The Breast 30 (2016) 80–86

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Predictive value of DCE-MRI for early evaluation of pathological complete response to neoadjuvant chemotherapy in resectable primary breast cancer: A single-center prospective study

Ying-Shi Sun [a, *, 1], Ying-Jian He [b, 1], Jie Li [a], Yan-Ling Li [a], Xiao-Ting Li [a], Ai-Ping Lu [c], Zhao-Qing Fan [b], Kun Cao [a], Tao Ouyang [b, **]

[a] From Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Radiology, Peking University Cancer Hospital & Institute, Beijing, 100142, China
[b] From Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Breast Center, Peking University Cancer Hospital & Institute, Beijing, 100142, China
[c] From Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Pathology, Peking University Cancer Hospital & Institute, Beijing, 100142, China

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form
30 August 2016
Accepted 30 August 2016

Keywords:
Breast cancer
Magnetic resonance imaging
Pathological complete response
Therapeutic response
Prediction

ABSTRACT

Objective: This study proposed to establish a predictive model using dynamic enhanced MRI multi-parameters for early predicting pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in breast cancer.

Methods: In this prospective cohort study, 170 breast cancer patients treated with NAC were enrolled and were randomly grouped into training sample (136 patients) and validation sample (34 patients). DCE-MRI parameters achieved at the end of the first cycle of NAC were screened to establish the predictive model by using multivariate logistic regression model according to pCR status. Receiver operating characteristic curves were conducted to assess the predictive capability. The association between MRI-predicted pCR and actual pCR in survival outcomes was estimated by using the Kaplan–Meier method with log-rank test.

Results: Multivariate analysis showed ΔAreamax and ΔSlopemax were independent predictors for pCR, odds ratio were 0.939 (95%CI, 0.915 to 0.964), and 0.966 (95%CI, 0.947 to 0.986), respectively. A predictive model was established using training sample as "Y = −0.063*ΔAreamax − 0.034*ΔSlopemax", a cut-off point of 3.0 was determined. The AUC for training and validation sample were 0.931 (95%CI, 0.890 −0.971) and 0.971 (95%CI, 0.923−1.000), respectively. MRI-predicted pCR patients showed similar RFS (p = 0.347), DDFS (p = 0.25) and OS (p = 0.423) with pCR patients.

Conclusion: The multi-parameter MRI model can be potentially used for early prediction of pCR status at the end of the first NAC cycle, which might allow timely regimen refinement before definitive surgical treatment.

Introduction

Neoadjuvant chemotherapy (NAC) for breast cancer has been widely promoted in recent years, and NAC has been made a necessary step for operable patients with breast cancer according to NCCN guidelines [1]. NAC can effectively control the potential metastases at the earliest time and reduce the size and stage of tumor, which to the greatest extent enables breast-conserving surgery, and therefore improves the life quality of breast cancer patients [2].

* Corresponding author. From Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Radiology, Peking University Cancer Hospital & Institute, No. 52 Fu Cheng Road, Hai Dian District, Beijing, 100142, China. Fax: +86 10 88196822.
** Corresponding author. From Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Breast Center, Peking University Cancer Hospital & Institute, No. 52 Fu Cheng Road, Hai Dian District, Beijing, 100142, China. Fax: +86 10 68236666 8018.
E-mail addresses: sys27@163.com (Y.-S. Sun), ouyanghongtao@263.net (T. Ouyang).
[1] Ying-Shi Sun and Ying-Jian He contributed equally to this work.

http://dx.doi.org/10.1016/j.breast.2016.08.017
0960-9776/

Several studies proved that patients achieving pathological complete response (pCR) after NAC presented significantly better survival outcomes that those not achieving pCR [3–6]. Thus, pCR is regarded as a surrogate endpoint for improved survival in breast cancer patients with NAC.

Preoperative accurate prediction of pCR status enables timely regimen adjustment, which is especially crucial when a patient is resistant to NAC. The earlier the pCR status could be predicted, the more clinical benefit would be obtained. Presently, MRI is usually applied in preoperative evaluation of therapeutic response to NAC [7–9]. Researchers considered several MRI parameters, such as size, apparent diffusion coefficient (ADC), transfer constant (Ktrans), rate constant (Kep) and relative blood volume (rBV) for predicting pCR. However, most of present studies were of small sample size, and used complexly calculated MRI parameters.

Thus we proposed this prospective study to investigate the value of dynamic enhanced MRI (DCE-MRI) for predicting pCR at the end of the first NAC cycle, based on the findings to establish a multi-parameter MRI model for early prediction of pCR.

