MRI assessment of response to treatment in NAC

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Neoadjuvant chemotherapy (NAC) is offered to women with large, locally invasive breast tumours with an aim to downstage the tumour and enable breast conserving surgery. Traditionally it has been given to women with locally advanced disease, but increasingly now it is being offered to women with much smaller cancers and lower stage disease (IIb or IIa) to facilitate the best cosmetic surgical outcome. This is following publication of important data sets such as the NSABP B-18 trial which showed that NAC could be offered primarily as an alternative to adjuvant chemotherapy without an adverse effect on survival.1 A standard NAC regimen routinely involves eight cycles of treatment: Four cycles of anthracycline-based epirubicin (90mg/m²) and cyclophosphamide (600mg/m²) for 12 weeks followed by four cycles of a taxane-based therapy with paclitaxel (175mg/m²) for eight weeks (total 20 weeks). Variation in therapy regimens offered exists but the vast majority of patients will achieve some response.2,3 A subset of patients will also go on to achieve a pathological complete response (pCR) at final surgery4 with pCR rates being highest in triple negative breast cancers and HER2 subtypes.5,6 Achieving pCR is highly desirable as it is associated with improved overall and improved disease free survival.7,8

Traditionally mammography and ultrasound have been used to monitor response to NAC. However, limitations with these techniques in assessing response have fuelled the argument for MRI scanning. Breast cancers can vary significantly in the way they respond to chemotherapy which significantly in the way they respond to chemotherapy which makes accurate assessment of response on standard techniques difficult. Some cancers reduce circumferentially while others fragment and cluster forming multiple smaller foci within the breast. High breast density also has a masking effect on mammography and malignant microcalcifications, if present, representing ductal carcinoma in situ (DCIS) do not regress in response to chemotherapy.9 This makes assessment of the true extent of disease on mammography and ultrasound difficult if there is an extensive intraductal component and poses challenges for appropriate surgical management of the patient. In cases of extensive DCIS when mastectomy is recommended, MRI is of no value.

MRI consistently gives better agreement with pathological size at surgery following the completion of NAC.9,10 A recent meta-analysis on 19 studies showed that following NAC, MRI marginally overestimated pathological size by a pooled mean difference of 0.1cm (95% confidence intervals (CI): -0.2cm, 0.3cm) but this was comparable to ultrasound which also overestimated size by 0.1cm (95% CI: -0.1cm, 0.4cm). Mammography overestimated pathological size by a pooled mean difference of 0.4cm (95% CI: -0.4cm to 0.3cm) and clinical examination underestimated pathological size by a pooled mean difference of -0.3cm (95% CI: 0.7cm, 0.0cm).10 Figure 1 illustrates a case where MRI was used to assess response. The controversy between the utility of MRI versus ultrasound in assessing response persists. While MRI is more accurate than mammography, more studies comparing ultrasound and MRI are needed. In a recent meta-analysis comparing the accuracy of residual disease in these two groups there was no statistical difference.13 These ambiguous published results reflect practice nationwide in the UK. While MRI may be more frequently used to assess response in North America and Europe, constraints on time and cost in the UK mean that we have a far more varied practice. A poll at the British Society of Breast Radiologists meeting in November 2014 suggested that approximately one third of radiologists were evaluating response using MRI alone, a third were using ultrasound alone and a third were using both. While MRI may be appropriate in selected cases where the true extent of disease cannot be determined by standard evaluation, and while it may be the preferred method of assessment for many breast radiologists, it is undoubtedly a poor use of resources to be using both MRI and ultrasound to assess response.

There are several time points during a course of NAC when MRI scans can be performed to evaluate response. Baseline scans inform on the extent of disease and can identify additional sites of disease that can alter surgical options. The main utility of a final scan following therapy is to guide the subsequent surgery, but an isolated scan at the end of treatment without a baseline to compare to is of limited value. There can also be issues with over- and under-estimation of residual disease on final MRI studies that one should be aware of when reporting and making management decisions regarding breast conserving surgery in multi-disciplinary meetings. Underestimation of residual disease is reported in the literature up to 30%14 and is particularly seen in women who are taking taxane chemotherapeutic agents which have a significant anti-vascular and anti-angiogenic effect; the consequence being that the damaged vascularature does not always deliver intravascular contrast to viable tumour cells. Conversely, overestimation of residual disease is reported up to 20% and can guide the MDT towards more extensive surgery than may be needed.15,17 Figure 2 is an example where MRI has underestimated residual disease.

