Evaluation of MR accuracy in neoadjuvant chemotherapy response assessment in patients showing change of biomarker status

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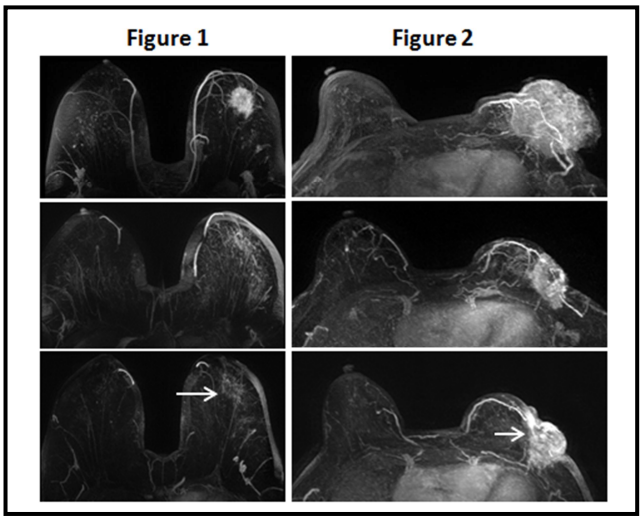
Background and Purpose: Although recent studies suggest high accuracy of breast magnetic resonance imaging (MRI) in predicting residual tumor extent after neo-adjuvant chemotherapy (NAC), its use may be affected by many factors, such as tumor type, tumor morphology, and pre-NAC biomarker status. When evaluating the profiles of tumor cells, we may observe that the features of post-NAC surgical tissue do not always correspond with those of pre-NAC biopsy specimens. Intratumoral heterogeneity as well as sampling variations can contribute to modification of the biomarker status after NAC [1]. Another theory to explain the differences in biomarker status pre- and post-therapy is the selection of tumor clones because of chemoresistance [2]. Change of biomarker status after NAC, in particular, the alteration of hormone receptor (HR) expression is very important for decision-making regarding postoperative endocrine therapy. Change of biomarker status may also impact on the long-term outcome in patients with primary breast cancer [3]. Nevertheless, it is so far not known that how the change of biomarker status after NAC will affect the tumor response and MR accuracy in evaluation of residual tumor. This study attempted to address these two unanswered questions.

Materials and Methods: This is a retrospective analysis of prospectively conducted studies. A total of 59 patients (28 to 82 y/o, mean 49 y/o) were identified and analyzed for this study. All patients had histologically-confirmed invasive breast cancer and elected to receive NAC and serial breast MRI for response monitoring. All studied subjects had both MRI and pathological tumor size available for analysis. Estrogen receptor (ER) or progesterone receptor (PR) was defined as positive if immunoperoxidase staining of tumor cell nuclei ≥10%. HER-2 was first determined by immunohistochemical (IHC) and, if undetermined, further confirmed by fluorescence in situ hybridization *(*FISH) test. Two radiologists (J.C. for 1.5 T and S.B. for 3.0 T), with 7 and 6 years of experience in interpreting breast MRI, performed the MRI tumor size measurement using the same measurement standard. The residual tumor size in the final MRI was measured based on subtracting the pre-contrast images from the post-contrast images, and the maximum intensity projections (MIPs) generated from the subtraction images. The longest tumoral dimension was used to correlate with pathological size. When there was no discernible enhancement or a faint enhancement equal to the background normal breast tissue in the previous lesion site, this case was determined as complete clinical response (CCR) on MRI. When measuring the residual tumor size in MRI, the two radiologists were blinded to the pathology results. The pathological findings were interpreted by an experienced pathologist (P.C.). If tumors were clearly visible, usually 2 cm or larger, only gross measurements were made. Small residual tumors, not clearly visible, were measured microscopically across slides of known thickness. If no invasive tumor was found within all examined slides, a diagnosis of pathological complete response (pCR) was made. The largest dimension provided by the pathologist was used in the comparative study. The tumor size difference between pathology and MRI was the absolute value between these two measurements. In this study, only those patients who had residual tumor in pathology and with both pre- and post-NAC biomarker information were analyzed.

Results: Changes of biomarker status mainly occurred in Her-2 and PR. Change of ER status was only noted in one patient (N=1) in this study. Of the 14 patients showing pre-NAC Her-2 positive cancer, 4 patients were changed to Her-2 negative after NAC. Of the 42 patients showing pre-NAC Her-2 negative cancer, 8 patients were changed to Her-2 positive after NAC. The change rate in Her-2 cancer was 22.2% (4+8/14+42). Of the 28 patients with PR positive cancer before NAC, 8 patients were changed to PR negative cancer, resulting in a change rate of 28.6%. The MR accuracy in diagnosis of residual tumor is evaluated by using the difference of tumor size measured by MRI and pathology, summarized in **Table 1**. Her-2 positive cancer without biomarker change had lower MR-pathology size difference than Her-2 positive cancer with biomarker change. But the difference in the two groups was not statistically significant (p=0.085). In the other two groups (Her-2 negative and PR positive cancers), change of biomarker status after NAC did not lead to a significant difference in MR accuracy when compared to pathological tumor size. **Figures 1 and 2** illustrate two examples of Her-2 positive cancer with/without biomarker change and the accuracy of MRI. **Figure 1** is a 53 y/o woman with a 4.4cm Her-2 positive cancer in the left breast. After the completeness of NAC, MRI showed a 3.0cm residual tumor (arrow). Final pathology showed that the residual tumor was a 2.0cm Her-2 positive cancer. **Figure 2** is a 56 y/o patient with a large Her-2 positive cancer in the left breast at the initial presentation. After the completeness of NAC, MRI showed a 3.3cm residual tumor (arrow). Final pathology showed that the residual tumor was a 5.0cm Her-2 negative cancer.

Table 1. Impact of biomarker change on the accuracy of MR-determined residual tumor size

	MR-pathology tumor size difference
Her-2 positive cancer without conversion (N=10)	0.71±0.35cm
Her-2 positive cancer with conversion (N=4)	1.65±0.76cm
P values	0.085
Her-2 negative cancer without conversion (N=34)	2.27±2.95cm
Her-2 negative cancer with conversion (N=8)	1.84±2.42cm
P values	0.67
PR positive cancer without conversion (N=20)	1.98±3.16cm
PR positive cancer with conversion (N=8)	1.16±1.72cm
P values	0.39



Conclusions: The results from our study showed that change of biomarker status following NAC did not impact the accuracy of MRI in determining residual tumor size in Her-2 negative and PR positive breast cancer. In Her-2 positive cancer, when changed to Her-2 negative cancer following NAC, the MR-pathology tumor size difference was larger than Her-2 positive cancer without biomarker change. The results suggest that when a mixed clone of Her-2 positive and negative cancers is present, administration of Herceptin may not have a good therapeutic efficacy for the Her-2 negative residual cancer.

References: 1. Varga Z, et al. Virchows Arch. 2005 Feb;446(2):136-41.; **2.** Adams AL, et al. Breast J. 2008 Mar-Apr;14(2):141-6.; **3.** Hirata T, et al. British Journal of Cancer 2009;101:1529-36.

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