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Evaluation of dynamic contrast-enhanced MRI in monitoring early response of locally advanced breast cancer to neoadjuvant chemotherapy

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Abstract ***Objective:*** The aim of our study was to assess the value of dynamic contrast-enhanced magnetic resonance imaging (DMRI) in predicting early response to neoadjuvant chemotherapy (NAC) in patients with locally advanced breast cancer (LABC) and to assess the accuracy of DMRI in evaluating residual disease after NAC. ***Methods:*** DMRI were performed in 43 women with LABC (44 lesions, all were invasive ductal carcinoma) before, after the first and final cycle of NAC. Tumour volume, early enhanced ratio (E1), maximum enhanced ratio (Emax), and maximum enhanced time (Tmax), dynamic signal intensity-time curve were obtained during treatment. Residual tumour volumes obtained using DMRI were compared with pathological findings to assess the accuracy of DMRI. ***Results:*** After 1st cycle of NAC, the mean volume of responders decreased insignificantly, $P > 0.05$, but after NAC, mean volume of residual tumor decreased significantly ($P < 0.01$). Morphology change: 29 cases showed a concentric shrinkage pattern while 7 cases showed a dendritic shrinkage pattern. Significant differences were found in E1, Emax and Tmax between responders and non-responders ($P < 0.05$). After 1st cycle of NAC, E1, Emax and Tmax of responders changed significantly ($P < 0.001$); while there is no significant change in non-responders ($P > 0.05$). After NAC, dynamic signal intensity-time types were changed in responders, and tended to be significantly flattening, while no significant change was found in non-responders. The residual tumour volume correlation coefficient between DMRI and pathology measurements was very high ($r = 0.866$, $P = 0.000$). ***Conclusion:*** DMRI is useful to evaluate the early response to NAC in LABC. The presence and volume of residual disease in LABC patients treated with NAC could be accurately evaluated by DMRI.

Key words breast carcinoma; magnetic resonance imaging (MRI); signal intensity-time curve; neoadjuvant chemotherapy (NAC); dynamic contrast-enhanced MRI (DMRI); locally advanced breast cancer (LABC)

Breast cancer is the most common cancer in women. With the optimizing of treatment strategy, survival rates for women with breast cancer are improving; but are still poorest for patients who present with late stage disease. Neoadjuvant chemotherapy (NAC) followed by surgery has become the standard treatment for patients with locally advanced breast carcinoma (LABC) [1]. Monitoring a patient's response to NAC accurately is very important. Dynamic contrast-enhanced magnetic resonance imaging (DMRI) permits evaluation of tumor neovasculature, thereby allowing accurate assessment of the pathophysiological response to therapy. In this study, we performed DMRI in 43 patients with LABC before and after 1st cycle of NAC, respectively. Our purpose was to find the value of DMRI in assessment of early response to NAC in LABC, so that we can aid eventual clinical effective planning. We also tried to evaluate residual disease after NAC by DMRI.

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Materials and methods

Patients

Forty-three patients with the pathologically proved diagnosis of LABC (stage II, III), who all had DMRI scans before and after 1st and final cycle of NAC between April 2008 and March 2009 in Cancer Hospital of Fudan University (Shanghai, China) were selected into our study. All the patients were women (age range, 34–69 years; average age, 48.0 years). Totally 44 lesions (23 lesions located in left, 19 located in right, 1 case with two lesions located in both side). All lesions were proved invasive ductal car-

cinoma pathologically. All the patients underwent NAC. Chemotherapy strategy were: taxol (80 mg/m^2) + Carboplatin [AUC = 2 mg • mL^{-1} • min^{-1}].

Instruments and methods

DMRI technique

All MRI examinations were undertaken on a 1.5 T scanner (GE Signa Twin Speed with excite) with a dedicated bilateral breast coil. Patients were scanned before, after 1st cycle and final cycle of NAC, respectively. All imaging sequenses were acquired in the sagittal or coronal plane. Sequences comprised: (FSE) T1WI (TR 480 ms, TE 10 ms, ETL = 2), T2WI with fat-suppressed (TR 3200 ms, TE 85 ms), slice thick 5 mm, slice gap 1 mm, matrix 256 × 160, next 4. The dynamic imaging sequence (volume imaging for breast assessment, VIBRANT): TR 3.9 ms, TE 1.1 ms, TI 14 ms, slice thick 3.2 mm, no space gap, flip angle 15o, FOV 32 cm, matrix 416 × 288, next 1. Sequence was acquired with a temporal resolution of 20 s before, during and after a bolus injection of 0.2 mmol/kg body weight of dimeglumine gadopentetate (Magnevist, Schering, Berlin, Germany) lasting no longer than 10 seconds, which was followed by a 10 mL saline flush.

