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FULL PAPER

Diagnostic accuracy of magnetic resonance imaging to evaluate axillary lymph node status in breast cancer patients receiving neoadjuvant chemotherapy

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Objectives: Axillary lymph node status is an important prognostic factor for breast cancer patients. This study aimed to assess the accuracy of MRI in assessing the axillary nodal status in breast cancer patients receiving neo-adjuvant chemotherapy (NACT).
Methods: Data were retrospectively collected for 88 patients between 2011 and 2016 from the hospital records. All patients had baseline MRI, followed by the end of neoadjuvant chemotherapy MRI. Patient demographics, cancer type, grade, stage, receptor status, and the number of positive lymph nodes identified on the baseline and preoperative MRI were recorded. The imaging results were compared to post-operative histopathological lymph node findings. The median patient age of the patients was 54 years (32–77 years)
Results: There were 67 (76.1%) patients with histologically proven positive axillary lymph nodes on baseline MRI. The overall conversion from abnormal to normal axillary nodes following chemotherapy (ypN0) was 38.8% (26 patients out of 67). The sensitivity and specificity of MRI for predicting axillary status was 68.85 and 85.71%, respectively, with an overall MRI diagnostic accuracy of 73.07%.
Conclusion: MRI has low sensitivity and diagnostic accuracy in predicting axillary nodal status in breast cancer patients receiving neoadjuvant chemotherapy. Given the low NPV of MRI of the axilla, a negative MRI does not obviate the need for definitive axillary surgery.
Advances in knowledge: In its current state, MRI cannot obviate the need for axillary surgery in patients receiving NACT. Long: short axis ratio (L: S) of the axillary lymph node is not a good predictor of axillary metastases.

INTRODUCTION

Axillary nodal status (LN) is one of the most important factors for predicting prognosis and management in breast cancer patients.[1] Accurate preoperative assessment of the axillary status with imaging is particularly crucial in patients who receive neoadjuvant chemotherapy (NACT) before surgery. Patients in which clinically abnormal axillary lymph nodes (cN+) convert to normal following NACT (yrN0) are a vital subgroup in which management/surgical decisions may be influenced by post-NACT imaging of the axilla. There has been a recent trend towards a limited ‘three to four node’ sentinel lymph node sampling in such patients.[2–4] However, both sentinel lymph node biopsy (SLNB) and axillary dissection are invasive procedures, adversely affecting the quality of life.[5,6]

Predicting axillary LN status after NACT may be challenging. Whilst axillary US is the most widely accessible imaging technique for restaging after NACT,[7–11] there is still controversy regarding the best imaging technique to restage the axilla following NACT.[12–15] MRI has benefits over ultrasound of potential operator independence, making the evaluation of deep and higher axilla more feasible. Management of the breast is often independent of axillary management following NACT. Whilst there is plenty of literature for imaging evaluation of breast response to NACT, there is scant literature evaluating MRI accuracy in predicting axillary status[16,17] This study aimed to assess the diagnostic accuracy of MRI to evaluate LN status in breast cancer patients receiving NACT before surgery by correlating with pathology (gold standard). The purpose of this study was also to evaluate MRI imaging criteria for LN morphology to determine axillary staging.

The results of this study would allow meaningful discussion between radiologists, surgeons and oncologists to guide further therapeutic decision-making.

