mastectomy for different reasons - 4 were multifocal, 12 had extensive calcifications, 7 for residual size and/or location, and in 5 patient's choice. In the inflammatory group, all 10 tumours showing either PR or ACR on final imaging underwent a mastectomy.

DISCUSSION:

Our retrospective study of NAC over a 5-year period showed that MRI had sensitivity rate of over 90% in predicting response to NAC. Early identification of non-responders on MRI resulted in early tailoring of NAC, with improved rates of tumour response seen in 74.2% following switching NAC.

Literature suggests that patients achieving pCR after NAC have improved survival outcomes [9]. In our study serial MRI correctly predicted pCR in nearly 52% (15 of 29) of all tumours; higher pCR rates seen amongst hormone negative (46.2%) and triple negative tumours (35.8%) as well as inflammatory tumours (40.9%). Chen et al reported rates up to 74% (26 of 35) of MRI correctly predicting pCR [23], their higher rates is likely related to having their last MRI scan following completion of treatment. It was not part of our practice to perform an end of treatment scan routinely, we prioritised early scans and change of treatment scans to assess the need to tailor NAC and to help surgical decision-making. Recently we have introduced an end of treatment scan as standard of care for our patients.

We found that MRI correlates significantly with pathological response and can be used as a clinical predictor to monitor response and guide treatment. Higher rates of correlation were seen in tumours showing PR and ACR. Final MRI, although not performed routinely following completion of treatment, has high sensitivity rates (93.1%) with fair agreement to post-surgical pathology in predicting response (K=0.31). Subgroup analysis shows more agreement with HR-/HER2-, HR+/HER2+ than HR+/HER2- groups, and poor agreement in HR-/HER2+. Conversely, low specificity rates (30.8%) suggest that MRI is prone to overestimating tumour response where minimal or no pathological response is observed. We suspect that tumours showing improved response on final pathology (n=21) are likely related to receiving further NAC following their last MRI scan. On the other hand, response was overestimated on final MRI (n=7) suggesting PR to treatment where no response was seen on final pathology.

We found serial MRI a useful tool to identify non-responding tumours early and aid in tailoring of NAC. Improved tumour response was observed in majority of the tumours showing PR to switching treatment and

a small percentage showing pCR to second-line treatment. The greatest relative benefit in assessing tumour response was observed in detecting early responders on second MRI scan after 2 NAC cycles, which was shown to be the most sensitive predictor of pCR. Higher rates of pCR were seen in early responders on MRI compared to late responders (34.9% vs. 13.2%). These results were comparable to the GEPARTRIO trial where early responders and non-responders (after 2 NAC cycles) were reported to have pCR rates of 32.1% and 5.3% respectively. In addition, early identification of non-responders resulted in switching NAC and increased the chances of achieving pCR amongst the late responders compared to non-responders to both treatments (13.2% vs. 0%) [24]. The GEPARTRIO phase-III study showed improved DFS in non-responders that showed improved response after switching treatment [27].

Early identification of resistant cases to first-line treatment and switching NAC increased the chances of tumour response. The benefit of detecting non-responders soon after starting NAC questions whether MRI could be performed even earlier than after 2 cycles as this may help to identify non-responders sooner. It would help reduce the risks associated with non-beneficial NAC and potentially improve tumour response by using an alternative NAC regime. Early imaging has been advocated following a recently published trial (ACRIN 6657/I-SPY TRIAL), their second MRI scan was performed after one NAC cycle, a third scan between AC and taxane-based NAC if taxane was given, and a final scan after completion of NAC. The greatest relative benefit was associated with tumour volume change at the second MRI scan, which was reported to be the strongest predictor of pCR [28]. We do not routinely measure tumour volume on MRI, which can be considered a limitation, but more rely on the percentage change in whole tumour size and changes in enhancement curves for response assessments. Other limitations include our study's retrospective nature and limited data size that could not be controlled for many factors. Therefore our results cannot be compared accurately with prospective or randomized trial results. Having said that, our results reflect our standard clinical practice. We elected to include inflammatory tumours in this study, although the scope of NAC in these tumours is different, as a true reflection of our patient cohort.

We conclude that serial MRI imaging is a useful predictive tool in assessing early response to chemotherapy. It facilitates tailoring of the NAC regimen that will improve response to treatment in a proportion of patients. This allows us to offer breast conservation to a greater proportion of women. Whether or not early tailoring of NAC determined by serial MRI as opposed to other criteria of response leads to better outcomes would be better addressed through a randomized clinical trial.

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