Predicting Nodal Status Using MRI-Based Clinical Response and Pathological Response of the Primary Tumor in Patients with Locally Advanced Breast Cancer Undergoing Neoadjuvant Chemotherapy

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Purpose:

The optimal management of axillary lymph nodes in patients with locally advanced breast cancer (LABC) remains a complex therapeutic problem. During the past several decades, treatment for LABC has evolved from radical mastectomy to the use of neoadjuvant chemotherapy (NAC) followed by a mastectomy and an axillary node dissection. The possibility of "lesser" surgery (breast conservation) has only recently been introduced because of the increased effectiveness of NAC regimens. The increasing use of NAC in LABC, coupled with the improved efficacy of newer regimens, raises questions concerning the efficacy of routine axillary lymph node dissections performed in this group of patients. NAC not only downstages the primary tumor, it can also downstage the nodes. Currently, controversy exists about the utility of sentinel node biopsy (SLNB) and the timing of the procedure (either before or after NAC). Until this question of the timing of SLNB is resolved, other means or imaging modalities are needed to assess or predict disease status in the axilla after NAC. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) was shown to be accurate in determining both the tumor response and the amount of residual disease remaining in the breast. The aim of this study is to evaluate the use of DCE-MRI in the measurement of primary tumor response as a surrogate maker for predicting nodal status for patients with LABC undergoing NAC. The prediction accuracy based on final pathological response of the primary tumor was also analyzed and compared to MRI-based prediction results. We also evaluated the possible association between the nodal status and morphology of primary tumor.

Methods:

48 subjects (29-75 yo, median 48) enrolled from July 2003 to April 2006 were included in this study. The tumor size ranged from 0.9 cm to 8.5 cm (median 2.4 cm). All patients received 2-4 cycles bi-weekly AC (doxorubicin and cyclophosphamide) with growth factor support, followed by Taxane regimen (TCa ± H), including paclitaxel or Nab-paclitaxel (Abraxane) and Carboplatin, with Trastuzumab (Herceptin) for Her-2 positive patients, then surgery. The Taxane regimen consisted 3-4 cycles, each cycle with 3-weeks on and 1-week off Taxane and Carboplatin, and weekly Herceptin. MRI protocol included a T1-weighted pre-contrast Sagittal view scan from the concerned breast, and an axial view dynamic contrast enhanced scan using a 3D SPGR (RF-FAST) pulse sequence. Thirty-two axial slices with 4 mm thickness were used to cover both breasts. The subtraction images at 1-min after injection were used to determine the MRI phenotype and the size of the lesion (the index lesion in case of multi-nodular pattern). Based on the 3D morphological pattern of the lesion, they were classified into three MRI phenotypes: I- solitary mass; II- multi-nodular pattern (separately differentiable masses); III- non-mass type enhancements (a regional enhancement without well-defined border). The response to the AC regimen was evaluated based on MRI. When the 1-D size reduction was greater than 10% after 1 cycle AC, 20% after 2 AC, or 30% after 4 cycles it was determined as a AC responder (AC-R), otherwise a non-responder (AC-NR). After taxane when the tumor has shrunk to barely differentiable, as long as a noticeable enhancement from the previous cancer site which was higher than that of normal tissues, it was considered as residual disease. After the patient completed chemotherapy, the final definitive surgery was performed. The pathological response was classified into pCR (no invasive tumor), and non-pCR (with residual invasive cancer). The nodal status was evaluated in all patients. Of 48 patients, 41 received axillary node dissection, 7 did not, due to the negative sentinel node biopsy finding.

Results:

Table 1 summarizes the pCR rate and the nodal status in Her2 +/– cohorts, separated by AC response as AC-R vs. AC-NR. Her2 + cancers receiving Herceptin had a significantly higher pCR rate (78%) compared to Her2 – cancers (36%, $p = 0.015$). In Her2 –, AC-NR group, not a single case achieved pCR (0/8, 0%), which was lower than that in AC-R group (9/17, 53%, $p = 0.007$). The results of nodal status paralleled that of pCR. Her2 + patients after NAC also had a lower rate with positive nodes (2/23, 9%) compared to that in Her2 – patients (12/25, 48%, $p = 0.004$). Interestingly, in Her2 –, AC-NR group, all 8 patients had positive nodes (100%). The rate was lower in AC-R group (4/17, 24%, $p < 0.001$).