METHODS

Patients

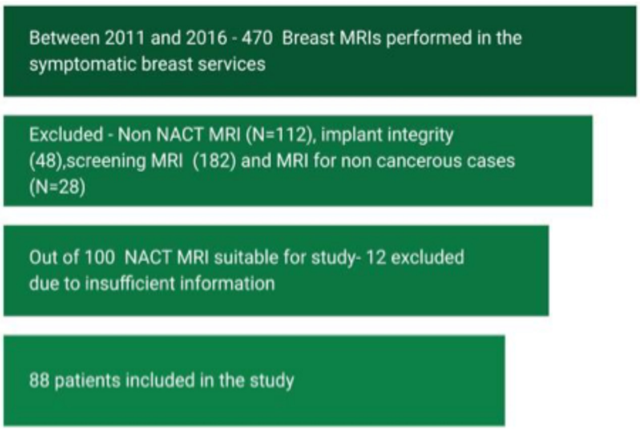
The study design involves retrospective data collection from the university hospital database between January 2011 and December 2016. This study was registered as the institute's student selection component (SSC) project and service evaluation project. Good clinical practice guidelines were followed. Local ethics committee approval or informed consent was waived as per local guidelines.

Between 2011 and 2016, approximately 1500 patients were treated for breast cancer at the institute.[18] Whilst there were no definite institutional guidelines for selecting patients for NACT, this decision was made at the Breast multidisciplinary team meeting (MDTM), based on the type of cancer, clinical T and N stage and patient preferences. The departmental policy was to perform MRIs on all patients who received NACT. The standard protocol involves a baseline MRI before the start of NACT and an MRI at the 'end of chemotherapy', with some patients receiving a mid-chemotherapy MRI.

Data were collected from the hospital radiology MRI PACS (Picture archiving and communication system) database. There was a total pool of 470 breast MRIs (all indications) performed in the centre between 2011 and 2016. After excluding routine surveillance MRIs (N = 182), MRI for checking implant integrity (48), non-cancerous cases (28) and non-NACT cases (112), there were 100 NACT breast cancer cases. Inclusion criteria for the study included all breast cancer patients receiving NACT and undergoing pre-operative MRI with adequate 'in-house' data. This included essential clinical information, preoperative mammogram or ultrasound, and availability of preoperative and postoperative histopathological results. 12 patients were excluded due to lack of enough information. Following these exclusions, 88 patients were considered appropriate for the evaluation. An overview of patient selection flow chart is displayed in Figure 1.

In most patients, NAC was a Taxane-based regimen with additional treatment with Trastuzumab for patients with Human epidermal growth factor receptor (HER2) positive breast cancer.

Figure 1. An overview of inclusion and excluded patients are displayed.



MRI

MRI was performed on a 1.5T magnet (GE HDxt 1.5 T, GE Healthcare, Tokyo, Japan) using an eight-channel phased-array breast coil. Imaging was performed with a patient lying in a prone position. 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 gadopentetate dimeglumine (0.1 mmol/kg body weight). Fat-suppressed subtracted images were obtained approximately every minute for 8 min in the axial plane. T1 pre-contrast non-fat suppressed sequences were used to assess axillary lymph nodes. The images were initially reviewed by GKW, a medical student. MRIs were secondarily reviewed by an experienced consultant breast radiologist (GJB), reporting>120 Breast MRIs per year and more than ten years of experience. Both readers were blinded to the histopathological results when evaluating MRI images. Any disagreement in imaging findings (n = 4) was discussed and final result agreed by consensus.

The following criteria were used to assess the axillary lymph nodes on MRI[16] (Figure 2):

- Cortical thickness
- Long: Short (L: S) axis ratio
- Presence or absence of fatty hilum

A node was designated as imaging normal (yrN0) for the study if all of the following MRI criteria were met, namely, cortical thickness<2 mm, L: S ratio>2 and a central fatty hilum. This study considered any deviation from these imaging criteria an imaging abnormal (yrN+) node. 'End of chemotherapy' MRI was used for all axillary nodal measurements, with baseline MRI used as a reference. The total number of abnormal nodes was counted, and the most abnormal node (based on the combination of the three criteria above) was used for MRI measurements.