Analysis of MR images

(1) Change of tumor volume: Volume calculations were derived from the post-contrasted VIBRANT sequence. ROIs were drawn around all areas of tumour on subtracted slices. The area of the pixels within all the ROIs was then summated and multiplied by 3D MIP (maximum intensity projection) to give the overall tumour volume. We calculated tumor volume before and after 1st cycle, final cycle of NAC, respectively. (2) Change of tumor morphology: We classified shrinkage pattern by concentric shrinkage and dendritic shrinkage pattern. Concentric shrinkage pattern, tumor shrinked to the centre, and to be isolated node finally; dendritic shrinkage pattern, tumor shrinked to be dendritic or multifocal lesions finally. (3) Enhanced parameter:E1,early enhanced ratio during the first phase after contrast-enhanced. Emax means the maximal enhanced ratio. Tmax means the time to be maximal signal intensity after enhanced. (4) Signal intensity-time curve: We used Functool software to analyse the enhanced lesion on SUN ADW4.3 workstation. The greatest mean maximum percentage enhanced area was chosen to be region of interest (ROI). The types of curves were classified to be I type (gradual enhanced), II type (plateu enhanced) and III type (wash-out enhanced) [2].

Pathological diagnosis after surgery

All the patients underwent surgery after the final cycle of NAC. The pathologic response to treatment was assessed at examination of postsurgical tumor specimens. Patients with no evidence of residual tumor after treatment were classified as pathologically complete responders. Patients with morphologic response but with residual tumors were classified as pathologically partial responders. Patients were classified as 'responders' based on total tumour volume reduction between the pre treatment measurement and the final treatment cycle visit. Patient's with a < 65% reduction in total tumour volume was categorized as "non-responders", while with a ≥ 65% reduction was categorized as "responders" [3, 4]. We compared the tumor volume measured by pathology with measured by DMRI. Tumor volume was underestimated by DMRI (results compared by pathology < 70%) and overestimated (> 30%) [3].

Statistical analysis

All analyses were performed with SPSS 16.0 statistical software; Deviation from normal distribution was demonstrated via the Kolmogorov-Smirnov test. The independent samples and paired sample *t*-tests when the parameters were normally distributed. The correlation between tumor volumes obtained with DMRI and pathologically was analyzed with Pearson's correlation test. *P* value of < 0.05 was considered to be statistically significant.

Results

Change of tumor volume measured by DMRI

Tumor volumes were 27.4 ± 18.4 cm^3, 24.4 ± 16.5 cm^3, 10.5 ± 8.6 cm^3, before NAC, after 1st and final cycle of NAC, respectively. Among the total 44 lesions, 36 cases were responders (including CR 3, PR 33) 8 cases were non-responders. After 1st cycle of NAC, the median of tumor volume reduction was 0.8 cm^3, $\chi^2 = 0.55$, $P > 0.05$, there was no significant difference. After NAC, tumor volume decreased significantly (median 18.5 cm^3, $\chi^2 = 34.03$, $P < 0.01$). While volume of non-responders changed insignificantly (Table 1).

Change of tumor morphology on DMRI

Among 36 responders, 29 lesions (80.6%) showed a concentric shrinkage pattern (Fig. 1), 7 lesions (19.4%) showed a dendritic shrinkage pattern (Fig. 2). Non-responders showed no significant reduction or partially developed.

Change of enhanced parameters

Before NAC, significant differences were found in E1, Emax and Tmax between responders and non-responders. ($P < 0.05$). After 1st cycle of NAC, E1, Emax of responders decreased significantly, and Tmax increased significantly ($P < 0.01$); while there is no significant change in non-responders ($P > 0.05$; Table 2).

