MR Imaging Response Prediction of Neoadjuvant Chemotherapy in HER2+ Breast Cancer

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Purpose

Breast cancer is a heterogeneous disease at the morphologic, immunohistochemical and molecular level. Traditionally, the major molecular subtypes of breast cancer determined by gene expression profiling are: luminal (A and B), HER2+ and basal. Recent studies propose that the estrogen receptors positive/HER2+ tumors could similarly be subdivided into luminal A-HER2 hybrid and luminal B-HER2 hybrid, based on estrogen receptors expression levels (1,2,3).

Approximately one quarter of patients with breast cancer demonstrate overamplification of the human epidermal receptor type 2 (HER2) gene, resulting in an overexpression of the HER2 receptor, the activation of which is known to result in increased activity of a variety of molecular pathways associated with tumor growth and progression (Fig. 1 on page 3)(4).

Neoadjuvant chemotherapy (NAC) was initially introduced for the treatment of inoperable locally advanced or inflammatory breast cancer. Currently, NAC is using to downstage the tumor, thus improving the survival of patients treated by breast-conserving surgery (5). Additionally, NAC has also been expected to improve survival of patients by the early treatment of undetectable micrometastasis (6). In the cases with overexpression of HER2 receptor, the treatment with recombinant monoclonal antibody drugs was already demonstrated (4,7,8).

Several studies investigated the role of MRI in evaluating breast cancer response after NAC and complete response determined by MRI was highly correlated to pathologically complete response (pCR) in HER2+ patients and complete response had a high false-negative rate in HER2 negative patients. Predicting the pCR or the presence of a residual tumor, MRI interferes in preoperative surgical planning (9,10).

The objective of this study was to analyse the value of MRI to predict complete or partial remission to NAC in HER2+ breast cancer and to assess whether there are differences in MRI prediction accuracy depending on the positivity (ER+) or negativity (ER-) of estrogen receptors in HER2+ breast cancer (HER2+/ER+ and HER2+/ER-).
Fig. 1: Immunohistochemistry study: positive for HER-2 protein expression.

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Methods and Materials

Eligible patients included 58 women (mean age 50.9) with biopsy proven invasive cancer and overexpression of the HER2 receptor who received NAC between May 2004 and September 2010.

Inclusion criteria included receiving one MRI examination before chemotherapy and a second afterwards, and undergoing surgery after NAC. All patients received trastuzumab (monoclonal antibody) as their first-line regimen (main line of treatment).

MRI was performed using a 1.5T MRI system and a phased-array bilateral breast coil. The MRI protocol consisted of pre-contrast T2-weighted axial images and 3D axial dynamic contrast enhanced imaging (DCE MRI). DCE MRI including pre-contrast T1-weighted axial images and six post-contrast series. The post-contrast series were acquired every 60 s. The contrast agent was administered at a dosage of 0.1 mmol/kg body weight.

MRI examinations were performed before and after NAC, and included lesion morphology, size, and contrast uptake kinetics.

The size of the primary tumor was determined on the basis of pre-therapeutic MRI findings, using the largest measured diameter. In the cases with multifocal disease, the diameter of the entire affected breast volume was defined as the tumor size.

In each case we compared the findings of MRI examination obtained before NAC with the MRI examination following treatment and previously to surgery, and the patients were classified according to the degree of tumor size reduction into three groups: complete response (CR - non enhancement pattern) (Fig. 2 on page 6: a-d), partial response (PR - a measurable tumor size reduction) (Fig. 3 on page 6: a-d and Fig. 4 on page 7: a-d) and no response (NR - no measurable change in tumor size).

Treatment response was assessed through the presence or absence of residual tumor in the surgical specimen using the histopathological Miller&Payne (pathological remission: G1-G5).

Adopting the histopathological Miller&Payne scale as reference standard we analysed the accuracy of MRI for pathological complete and partial response. To calculate the test parameters (sensitivity, specificity, positive predictive value and negative predictive value) the radiological complete remission was correlated with G5 and radiological partial remission with G2, G3 and G4 (Fig. 5 on page 8).