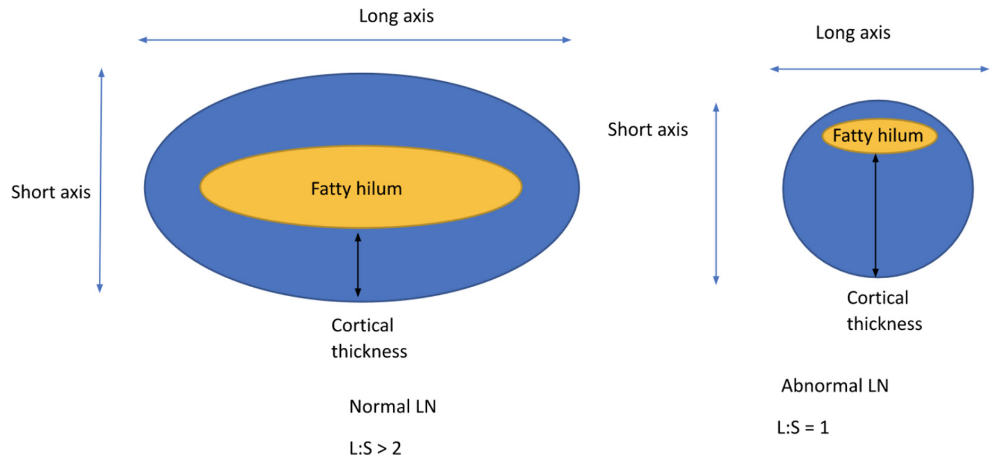
Routine management pathway of the axilla

All patients in the study cohort had an axillary ultrasound and baseline MRI at breast cancer diagnosis. All 'imaging abnormal' axillary nodes were histologically proven by core biopsy with ultrasound (US) guidance to prove involvement at the time of diagnosis. Post biopsy marker placement within the node was not routinely performed but was deployed in some patients. As per departmental policy, nodes that stayed abnormal (yrN+) on post-chemotherapy MRI proceeded straight to axillary nodal clearance (ANC). In patients showing complete imaging response within the axilla (yrN0), surgeons performed a limited sentinel lymph node sampling (a minimum of three to four nodes were harvested) following discussion at MDTM. If no metastasis was found on SNLB, then no further ANC was performed. Breast management comprised mastectomy or breast-conserving surgery depending on the response of the tumour.

Histopathology

All patients had either Sentinel lymph node biopsy (SLNB) or axillary node clearance (ANC) as the reference histological standard. The final pathological nodal stage (ypN) was determined based on histopathological results of surgical specimens. The

Figure 2. Pictorial depiction of normal (left) and abnormal (right) morphology of an axillary lymph node.



total number of abnormal nodes found in SLNB and ANC was used as the postoperative result. pN1 was defined as 1–3 axillary nodes, pN2 as 4–9 nodes and pN3 as >9 axillary lymph nodes, according to American Joint Committee on Cancer (AJCC) recommendations.[18] This study considered nodes with macrometastases (>2 mm deposit) abnormal. Axillary nodes with micrometastases (<2 mm deposit) and isolated tumour cells (ITC < 0.2 mm) were considered normal (ypN0) for this study.[18]

Data evaluation

The following variables were recorded for all patients, including clinical T and N stage (cTN) at the time of diagnosis, age at diagnosis, histological type and grade of cancer, receptor status, ultrasound findings, the conversion rate of axillary lymph nodes following chemotherapy and MRI imaging parameters of nodes. Post-treatment pathologic TN (ypTN) result was recorded. The total number of abnormal nodes after surgery was recorded. 'y' indicated the patient has received NACT with ypN0 meaning complete absence of metastasis after surgery. MRI sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio (LR) and diagnostic accuracy were calculated for predicting axillary metastases. 95% confidence intervals (95% CI) were calculated to test for significance. All patients were followed for a maximum of 10 years and a minimum of 5 years.

RESULTS

The median age of the patients was 54 years, ranging from 32 to 77 years. The most common breast cancer type was invasive ductal cancer and Grade 3 at 71.6%(n = 63) and 62.5%(n = 55), respectively. The most common T and N stages at baseline were T2 and N1 at 45.5%.