Table 1 Change of tumor volume during NAC on DMRI (median, cm^3)

Group	Lesion number	Before chemotherapy	After 1st cycle of NAC	After final cycle of NAC
Responders	36	23.4	22.6	4.9
Non-responders	8	24.1	23.6	20.1

Table 2 Change of enhanced parameters of 44 lesions during NAC

Group	Lesion number	Before NAC			1st cycle of NAC later		
		E1 (%)	Emax (%)	Tmax (s)	E1 (%)	Emax (%)	Tmax (s)
Responders	36	116.8 ± 30.1[a]	175.6 ± 33.1[a]	116.5 ± 10.3[a]	66.3 ± 20.5[b]	131.0 ± 34.9[b]	178.4 ± 13.5[b]
Non-responders	8	82.6 ± 21.7	144.0 ± 29.5	179.4 ± 13.5	109.1 ± 44.3	156.0 ± 36.2	178.6 ± 19.5

Group	After NAC		
	E1 (%)	Emax (%)	Tmax (s)
Responders	47.3 ± 18.8[b]	91.8 ± 41.7[b]	304.9 ± 15.1[b]
Non-responders	111.2 ± 36.8	163.0 ± 34.9	134.9 ± 11.8

Compared with non-responders, [a] $P < 0.05$; Compared with pre-NAC, [b] $P < 0.01$

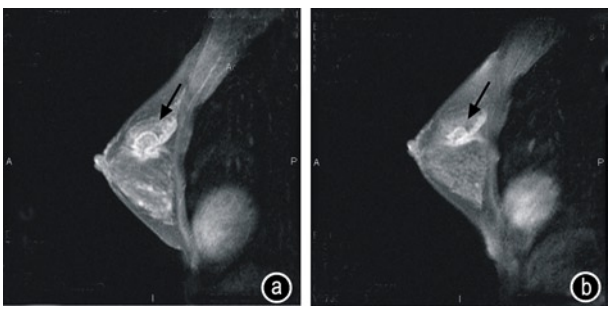

Fig. 1 MRI scan picture of breast cancer (arrow). (a) Before; (b) After neoadjuvant chemotherapy (concentric shrinkage pattern)

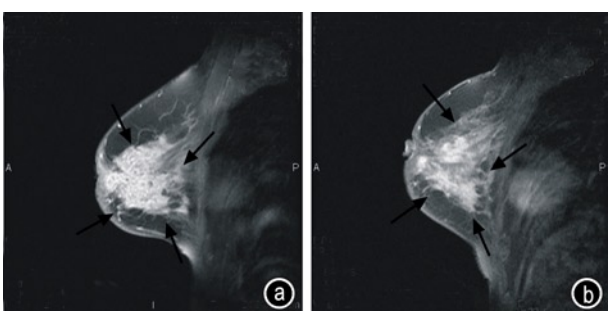

Fig. 2 MRI scan picture of breast cancer (arrow). (a) Before; (b) After neoadjuvant chemotherapy (dendritic shrinkage pattern)

Change of SI-time curve

Dynamic signal intensity-time curve types of responders before NAC were classified, I type ($n = 5$), II ($n = 11$), III ($n = 20$), mostly were wash-out and plateu type (occupied 86.1%). After 1st cycle of NAC, SI-Time curve types were changed (17 cases of I type, 12 of II type, 7 of III type), mostly were gradual enhanced type, Emax decreased distinctly (Fig. 3); When NAC was finished, SI-time curve type changed to be I type ($n = 23$), II ($n = 8$), III ($n = 5$) tended to be significantly flattening (I type occupied 63.9%), while in non-responders' group, before NAC SI-time curves were classified by I type ($n = 2$), II type ($n = 5$), III ($n = 1$), mostly were plateu type. After 1st cycle of NAC, curve were changed to be I type ($n = 2$), II type (n = 4), III ($n = 2$), Emax increased (Fig. 4). After NAC, there were I type ($n = 3$), II type ($n = 3$), III ($n = 2$), mostly were gradual enhanced type (63.9%).

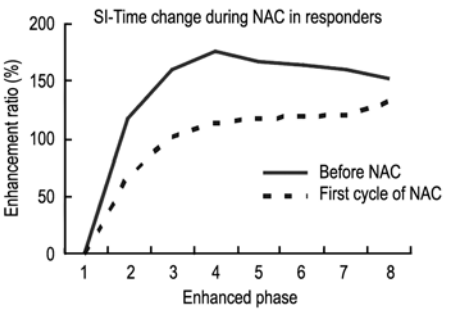

Fig. 3 Change of SI-Time curve before and after 1st cycle of NAC in responders

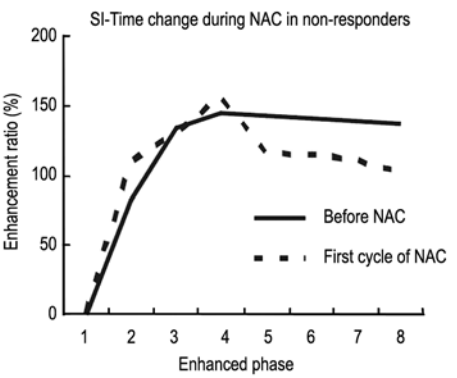

Fig. 4 Change of SI-Time curve before and after 1st cycle of NAC in non-responders