The patients were divided into two subgroups according to the positivity or negativity of estrogen receptors (ER+/ ER-). The sensitivity, specificity, PPV and NPV of MRI to predict partial and complete remission were estimated for the entire group of patients (global parameters) and for the two subgroups.
For both subgroups we determined the recurrence rate, considering as recurrence the presence of local or metastatic disease in the follow-up studies.
Images for this section:

Fig. 2: Pretreatment MRI (a: dynamic study and b: subtraction image) with an anterior tumor and cutaneous thickening. MRI post-NAC (c: dynamic study and b: subtraction image) showing a lack of contrast medium uptake. The pathological response was complete (G5).

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**Fig. 3:** Pretreatment MRI (a: dynamic study and b: subtraction image) showing a tumor with a longest diameter of 19.6 mm. MRI post-NAC (c: dynamic study and b: subtraction image) showing a partial remission. The pathological response was > 90% (G4).

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Fig. 4: Pretreatment MRI (a: dynamic study and b: subtraction image) showing a multifocal tumor with diameter of 55 mm. MRI post-NAC (c: dynamic study and b: subtraction image) showing a partial remission (diameter of the residual lesion of 49 mm). The pathological response was < 30% (G2).

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<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>COMPLETE</th>
<th>PARTIAL</th>
<th>NO-RESPONSE</th>
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<tbody>
<tr>
<td><strong>RADIOLOGICAL RESPONSE</strong></td>
<td>Non-enhancement pattern</td>
<td>Measurable tumor size reduction</td>
<td>No measurable change in tumor size</td>
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<td><strong>PATHOLOGICAL RESPONSE</strong></td>
<td>G5</td>
<td>G4, G3, G2</td>
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**Fig. 5**: Correlation between radiological and pathological response.

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Results

The distribution according to the positivity or negativity of estrogen receptors were: 31 (53.4%) HER2+/ER- and 27 (46.6%) HER2+/ER+.

To determine the pathological complete remission we obtained a global sensitivity and specificity of 82% and 83%, respectively, with a sensitivity of 84% in the ER- subgroup compared to 78% in the ER+ subgroup (Fig. 6).

<table>
<thead>
<tr>
<th>MRI parameters to predict CR</th>
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<th>HER2+/ER-</th>
<th>HER2+/ER+</th>
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<tr>
<td>Sensitivity</td>
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<td>Specificity</td>
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<td>PPV</td>
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Fig. 6: The accuracy of MRI to predict complete response: global, HER2+/ER-, HER2+/ER+.

References: - Zaragoza/ES

Analysing the pathological partial remission we found a global sensitivity and specificity of 81% and 78%, respectively, with similar sensitivity in the both subgroups (82% and 80%) but with better specificity for ER- subgroup (85% compared to 67%)(Fig. 7).
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<tr>
<td>Specificity</td>
<td>78%</td>
<td>85%</td>
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<tr>
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<tr>
<td>NPV</td>
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**Fig. 7:** The accuracy of MRI to predict the partial remission: global, HER2+/ER-, HER2+/ER+.

**References:** - Zaragoza/ES

Considering as recurrence the presence of local or metastatic disease in the follow-up studies we observed a recurrence rate higher in HER2+/ER+ subgroup in comparison with HER2+/ER- subgroup (14.8% as opposed to 9.7%)(Fig. 8).
**Fig. 8:** The recurrence rate (local or metastasis disease) in function to the positivity or negativity of estrogen receptors (HER2+/ER- and HER2+/ER+).

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Fig. 8: The recurrence rate (local or metastasis disease) in function to the positivity or negativity of estrogen receptors (HER2+/ER- and HER2+/ER+).

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Conclusion

The MRI presents intermediate-high sensitivity and specificity to assess pathological complete and partial remission to NAC in HER2+ breast cancer for which reason it has an important role in preoperative surgical planning.

The accuracy of MRI to predict the pathological response is slightly better in the cases with negative estrogen receptors in comparison to the ones with overexpression of estrogen receptors.

It seems that the coexistence of estrogen receptors in the patients with HER2+ breast cancer gives a greater recurrence rate and consequently a poorer prognosis.
References