There were 67 (76.1%) patients with positive axillary lymph nodes on baseline MRI. The overall pCR (abnormal to normal axillary nodes) rate of axillary nodes following chemotherapy was 38.8% (26 patients out of 67). Table 1 summarises basic patient demographics and tumour characteristics.

On the left arm of the flow chart (Figure 3), 21 (23.9%) patients had normal LN at the baseline and end of NACT MRI, of which 19 stayed normal following SNLB. Two of these 21 had positive nodes on SNLB (ypN+), leading to ANC. On the right side-of the flowchart, of the 39 patients with negative nodes on post-NACT MRI (yrN0), 17 (43.5%) were found to be positive (ypN+) following SNLB and proceeded to ANC. Of 28 patients, who were positive on post-NACT MRI (yrN+), four were found to be negative (ypN0) following ANC.

There was a significantly strong correlation between the number of abnormal lymph nodes on preoperative MRI and postoperative histopathological results with a Pearson correlation coefficient of 0.433(p = 0.001).

Table 2 demonstrates the sensitivity and specificity profile of MRI for the end of the NACT. There were four patients with micrometastases (<2 mm deposit) and one patient with ITC, which were treated as normal lymph nodes (ypN0) for this study. The numbers demonstrate a low sensitivity (68.85%) and negative-predictive value (47.84%) for MRI for predicting axillary status in post-NACT breast cancer cases. The overall diagnostic accuracy of post-NACT MRI for axillary nodal status was 73.07%.

Table 3 depicts the MRI axillary nodal morphology difference across the two groups (pathologically normal and abnormal). Fatty hilum and cortical thickness differed significantly between normal and abnormal nodes across the two groups, p = 0.004 and <0.001, respectively). The mean cortical thickness of normal lymph nodes was 2.20 mm compared to 4.40 mm in abnormal lymph nodes. However, there was no significant difference in the MRI long-to-short axis ratio (L: S) of the axillary nodes in the pathologically proven normal and abnormal nodes (p = 0.388). The mean long to short axis ratio was 2.11 in normal lymph nodes and 1.71 in abnormal lymph nodes, suggesting a rounder appearance of pathological abnormal nodes, but this was not statistically significant (p = 0.388).

All patients were followed up for a minimum of 5 years and a maximum of 10 years. There was a metastases rate of 36.3% in this cohort of patients with most (80%) metastases occurring at less than 5 years. Of all patients who later developed metastases, 27 (84.3%) had the residual nodal disease at the end of NACT.

Table 1. Summarises basic patient demographics and tumour characteristics

Patient and tumour characteristics		
Variable		(n = 88) N (%)
Age	Median ± SD	54.0 ± 11.610
	Min - Max	32–77
Tumour Type	Invasive ductal	63 (71.6)
	Invasive lobular	2 (2.3)
	Ducto-lobular (mixed)	6 (6.8)
	Invasive ductal + DCIS	13 (14.8)
	Other	3 (3.4)
Receptors	ER + ve	22 (25.0)
	HER2 + ve	16 (18.2)
	ER + ve, HER2 + ve	16 (18.2)
	Triple negative	31 (35.3)
	Unknown	3 (3.40)
Grade	1	1 (1.1)
	2	30 (34.1)
	3	55 (62.5)
	Unknown	2 (2.3)
Tumour size	Mean (mm)	50.45 ± 26.660
	Min - Max	10–104
LN positive on baseline MRI (n)	Abnormal	67 (76.1)
	Normal	21 (23.9)
Staging of tumour	T1	9 (10.2)
	T2	40 (45.5)
	T3	35 (39.8)
	Unknown T stage	4 (4.5)
	N0	20 (22.7)
	N1	40 (45.5)
	N2	28 (31.8)
	N3	0 (0)

Regarding breast management, the mastectomy rate was 32.9%(n = 29) in this cohort of patients. Forty eight patients showed partial response to NACT, seven had no response to chemotherapy, and 33 had complete/near complete response.

