The Breast 24 (2015) 159–165

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Prediction of pathological complete response to neoadjuvant chemotherapy by magnetic resonance imaging in breast cancer patients

Shintaro Michishita, Seung Jin Kim*, Kenzo Shimazu, Yoshiaki Sota, Yasuto Naoi, Naomi Maruyama, Naofumi Kagara, Masafumi Shimoda, Atsushi Shimomura, Shinzaburo Noguchi

Department of Breast and Endocrine Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan

ARTICLE INFO

Article history:
Received 6 September 2014
Received in revised form
14 December 2014
Accepted 1 January 2015

Keywords:
MRI morphology
Neoadjuvant chemotherapy
pCR
Predictor
Intrinsic subtype

ABSTRACT

The purpose of this study was to evaluate whether the baseline breast MRI findings would be useful for the prediction for pathological complete response (pCR) by breast cancer patients to neoadjuvant chemotherapy. Primary breast cancer patients (stage II–III) preoperatively treated with sequential paclitaxel (12 cycles) and fluorouracil, epirubicin, and cyclophosphamide (4 cycles), followed by surgery were retrospectively enrolled, and 229 patients were eligible. Before chemotherapy, breast MRI studies were performed. Breast tumors were dichotomized into round + oval and irregular types based on MRI morphology. The round + oval tumors showed a significantly higher pCR rate than the irregular tumors (42.0% vs 17.3%; $P < 0.001$). In addition, PAM50 analysis revealed that basal and HER2-enriched tumors were significantly more prevalent among round + oval than irregular type tumors ($P = 0.015$). Baseline MRI morphology appears to be a significant predictor for pCR. The higher rate of the basal and HER2-enriched tumors among the round + oval tumors may explain their better chemo-sensitivity.

Introduction

Neoadjuvant chemotherapy (NAC) is widely accepted as the standard treatment for not only locally advanced breast cancer but also stage II–III breast cancer [1–3]. The aim of NAC is to increase the operability of locally advanced breast cancer as well as the feasibility of breast conserving surgery for stage II–III breast cancer [4,5]. Another aim is to determine tumor sensitivity to NAC since a pathological complete response (pCR) is associated with a good prognosis, indicating that pCR is an important "short term" end-point in NAC [2,6,7]. In addition, prediction of pCR is important from the surgical point of view since a more limited resection of the breast can be planned if a high probability of pCR is expected. Consequently, much effort has been devoted to the development of predictors for pCR since they would be helpful in decision making about indication for NAC. These predictors include biomarkers such as hormone receptor (HR), Ki67, human epidermal growth factor receptor 2 (HER2), and more recently multi-gene classifiers and intrinsic subtypes [8–13].

Dynamic contrast-enhanced magnetic resonance imaging (MRI) of the breast is increasingly used for breast cancer patients before surgery since it is useful for the evaluation of tumor extension as well as the detection of ductal spreads or daughter nodules [14,15]. MRI is also used to predict pCR by patients treated with NAC. It has been reported that MRI findings after NAC or changes in these findings during NAC can predict pCR with a relatively high accuracy [16–19]. Such a prediction, however, requires MRI findings after NAC, which can therefore not be used to predict pCR before NAC. On the other hand, if MRI findings before NAC could be used to predict pCR, it would be most helpful for deciding whether NAC is indicated.

Several studies have been reported which suggest that MRI findings before NAC, including the morphology and contrast-enhancement of breast tumors, are related to response to NAC [20–23]. However, the regimens for NAC used in these studies were not always current standard regimens including sequential or

* Corresponding author. Department of Breast and Endocrine Surgery, Graduate School of Medicine, Osaka University, 2-2-E10 Yamadaoka, Suita City, Osaka 565-0871, Japan. Tel.: +81 6 6879 3772; fax: +81 6 6879 3779.
E-mail address: kimsj@onsurg.med.osaka-u.ac.jp (S.J. Kim).

http://dx.doi.org/10.1016/j.breast.2015.01.001
0960-9776/

concurrent taxane and anthracycline. Moreover, in some studies clinical response but not pCR was evaluated as an endpoint. Furthermore, the numbers of patients analyzed in these studies were relatively small, and the predictive value of the MRI findings for pCR was not evaluated as thoroughly as that of conventional biomarkers including HR, Ki67, and HER2. We therefore believe that it still remains to be established whether MRI findings obtained before NAC are truly associated with pCR and thus can serve as significant and independent predictors for pCR.

The purpose of this study was thus to assess the value of MRI findings, in comparison with that of conventional biomarkers, for prediction of pCR by breast cancer patients treated with a single regimen consisting of paclitaxel followed by FEC.