Materials and methods

Patients

This study was approved by the Medical Ethics Committee of Peking University Cancer Hospital. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We enrolled consecutive patients from December 2005 using following inclusion criteria: a) histologically or cytologically confirmed primary breast cancer by core biopsy; b) female, age ≤65 years; c) no previous treatment for breast cancer; d) no history of other malignancies; e) all ER/PR status, scheduled to receive neoadjuvant chemotherapy and not scheduled to receive neoadjuvant anti-Her-2 therapy; f) no concurrent uncontrolled disease (e.g., ongoing cardiac dysrhythmias, unstable diabetes) or active infection; g) not pregnant or breast feeding, and on appropriate birth control if of child-bearing potential; h) adequate cardiovascular, hematologic, hepatic and renal function; i) willingness and ability to give informed consent. Patients were excluded if there were a) known or suspected distant metastases; b) concurrent malignancy or history of other malignancy; c) uncontrolled adverse conditions; d) allergy to chemotherapy; e) severe adverse reactions; f) MR contraindication; g) unsatisfactory MR images for diagnosis or measurement; h) incompliance with study procedure or withdraw from the study.

MR imaging project

Patients were scheduled to receive three MR examinations at three timepoints of within 7 days before NAC (baseline), within 3 days after completing the first NAC cycle (early timepoint) and within 3 days after completing all NAC cycles (late timepoint).

MR examinations were performed with a 1.5-T MR scanner using a dedicated four-channel phased array breast coil (Echospeed Plus with EXCITE II, GE Medical Systems, Milwaukee, USA). The study protocol consisted of a sagittal, fat-suppressed, T2-weighted pulse sequence; a sagittal, 3D Vibrant SPGR sequence for dynamic imaging (TR = 6.4 ms, TE = 3.0 ms, TI = 7.0 ms, flip angle = 10°, slice thickness = 4 mm without any inter-slice gap, matrix size = 256 × 256, field of view = 20–22 cm, NEX = 1, ZIP2, and scan time per acquisition = 68 s); and an axial, fat-suppressed, T1-weighted pulse sequence with enhancement. The Vibrant sequence was continuously repeated six times, with one precontrast and five post-contrast images for dynamic acquisition. The contrast agent (Gd-DTPA) was injected into the antecubital vein by a power injector at a rate of 2.0 ml/s based on patient body mass (0.2 mmol/kg), followed by a saline flush.

Image interpretation

All imaging analysis was performed on a post-processing workstation (AW4.2, GE Medical Systems, Milwaukee, USA). We analysis the lesion on the images of the first sequence after the contrast was injected. Three regions of interest (ROIs) were placed in the obvious enhanced areas, avoiding areas of non-enhancement within the lesion. It is ensured that there was no any significant movement of the breast on the images during the whole vibrant scan. The most characteristic enhanced ROI among the three was used for MRI parameters measurements. The size of ROI was between 4 and 9 pixels (Fig. 1). Two radiologists (Sun YS and Li YL with 18 and 10 years of diagnostic experience in breast MRI) worked together to identify the region of interest (ROI) and conducted measurements. In case of discrepancy, consensus was reached with a third radiologist (Cao K with 13 years of diagnostic experience). The radiologists were blinded to the clinical and pathological information.

The following MRI parameters were measured from MR images taken at three timepoints:

D_{max} (Unidimensional size): The largest diameter on the largest cross-section; $Area_{max}$ (Bidimensional size): The product of the diameter and its vertical diameter on the largest cross-section;
I (Positive enhancement integral): $= \sum_{i=0}^{n} Si$, Si: signal intensity, i: phase No.;
$Slope_{max}$ (Maximum slope of increase): = (Sa − Sb)/t, Sa, Sb: signal intensity of two timepoints of the fast-rising enhancement;
TIC (Time signal intensity curve): I: delayed; II: plateu; III: washout.

The changes of MRI parameters between early/late timepoint and baseline were calculated as follows:

$\Delta \mathbf{D_{max\text{-}early/late}}$: $(\mathbf{D_{max\text{-}early/late}} - \mathbf{D_{max\text{-}baseline}})/\mathbf{D_{max\text{-}baseline}} \times 100\%$

$\Delta \mathbf{Area_{max\text{-}early/late}}$: $(\mathbf{Area_{max\text{-}early/late}} - \mathbf{Area_{max\text{-}baseline}})/\mathbf{Area_{max\text{-}baseline}} \times 100\%$

$\Delta \boldsymbol{I_{early/late}}$: $(\boldsymbol{I_{early/late}} - \boldsymbol{I_{baseline}})/\boldsymbol{I_{baseline}} \times 100\%$

$\Delta \mathbf{Slope_{max\text{-}early/late}}$: $(Slope_{max\text{-}\mathbf{early/late}} - Slope_{max\text{-}\mathbf{baseline}})/Slope_{max\text{-}\mathbf{baseline}} \times 100\%$

$\Delta \mathbf{TIC_{early/late}}$: I (Ascending): I ~ II, II ~ III, I ~ III

II (Stable): I ~ I, II ~ II, III ~ III

III (Descending): III ~ I, III ~ II

Neoadjuvant chemotherapy regimens

All patients received neoadjuvant chemotherapy. The NAC regimens included four cycles of CEF (epirubicin 80–100 mg/m^2 Q21, cyclophosphamide 600 mg/m^2 Q21, 5-Fu 600 mg/m^2 Q21 or