Figure 4 and Figure 5 depict examples of false-negative and false-positives MRI studies, respectively.

DISCUSSION

Patients with breast cancer undergoing neoadjuvant chemotherapy (NACT) are increasingly considered for de-escalated axillary surgery following the reduction of axillary nodal burden. The axillary nodal pCR rate following NACT varies between 23 to 41% in earlier studies.[16] In the present study, we had a pCR rate of 38.8%, in keeping with previous studies. Following complete imaging resolution of axillary nodes, limited axillary surgery has been recommended in earlier studies.[2–4]

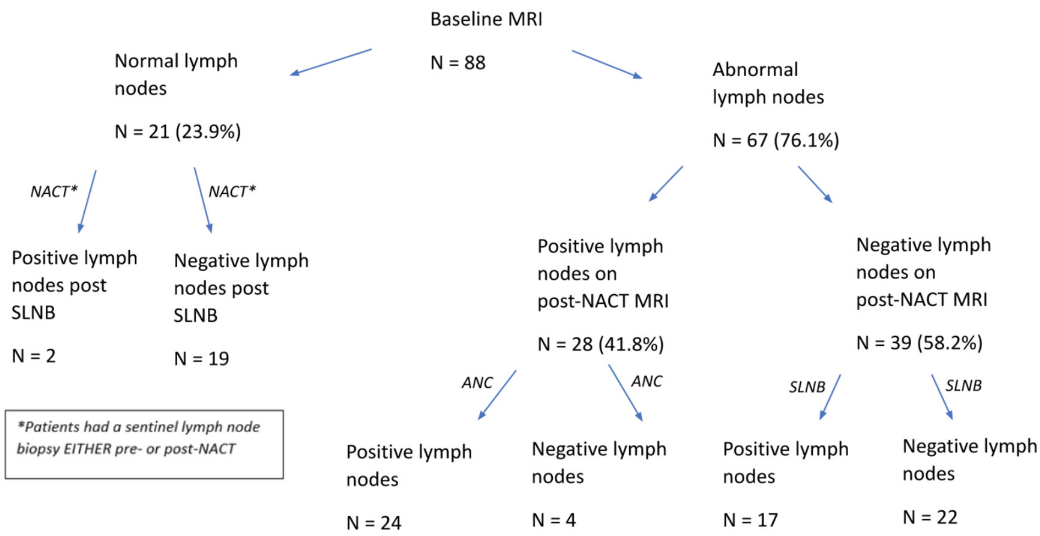
Our results demonstrate a low (47.84%) negative predictive value of MRI for predicting axillary status in the NACT patients. Theoretically, if we were to omit SLNB based on normal axillary MRI findings, the NPV of MRI should be at least non-inferior to SLNB. SLNB has a false negative rate of 8.61% (95%CI: 8.05–9.2%), leading to an NPV of 94.5%.[19]The diagnostic performance of MRI was inferior to SLNB for excluding axillary disease. This finding is in keeping with previous studies.[16,20–22] In study[20] with 129 breast cancers receiving NACT, MRI demonstrated an NPV of 65.6% and a PPV of 66.7% in predicting nodal ypCR. Similar findings were seen in a specific subgroup of invasive lobular cancer (ILC) receiving NACT, where the NPV for the axillary status of post-treatment MRI was 40%.[21] In study[22] with 33 patients receiving neoadjuvant endocrine therapy, Reis et al evaluated the diagnostic accuracy of MRI for assessing pre-operative axillary burden in locally advanced breast cancer. The authors did not find the performance of MRI adequate to preclude definitive axillary surgery. None of the above studies, including ours, used a dedicated axillary coil.