Table 2 summarizes the diagnostic results of the nodal status based on the MRI-evaluated response and the final pathological response of the primary tumor, reporting TN, FN, FP, and TP cases numbers. The resulted sensitivity, specificity, positive predicting value, negative predicting value, and the overall accuracy are summarized in Table 3. The nodal status predicting accuracy was only fair for Her2 – patients, with comparable results based on MRI-response (16/25, 64%) or pathological response (17/25, 68%). The predicting accuracy was higher for Her2 + than for Her2 – patients, with the same accuracy of 87% (20/23) based on either MRI, or pathological response. The sensitivity, specificity, or positive and negative predicting value in Her2 – patients evaluated based on MRI and pathological responses were comparable.

In analysis of nodal status with tumor phenotype, there was not a strong link. In all 3 morphology (mass, multiple, and non-mass) groups, some cases had positive nodes, and some had negative nodes.

Table 1: The pCR rate and Nodal Status in Her2 +/-, AC-R vs. AC-NR Groups

	Her2 Negative (N=25)		Her2 Positive (N=23)	
Overall pCR*	9/25 (36%)		18/23 (78%)	
Positive Nodes*	12/25 (48%)		2/23 (9%)	
	AC-NR (N=8)	AC-R (N=17)	AC-NR(N=12)	AC-R (N=11)
Group pCR **	0/8 (0%)	9/17 (53%) *	9/12 (75%)	9/11 (82%)
Positive Nodes**	8/8 (100%)	4/17 (24%) *	2/12 (17%)	0/11 (0%)

***: pCR rate and nodal status significantly different between Her2 +/- group**
****: significant between AC-NR and AC-R group in Her – patients, not in Her2+ patients**

Table 2: Diagnostic Performance of Nodal Status Based on MRI, and Pathology Response

	Her2 Negative (N=25)		Her2 Positive (N=23)	
	MRI	Pathology	MRI	Pathology
True Positive	7	10	2	2
False Negative	5	2	0	0
False Positive	4	6	3	3
True Negative	9	7	18/	18

Table 3: Diagnostic Accuracy of Nodal Status Based on MRI, and Pathology Response

	Her2 Negative (N=25)		Her2 Positive (N=23)	
	MRI	Pathology	MRI	Pathology
Sensitivity	7/12 (58%)	10/12 (83%)	2/2 (100%)	2/2 (100%)
Specificity	9/13 (69%)	7/13 (54%)	18/21 (86%)	18/21 (86%)
Positive PV	7/11 (64%)	10/16 (63%)	2/5 (40%)	2/5 (40%)
Negative PV	9/14 (64%)	7/9 (78%)	18/18 (100%)	18/18 (100%)
Accuracy	16/25 (64%)	17/25 (68%)	20/23 (87%)	20/23 (87%)

Discussion:

As a surrogate marker for axillary disease status, the sensitivity, specificity, PPV, NPV and accuracy of the DCE-MRI results in predicting nodal status were 58%, 69%, 64%, 64%, and 64%, respectively in Her2 – groups; and were 100%, 86%, 40%, 100%, and 87%, respectively in Her2 + groups. The prediction based on pathological response of primary tumor was only comparable to that based on MRI response. The increasing efficacy of NAC for treating LABC mandates an individualized surgical approach based on response to therapy. The results of DCE-MRI of the breast were accurate in predicting the nodal status in Her2 + patients receiving chemotherapy with AC followed by taxane combined with Carboplatin and Herceptin. The Her2 + patients with a complete clinical response on DCE-MRI had 100% accuracy predicting negative nodes after NAC, and these patients are highly unlikely to benefit from an axillary lymph node dissection. For Her2 – patients, sentinel lymph node sampling is warranted for evaluation of the axillary nodal status after NAC.

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