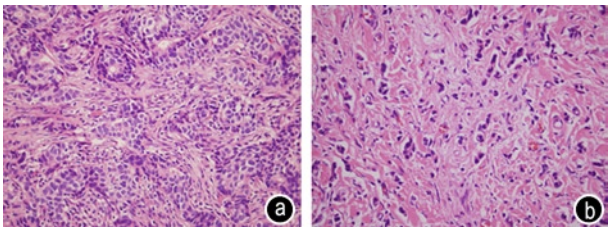

Fig. 5 The histopathological examination of invasive ductal carcinoma in responder. (a) Before; (b) After neoadjuvant chemotherapy (HE staining × 200). Before NAC, tumor with enriched cellularity. After NAC, tumor cell degenerated to be fibrosis

Compare of pathological slices before and after NAC

Before chemotherapy, enriched tumor cellularity were found; after NAC, tumor cells degenerated to be fibrosis (Fig. 5).

Compare of tumor volume measure by histopathology and DMRI

After NAC, tumor volume measured by DMRI was 4.0 cm^3 (median), measured by histopathology was 4.50 cm^3 (median). Among those cases, DMRI underestimated 3 lesions, 2 lesions were overestimated. The residual tumour volume correlation coefficient between DMRI and pathology measurements was very high (r = 0.866, P < 0.01).

Discussion

Neoadjuvant chemotherapy has become the standard treatment for patients with locally advanced breast cancer before surgery. Knowledge of a patient's response to neoadjuvant therapy is essential and has important consequences for optimal and cost-effective management [4]. Patients can potentially undergo toxic therapy while their disease remains active and unresponsive. Additionally accurate response assessment also aids eventual surgical planning, facilitating the correct surgical procedure to be undertaken [5].

Dynamic contrast-enhanced MRI (DCE-MRI) appears not only to be applied to diagnose breast carcinoma but also provide quantitative information that reflects early changes in tumors due to chemotherapy, thereby allowing an assessment of the pathophysiological response to NAC, which occur prior to any volume changes [5, 6]. Response assessments are usually based on morphologic change. On RECIST (Response Evaluation Criteria in Solid Tumors) criterion, therapy responses were evaluated by measuring the maximum diameter of tumor [7]. This is also conventional method to make response assessments of solid tumors. Present researches indicated that it will be more effective if we used 3D volume change to make the assessments [8], especially for irregular or multifocal lesions [5, 6, 9]. MRI enables a true three-dimensional delineation of lesions. Implementing distinctly different imaging sequences already allows a considerable tissue characterization regarding its proton/water or fatty tissue content. In our study, we used 3D MIP to calculate tumor extent from different angles, so that we can recognize small residual lesions [10]. Our results showed that tumor volumes didn't change significantly after 1st cycle of NAC whether in responders or non-responders. Therefore, tumor volume didn't change much enough to be detected by radiologic examinations at early phase of NAC.

We classified shrinkage pattern by concentric shrinkage and dendritic shrinkage pattern. In responders' group, 80.6% of tumors showed concentric shrinkage pattern, tumor shrinked to the centre, and to be isolated node finally, always with clear margins; while 19.4% showed dendritic shrinkage pattern, tumor shrinked to be dendritic or multifocal lesions finally, with irregular and blurred margins. Residual tumor clusters were found at tumor region. Residual lesions with concentric shrinkage were easily to evaluate the extent, so that breast conserving surgery can be considered. While after tumor excision of tumors with dendritic shrinkage pattern, positive margins are always found, so that only radical mastectomy can be considered. Therefore, accurate assessment of tumor shrinkage pattern will aid to choose reasonable surgery strategy.

Compared with conventional radiological examinations, DMRI can accurately recognize residual multifocal or multicenteric lesions via the different enhancement. But because of different mechanism of chemotherapy drugs, tumor shrinkage patterns are complex. So it would be inevitably to overestimate or underestimate the residual lesions.