In other studies,[23,24] MRI demonstrated a high negative predictive value of 97.3% for excluding advanced axillary disease (>2 nodes), compared to the limited value of MRI in patients with a low burden of the axillary tumour. This difference could be related to the cortical thickness threshold of >3 mm used in their study versus 2 mm in the present study, accounting for slightly higher PPV and specificity in the current study (93.53 and 85.71%, respectively). Hyun et al compared two groups of patients and found a lower negative predictive value of MRI in excluding advanced nodal disease in the NACT group of 94versus 99.6% in the non-NACT group.[16]We have used one node involved with macrometastases as a cut-off point for the post-surgery axillary involvement (ypN+), which could account for the difference in findings. It was not possible to perform meaningful subgroup analysis based on axillary burden due to limited numbers in this study.

For this study, we did not include micrometastases or isolated tumour cells (ITC) in the count of abnormal nodes following surgery (ypN status). Studies have shown that micrometastases and ITC do not affect survival.[25]Consequently, imaging modality sensitivity for detecting small metastases is less critical. Micrometastasis will be difficult to detect with any imaging technique. Moreover, there is a recent trend of avoiding surgery with a low axillary burden, which is then mopped up by systemic therapy and radiotherapy. Henceforth, the actual value of an imaging modality in the current context is only to exclude advanced axillary disease.

Standard MRI is limited in assessing the axilla, particularly after neoadjuvant treatment. Whilst the assessment of breast imaging

Figure 3. represents the flow chart of patients divided into groups depending on their nodal status (pre- and postoperatively).



complete response uses enhancement characteristics utilising the full dynamic capability of MRI to assess response, these criteria cannot be used for axillary assessment as normal LNs enhance. Moreover, there is normal physiological variation in the size, number and morphology of axillary LNs. In addition, there is an issue with respiratory motion artefacts within the axillary regions. The authors found that comparing the involved axilla with the contralateral normal axilla and with baseline axillary appearances helped formulate a final axillary opinion. However, the subjectivity involved in nodal assessment cannot be completely removed.

L: S axis measurement was not significantly different between metastatic and non-metastatic nodes. Our findings are similar to previous studies,,[26–28] where no significant difference was found between L: S axis ratio between benign and malignant nodes. In the present study, loss of fatty hilum and cortical thickness significantly differed between malignant and normal nodes. In study[24] with 40 patients with primary breast cancers (but no NACT), authors found loss of fatty hilum as the only significant difference between metastatic and non -metastatic nodes. Kaur et al and Mortellaro et al[27,28] reported similar findings on fatty hilum between metastatic and non-metastatic nodes. Similar results were seen by Arslan et al.,[29]in which the L: S axis ratio was not significantly different between metastatic and non-metastatic axillary nodes and fatty hilum was the only significant difference.

This study highlights the low diagnostic accuracy of MRI in diagnosing axillary metastases in patients who received NACT. Henceforth, we recommend caution when interpreting the results of MRI axilla in post-NACT patients. Routine marker placement in the abnormal node before the start of NACT is suggested. Pre-NACT clipping of biopsy-proven nodes harvested in image-guided/localised post-NAC axillary staging surgery could be the way forward till we optimise imaging interpretations and techniques. This process could potentially reduce the false-negative

Table 2. Demonstrates the sensitivity and specificity profile of MRI for the end of the NACT

Sensitivity and Specificity of NACT MRI			
	Postoperative axillary lymph nodes (n)		
		Normal	Abnormal
End of NACT MRI axillary lymph nodes (n)	Normal	41	19
	Abnormal	4	24
Sensitivity (%)	68.85% (95%CI 55.71–80.01)		
Specificity (%)	85.71% (95%CI 67.33–95.97)		
Positive LR	4.82 (95%CI 1.92–12.13)		
Positive predictive value (%)	93.53% (95%CI 85.18–97.33)		
Negative LR	0.36 (95%CI 0.24–0.54)		
Negative predictive value (%)	47.84% (95%CI 38.01–57.84)		
Diagnostic accuracy (%)	73.07% (95%CI 62.62–81.93)		