In predicting pCR on a final scan following NAC there is marked variation in reported sensitivity and specificity.16,17 While this is likely due in part to the under- and over-estimation of residual disease on scans, it is also likely due to heterogeneous patterns of response across a range of breast tumour subtypes. Taking this into account, more recent studies have shown that MRI is more accurate when evaluating response in triple negative breast cancers.18,19 HER2 positive cancers and high grade tumours14,15 but less accurate in luminal subtype breast cancers and low grade tumours.20 Identification of response at an early time point (one or two cycles) after commencing NAC is probable the most valuable aspect of NAC monitoring as it enables subsequent management to be planned appropriately and alternative loco-regional or systemic therapies to be pursued if the preliminary treatment is ineffective. In poor responders particularly, continued ineffective therapy may be determen-
tal and adversely affect disease-free survival, decrease the patient’s quality of life due to the toxic side effects of NAC and increase costs to the healthcare system. Being able to predict a patient’s eventual response at an early time point would be highly advantageous as it would enable a subset of patients to be defined who would be more likely to undergo successful breast conserving surgery or a subset of patients with a better prognosis who would not benefit from additional systemic chemotherapy. Results from the multicentre I-SPY trial (Investigation of serial studies to predict your therapeutic response with imaging and molecular analysis) in the United States found that MRI findings were a stronger predictor of pCR than clinical assessment, with the greatest advantage observed with the use of volumetric measurement of response early in treatment.20

Finally, functional MRI techniques such as diffusion-weighted (DW)-MR offer the potential for providing more than just a tumour measurement as they provide an indirect assessment of tumour functionality. DW-MR imaging probably holds the most potential for incorporation into routine clinical practice as it is a quick, simple and non-contrast sequence that can be included into a clinical breast MRI protocol. Specifically, the apparent diffusion coefficient (ADC) value from DW-MR has been shown to indicate a response to NAC at an early time point prior to any change in tumour size22 and when combined with standard sequences could improve our assessment of response.23

References

Figure 1
Ultrasound and dynamic contrast enhanced (DCE)-MR images from a 24-year-old woman with a triple negative grade 3 invasive ductal carcinoma (IDC) of her left breast. Ultrasound prior to neoadjuvant chemotherapy (NAC) (A) showed that the tumour measured 32mm and a Hydromark was placed within it (B). The tumour was not well seen on mammography (C) and because of this and her young age, MRI was used to assess response. Prior to NAC the early axial subtracted DCE-MR (D) showed the invasive cancer to be unifocal and measure 30mm with the Hydromark visible within. Following NAC the tumour had reduced in size to 20mm on the early subtracted DCE-MRI (E). Surgical histology confirmed a triple negative grade 2 IDC measuring 19mm indicating that in this case MRI was accurate in assessing residual disease.

Figure 2
Ultrasound and DCE-MR images from a 41-year-old woman with a grade 2 invasive lobular carcinoma (ILC) of her right breast. Ultrasound prior to NAC (A) indicated that the tumour measured 40mm. Early subtracted axial DCR-MR (B) and a maximum intensity projection (MIP) image (C) showed that the disease extended over 80mm with satellite foci of ILC subsequently confirmed on core biopsy. Following NAC, ultrasound (D) showed the tumour to have reduced in size to 25mm. Early subtracted axial DCR-MR (E) and a MIP image (F) suggested a very good response to therapy with some persistent distortion but a minimal residual enhancement measuring 12mm. Surgical histology confirmed a grade 2 ILC with classic type lobular carcinoma in situ and fibrosis suggesting a partial response. However the invasive tumour was present over 65mm indicating that both MRI and ultrasound had underestimated the amount of residual disease. An abnormal lymph node (visible on the MRI studies C and F) was positive on cytology prior to NAC and also positive for metastasis at sentinel lymph node biopsy.