Patients and methods

Patients

Primary breast cancer patients (stage II–III, N = 276) who were treated with NAC followed by surgery at Osaka University Hospital between December 2005 and October 2013 were retrospectively enrolled in this study. NAC consisted of weekly paclitaxel (80 mg/m^2, 12 cycles) followed by FEC (fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2, q3w, 4 cycles). Of these patients, 16 who did not undergo dynamic contrast-enhanced breast MRI and 17 who discontinued receiving NAC were excluded. Fourteen patients treated with trastuzumab were also excluded from this study since we focused on the relationship between MRI findings and pCR induced by chemotherapy alone. Finally, 229 patients were eligible in this study (Table 1 and Supplementary Fig. 1). Of 229 patients, 113 and 116 underwent breast conserving surgery and mastectomy, respectively. Tumor samples were obtained before NAC with a vacuum-assisted core needle biopsy for assessment of histology, estrogen receptor (ER), progesterone receptor (PR), HER2, Ki67 and intrinsic subtypes. The tumor samples for histological examination were fixed in 10% buffered formaldehyde and those for gene expression analysis were snap frozen in liquid nitrogen and kept at −80 °C until use. Informed consent for this study was obtained from each patient before tumor biopsy.

Table 1
Eligible patient characteristics (N = 229).

Parameter	Category	No. of Patients (%)
Age (years)	Range	24–74
	Median	52
Menopausal status	Premenopause	109 (47.6)
	Postmenopause	120 (52.4)
Tumor size	≤3.0 cm	90 (39.3)
	>3.0 cm	139 (60.7)
Histologic type	Invasive ductal carcinoma	204 (89.1)
	Invasive lobular carcinoma	13 (5.7)
	Others	12 (5.2)
Histologic grade	1	42 (18.3)
	2	130 (56.8)
	3	57 (24.9)
Lymph node metastasis[a]	Negative	66 (28.8)
	Positive	163 (71.2)
HR	Negative	79 (34.5)
	Positive	150 (65.5)
HER2	Negative	175 (76.4)
	Positive	54 (23.6)
Ki67[b]	<20%	77 (38.5)
	≥20%	123 (61.5)

[a] Lymph node metastasis was cytologically confirmed.
[b] Ki67 of 29 patients could not be measured.

MRI

Before and after NAC, all patients underwent breast MRI, which was obtained with a field strength of 1.5T (Signa Excite; GE Healthcare, Milwaukee, Wisconsin) for 175 patients or 3T (Signa HDx; GE Healthcare, Milwaukee, Wisconsin) for 54 patients and use of a breast phased array coil. Dynamic contrast material-enhanced T1-weighted fat-saturated gradient-echo sequences ([1.5T/3T] = Scan plane [Sagittal/Sagittal], TR [6.3/6.5 ms], TE [3.1/3.2 ms], flip angle [10/10 degrees], FOV [20/20 cm], matrix size [256 × 160/256 × 160 mm], acquisition time [94/94 s], slice thickness [2.0/2.0 mm], respectively) were performed before and four times after bolus injection of a gadolinium chelate (Omniscan; Daiichisankyo, Tokyo, Japan) at 0.1 mmol per kilogram of body weight at a rate of 2 ml/s, followed by a 20-ml saline flush.

Morphology and enhancement parameters by MRI

Morphology of breast tumors was evaluated on sagittal slices by two surgical oncologists who had 12 years' and 6 years' experiences with breast MRI and 6 years' and 5 years' with BI-RADS, respectively. At first, MRI images were evaluated individually according to the Breast Imaging Reporting and Data System (BI-RADS, version 5) [24]. Tumors were classified into three categories in terms of the shape and margin, respectively (Fig. 1). The intra-observer and inter-observer variations in this study were shown in Supplementary Table 1. For cases with discordance results, we resolved them in consensus.

Regions of interest (ROI) were selected manually within the areas of most intense enhancement in the tumor (ROI size: 9 pixels). The enhancement rate was calculated with the following formula: [Signal Intensity (SI) after contrast injection for the second phase − SI before contrast injection]/SI before contrast injection × 100. The cutoff value of the enhancement rate was determined at the point that had the best discrimination in predicting pCR by a ROC analysis (Supplementary Fig. 2). Enhancement on post contrast enhanced sagittal slices was classified into rim enhancement and internal enhancement based on the site of enhancement in the tumor. SI was measured according to the phase, and consequently curve pattern and time to peak were evaluated.

Determination of ER, PR, HER2, Ki67, and intrinsic subtypes

For analysis of the tumor samples obtained before NAC, ER, PR, and Ki67 were determined immunohistochemically and HER2 amplification by means of FISH as previously described [25]. Cut-off values were 10% for ER and PR, 20% for Ki67 and 2.0 for HER2. HR positive were ER positive and/or PR positive. Intrinsic subtypes (luminal A, luminal B, HER2-enriched, basal-like, and normal breast-like) were determined with DNA microarray according to a previously described method for the PAM50 assay [26]. The normal breast-like tumors were excluded from further analysis since this subtype contains only a small number of tumor cells [27].

Evaluation of pathological response

The surgical specimens were used for pathological response evaluation. pCR was defined as complete absence of both invasive and non-invasive lesions in the breast regardless of lymph node involvement.

Statistical methods

Associations of the clinicopathological parameters with pCR were evaluated with the chi-square test. All test results with a