Table 3. Depicts the MRI axillary nodal morphology difference across the two groups (pathologically normal and abnormal)

Lymph node features on MRI			
MRI variables		Normal ($n = 60$) N (%)	Abnormal ($n = 28$) N (%)
Long axis – Short axis ratio ($p = 0.388$)	Mean ± SD	2.11 ± 0.545	1.71 ± 0.499
	Min - Max	1.26–4.61	1.00–2.31
Cortical thickness (mm) ($p < 0.001$)	Mean ± SD	2.20 ± 0.836	4.40 ± 3.182
	Min - Max	0.89–3.1	2.37–6.37
Presence of a fatty hilum (n) ($p = 0.004$)	Yes	60 (100)	18 (64.2)
	No	0 (0)	10 (35.7)

rate of the axillary staging procedure.[30,31]Increasing reliance should also be paid to limited (at least three nodes) sentinel lymph node sampling of yrN0 nodes in the interim.

This study has several advantages. Firstly, this is a unique cohort of patients with baseline and post-treatment MRI for radiological review and followed up for a minimum of 5 years. Secondly, by excluding micrometastases and isolated tumour cells from the count of abnormal nodes, we have focused our study on the relevant group with clinical impact.[32,33] Thirdly, to the best of our knowledge, this is the the only study which correlated the number of abnormal nodes on MRI with surgery. This is crucial as the number of nodes determines N staging and prognosis. Lastly, in this study, we have only focused on the axillary appearances and response without contaminating it with the breast tumour response. The axillary response and treatment are often independent of breast management, and MRI performs better in interpreting breast findings.

There are certain limitations of this study. Firstly, this is a single-centre retrospective study. A larger multicentre, multireader prospective study would undoubtedly improve upon the results of this study. Secondly, as previously mentioned, abnormal nodes were not clipped before the start of NAC, reducing the accuracy of post-NACT surgical histopathological results. However, surgery in the form of ANC and SLNB is considered the gold standard modality. Thirdly, subgroup analysis of MRI accuracy according to different receptor types of breast cancer was not performed. However, the numbers in the subgroups were too small to reach a statistical conclusion. Fourthly, a dedicated axillary coil and Diffusion-weighted imaging (DWI) were not used in the current study, which could have improved the negative predictive value of MRI. However, combined breast and the axillary coil are the most commonly used in clinical practice within the UK. DWI is not without technical limitations and has not been standardised across breast centres.

In conclusion, given the low NPV of MRI, a negative MRI does not obviate the need for definitive axillary surgery. However, due to satisfactory PPV, post-treatment MRI could be useful to identify a high burden of nodal disease and, therefore, direct informed management pathways. These results should be

Figure 4. (a) Baseline MRI in the NAC group, red arrow pointing to involved lymph nodes; (b) post-chemotherapy MRI showing complete imaging response within the axilla. Post-operative histopathology showed multiple lymph nodes involved.