Cancers are generally hypervascular and are detected on breast MRI as contrast-enhancing lesions. But disappearance of early enhancement in tumor vessels didn't mean completely degeneration of tumor cells [11], because false negative results may induce underestimate of residual lesions extent post-chemotherapy [5, 6]. In our study, those three lesions underestimated were all with dendritic shrinkage pattern. After NAC, former enhanced tumor shrinkage due to treatment became scattered spotted enhancement, and tumor margins were not clear because of a very low contrast-to-noise ratio or very slow rate of contrast medium uptake. Thus it would resulted in underestimate. While we could see degenerated residual tumor scattered in local breast tissue. We also have two cases overestimated, which maybe result from local inflammation around degenerated tumor cells and remaining neovascularization after NAC, those would account for obvious large-scale enhancement on DMRI [8].

DMRI is highly sensitive method for monitoring thera-

peutic success in cases of extensive or recurrent carcinoma treated with NAC, it's also credible radiological methods to evaluate residual carcinoma [8, 11]. Response assessments are usually based on volume. However, changes in volume occur after physiological changes in the tumour [12, 13]. Therefore, it's inaccurate only to monitor tumor volume change, and not enough to assess therapy response and prognosis.

New blood vessels must be developed to supply nutrients and oxygen in tumors, this process is termed neoangiogenesis. These new blood vessels are excessively permeable resulting in superior contrast enhancement compared to normal tissue. DMRI permits evaluation of tumour neovasculature, thereby allowing an assessment of the pathophysiological response to therapy, which occur prior to any volume changes.

In our study, after first cycle of treatment, a significant reduction from the baseline results were noted for the enhancement degree (E1, Emax) for eventual responders, and SI-time curve changed from typical malignant phenotype to less aggressive phenotype. E1 and Emax decreased significantly, and Tmax prolonged.

After NAC, partial residual lesions were almost no-enhanced. It indicated that pharmacokinetic modelling of tumor tissues tended to be character of benign lesions after effective chemotherapy [10, 11]. George [10] and Englmeier [14] found that reduction of E1 and Emax resulted from firstly, by the loss or reduction of immature tumour vessels, on the other hand, matureing of tumor vessels due to permeability reduced. Once the level of these factors was reduced, following sufficient tumour cell kill, these factors reduce and the tumour vessels can mature resulting in reduced permeability. All of these changes resulted in changes of pharmacokinetic modelling of DCE-MRI data.

In our results, pathological slices prior and post NAC in responders showed that: after effective chemotherapy, tumor cells receded apparently and tumor tissues degenerated to be fibrosis. These results proved that blood supply in tumors decreased significantly. Knopp's study [15] showed that after NAC, SI-time curve changed earlier than morphology change, which was the same as our results. But Knopp reported that pharmacokinetic parameters of breast carcinoma changed after the second cycle of NAC, while we found significant change after first cycle, meanwhile tumor volumes didn't change distinctly.

Our results showed that enhancement degrees of responders were significantly higher than those of non-responders prior to NAC, and SI-time curve were mostly wash-out type. It maybe because there were more enriched neoangiogenesis in tumor tissues of responders, so that showed early and rapid enhancement. However, in non-responders neoangiogenesis was relatively less, and vascular permeability were lower, with weak perfusion in tumor tissues. All of these made less contrast medium uptake in tumors, on the other hand, resulted in less concentration of locally chemotherapy drug, and weakened effect of drugs [16].

We acknowledge that limitations may affect our study findings. All the patients in our study were locally advanced breast carcinoma (LABC), and all were invasive ductal carcinoma (IDC), used the same chemotherapy strategy. But some breast cancers with special pathological phenotype have different interior structure, and their blood supply are also different, all of these maybe show different pharmacokinetic characteristic on DMRI. Meanwhile, different chemotherapy strategy impacted on tumor vessels may also lead to the difference between blood pharmacokinetic parameters of tumors on DMRI.

In conclusion, compared with conventional radiological examinations, DMRI can evaluate tumor morphology change after pre- surgery NAC, and accurately evaluate residual tumor extent. Therefore, DMRI can differentiate responders from non-responders at an early time point during treatment via measuring dynamic contrast enhancement parameters. At present, DMRI is reported to be one of the most sensitive, effective radiological examinations monitoring early response of patients with breast carcinoma to NAC.

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