Diagnostic Performance of MRI for Assessing Tumor Response in Her-2 Negative Breast Cancer Receiving Neoadjuvant Chemotherapy

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Background and purposes:

HER-2 positive cancer is known to be more aggressive than HER-2 negative cancer; however since there is a targeted therapy trastuzumab available, this type of cancer can be treated with a good response. For HER-2 negative but hormonal receptor (HR) positive cancer, although there is no targeted therapy yet hormonal treatment can be offered to these patients to achieve a favorable prognosis. For HER-2 negative and hormonal receptor negative cancers, they are known as triple negative (ER, PR and HER-2 negative), and since no targeted therapy nor hormonal therapy can be used to control the disease, patients are known to have poor prognosis. In addition to classifying tumors based on the molecular biomarkers, they can be classified based on genetic profiling. Triple negative cancers are more likely to be the basal type. The luminal type can be further separated into luminal-A and luminal-B. Although these sub-types can only be made based on genetic profiling, tumors with low proliferation determined by low Ki-67 are more likely to be luminal-A, and those with high Ki-67 are more likely to be luminal-B. Typically luminal-A cancer is not aggressive and the disease can be controlled very well by hormonal therapy alone. For other cancer that needs chemotherapy, the treatment can be given in a neoadjuvant setting, so the response to different drug regimens can be monitored. Usually the more aggressive cancer will have a better response to chemotherapy, but the response does not always translate to survival benefit. Nevertheless, for patients who can achieve pathologic complete response (pCR), they are expected to have a better survival outcome. Imaging evaluation of patients following their NAC is therefore crucial to determine how tumor responds to the therapy and which optimal surgical planning can be chosen. MRI has been proven as the most accurate breast imaging modality for evaluation of NAC response. Our previous studies [1, 2] have shown that the diagnostic accuracy was higher in HER-2 positive than HER-2 negative cancer. A higher false negative rate and a larger size discrepancy between imaging and pathology were more frequently found in HER-2 negative than HER-2 positive cancer. In this study we further evaluated the response in HER-2 negative cancer, and compared the imaging findings between HR positive and HR negative subgroups.

Methods:

Fifty-four patients enrolled into an NAC study from May 2002 to February 2010 with biopsy-proven HER-2 negative breast cancer were evaluated in this study. Biomarkers, including estrogen receptor, progesterone receptor, HER-2, and Ki-67, were determined from biopsy tissue samples. The neoadjuvant chemotherapy regimens included Adriamycin (Doxorubicin) and Cyclophosphamide, taxane-based regimen, or a combination of AC and taxane-based regimen. Every patient received several MRI scans during NAC, and the last MRI done after completing the treatment before definitive surgery was analyzed in this study. Following surgery, pathological residual tumor size was determined from the surgical specimen by a pathologist using uniform criteria. When there was no residual invasive cancer found in a cancer, the pathologic complete response (pCR) was achieved. No enhancement or faint enhancement relative to background breast tissue on MRI was diagnosed as a complete response. In cases with residual disease, the largest dimensions from both pathology and MRI were measured. If scattered cells or cell clusters were found, the region where the cancer cells were found was recorded as the residual size. Pearson's correlation was used to compare the size of the residual disease measured by MRI and pathological examination. Fisher's exact test was used to compare the lesion morphology, surgical type, and MRI diagnostic performance between HR+ and HR- groups. A student t test was used to evaluate tumor size discrepancy between HR positive and negative cases. The diagnostic response was correlated with Ki-67.

Results:

Table 1 shows the comparison of pCR rate, tumor morphology, surgical types, MRI diagnostic performance, and size discrepancy between MRI and pathology for the HR+ and HR- patients. Traditionally HR- cancers are known to respond better to chemotherapy than HR+ cancer. In this cohort, 50% (8/16) of HER- patients achieved pCR, which was much higher than 24% (9/38) in HR+ patients. Of these 8 HR- pCR patients, 6 received mastectomy, one received lumpectomy and one received excision. Of the 9 HR+ pCR patients, 3 received mastectomy, 4 received lumpectomy and 2 received excision. Since there was no residual cancer in the surgical specimen, which type of surgery is optimal is an interesting research question awaiting to be addressed. Of these 17 pCR patients, 15 (9 HR+ and 6HR-) cases were accurately diagnosed as complete responders on MRI; therefore, the response diagnosed by MRI may be used to plan for the surgery. HR+ patients were more likely to receive lumpectomy (15/38, 39%) than HR- patients (3/16, 19%). This may be due to that HR+ cancer can be controlled well by subsequent hormonal therapy, and patients are more willing to choose a less aggressive surgery. The correlation between MRI and pathological size was poor (R= 0.4567 for all patients; R=0.4598 for HR+ patients; and R=0.5323 for HR- patients) (**Figure 1**). The cancer was very likely to break into scattered cells or small nodules; and that make the measurement of residual disease on MRI difficult. MRI and pathological size discrepancy was analyzed for each case, and showed a higher size discrepancy in HR+ cancer than HR- cancer ($p < 0.006$); however, the diagnostic performance in true negative, true positive, false negative and false positive rates did not reach the significant level. The association between size discrepancy and the expression level of Ki-67 was analyzed using 40% as the cut-off value. Cancers with a low proliferation (Ki-67 <40%) show a higher size discrepancy than cancers with a high proliferation (p=0.04). High proliferating cancers are known to respond better to chemotherapy, and the result suggests that the diagnostic performance of MRI is more accurate when the cancers are showing a better response. This observation was consistent with our previous finding that the diagnostic performance in HER-2 positive cancer responding to trastuzumab is higher than in HER-2 negative cancer.

Table 1. Comparison between HR+ and HR– cancer

	HR +	HR –	P value
pCR Rate	9/38	8/16	0.11
Lesion Type			
Mass lesion	29/38	14/16	0.47
Non-mass lesion	9/38	2/16	0.47
Surgery			
Mastectomy	21/38	12/16	0.23
Lumpectomy	15/38	3/16	0.21
Excision	2/38	1/16	1.0
Diagnosis			
True Negative	9/38	6/16	0.33
True Positive	23/38	7/16	0.37
False Negative	6/38	1/16	0.66
False Positive	0/38	2/16	0.08
Δ (MRI – path) size range (cm)	0.1 ~ 14	0.2 ~ 3.2	0.0007
Δ (MRI – path) size mean (cm)	2.1±3.1	1.3± 1.0	0.0057

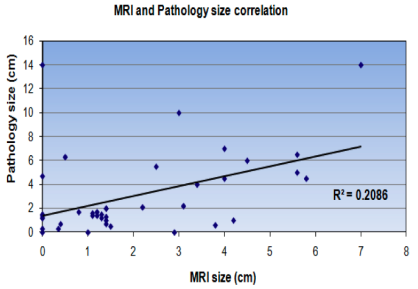

Fig.1: Correlation between MRI and pathological size.

Discussion:

The results were consistent with our previous findings and the expectation that the diagnostic performance of MRI is better in tumors that are showing a good response than those showing a poor response. Overall, the size discrepancy between MRI and pathology was higher in HR+ than HR- cancer, and also in low proliferating cancer with Ki-67 <40% than high proliferating cancers with Ki-67 > 40%. The results suggest that the diagnosis of MRI for breast cancer undergoing neoadjuvant chemotherapy may be used for planning of an optimal surgery after NAC. The accuracy is associated with molecular biomarker profile. This understanding, as well as the hormonal treatment that may be offered to patients with HR positive cancer, can be considered for choosing an optimal management plan for each breast cancer patient.