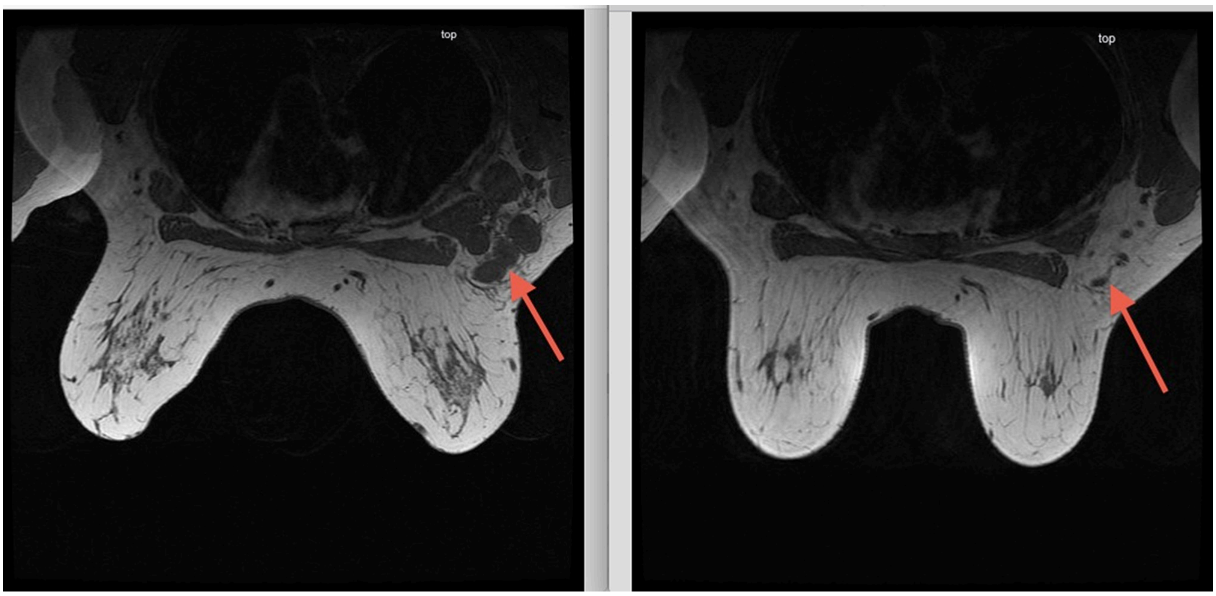
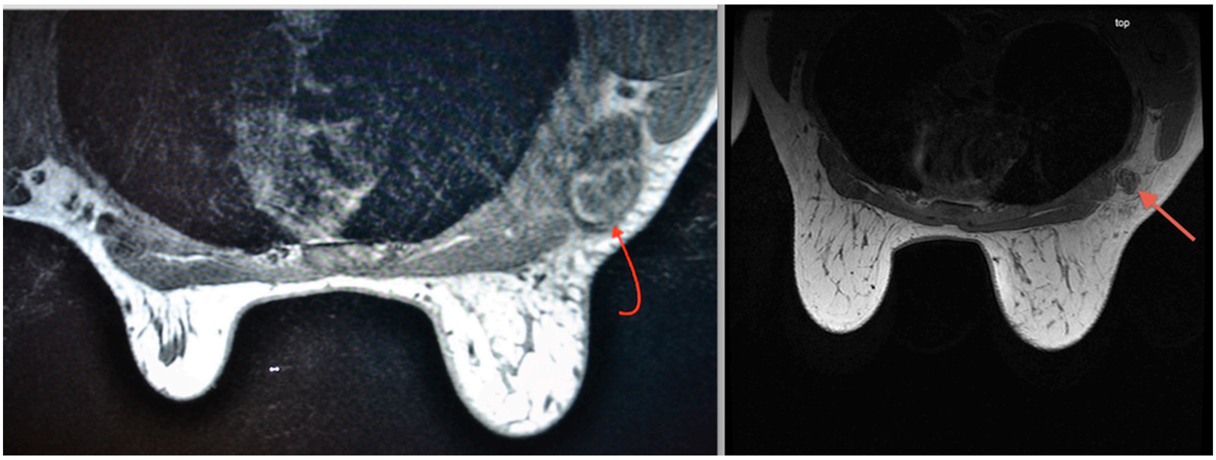


Figure 5. (a) Abnormal LN on baseline MRI (red arrow) (b) Post Chemotherapy MRI shows rounded lymph node within right axilla, but fatty hilum maintained (read as abnormal on MRI). Post-operative histopathology normal axillary lymph node (NAC group)



validated with more extensive, multicentre studies with multiple readers. In addition, routine clipping of abnormal nodes before the start of NAC could help guide image guidance and targeted axillary dissection.

COMPETING INTERESTS

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