Role of Diffusion-Weighted Magnetic Resonance Imaging in Prediction of Pathological Complete Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer and Its Molecular Subtypes

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Keywords
► apparent diffusion coefficient
► diffusion-weighted imaging
► locally advanced breast cancer
► neoadjuvant chemotherapy
► pathological complete response

Abstract

Purpose The aim of this study was to evaluate the role of apparent diffusion coefficient (ADC) and hence diffusion-weighted imaging in prediction of pathological complete response (pCR) to neoadjuvant chemotherapy (NACT) in locally advanced breast cancer (LABC) and its molecular subtypes.

Methods In this tertiary hospital-based prospective study, 30 patients aged 30 to 65 years, having clinically/cytologically diagnosed LABC, were included. Magnetic resonance imaging (MRI) was done to obtain prechemotherapy ADC (ADCpre), postchemotherapy ADC (ADCpost), change in ADC (ΔADC), and ΔADC% for each tumor and its subtype. Postsurgical pCR was used as the reference standard for determining tumor response. All four ADC parameters were compared between pCR and non-pCR groups.

Results Of the 30 patients, 19 (63.3%) patients showed pCR, while 11 (36.7%) patients did not. The pCR group showed significantly lower mean ADCpre (p < 0.001) and higher mean ADCpost (p < 0.05), ΔADC, and ΔADC% (p = 0.000) than non-pCR group. The best cutoff values to differentiate responders from nonresponders with receiver operating characteristic curve analysis of ADCpre, ADCpost, and ΔADC% were 0.98 × 10⁻³ mm²/s (68.4% sensitivity, 63.6% specificity), 1.31 × 10⁻³ mm²/s (68.4% sensitivity, 63.6% specificity), and 25% (84.2% sensitivity, 90.9% specificity), respectively. Human epidermal growth factor receptor 2 (HER2)-enriched subtype showed significant difference in mean ADCpre (p = 0.045), while triple-negative subtype showed significant differences in mean ADCpost (p = 0.032) and mean ΔADC (p = 0.019) between the two groups.

Conclusion ADCpre, ADCpost, and ΔADC can predict pCR to NACT in LABC. Among molecular subtypes, ADCpre was predictive only in HER2-enriched subtype, while ADCpost and ΔADC were predictive only in triple-negative subtype.
Introduction

Neoadjuvant chemotherapy (NACT) is routinely used in inoperable locally advanced breast cancer (LABC) to downstage the tumor and allow breast conservation surgery. However, NACT is associated with high toxicity and undesirable side effects. Therefore, reliable prediction of response to NACT is of utmost importance to avoid administration of unnecessary chemotherapeutic agents and offer tailored treatment.

Diffusion-weighted magnetic resonance imaging (DW-MRI) has shown promising role in prediction of response to NACT in patients with LABC, and pathological complete response (pCR) has been used as the reference standard for determining response to NACT. While some studies have reported the role of diffusion-weighted imaging (DWI) in pretreatment prediction of response to NACT, others have shown its role in prediction of pCR just after a few cycles of NACT, even earlier than morphological alteration. However, till date there is no clear consensus on practice guidelines for prediction of tumor response to NACT using DWI due to variations in NACT regimen, optimal timing for response assessment, type of breast cancer cases included, definition of regions of interest (ROIs) for calculation of apparent diffusion coefficient (ADC), and reference standard used to determine response to NACT (clinical/radiological/pathological).

The aim of this study was therefore to evaluate the role of ADC and hence DWI in prediction of pCR to NACT in LABC and its various molecular subtypes.

Material and Methods

Patient Selection

This was a hospital-based prospective study approved by institutional ethical committee. After written and informed consent, 83 patients aged 30 to 65 years, having clinically or cytologically diagnosed LABC, were enrolled. Patients who had metastasis at the time of presentation, comorbidities rendering them unfit for chemotherapy or surgery, undergone any biopsy or invasive procedure in breasts within the last 6 weeks, prior history of cancer over same or other site, synchronous malignancy, chemotherapy or radiotherapy, or contraindication to MRI or gadolinium-based contrast agent, or in whom histopathological investigation came out to be benign, who were relapsed or recurrent cases, or pregnant/lactating females were excluded from the study. Those patients who had undergone any diagnostic or therapeutic procedure involving breasts at another institution during the period of this study were also excluded. Finally, 30 patients were included in the study.

For all the patients, clinical details such as age, marital status, menstrual history, and laterality and quadrant of the mass were noted down. Work-up was done to rule out metastatic disease and to assess the fitness of the patients for chemotherapy. Multiparametric MRI was done for tumor assessment. The core biopsies were performed using a 20-gauge disposable core biopsy needle (Bard Max-Core 20GX16 cm Disposable Core Biopsy Instrument, MC2016; Becton, Dickinson and Company, Gurgaon, Haryana, India) with 16-cm needle length, 22-mm penetration depth, and 1.8-cm sample notch length. The sample obtained was sent in 10% formalin for histopathological examination (HPE) for confirmation of diagnosis of LABC and determination of stage and molecular subtype of the tumor. NACT was then administered to the patients for three cycles, and post-NACT MRI was also done. This was followed by breast conservation surgery or modified radical mastectomy as was required in the best interest of the patient. Postsurgery, the specimen was sent for final HPE.

MRI

MRI was done using 1.5T Superconducting magnet (MAGNETOM Avanto; Siemens Medical System, Erlangen, Germany) using a dedicated breast coil for optimal resolution and signal-to-noise ratio. The sequences included axial T2-weighted (T2W) fat-suppressed, precontrast axial T1-weighted, dynamic contrast-enhanced (DCE) imaging, and DWI. Postcontrast series was performed immediately after administration of gadopentetate dimeglumine (Magnevist) at a rate of 3 mL/s with a dose of 0.1 mmol/kg of body weight, followed by a flush of 10 mL of normal saline. Diffusion-weighted images were obtained using a short T1 inversion recovery. Scan parameters were as follows: time to repeat (TR)/time to echo (TE), 8,100/91 ms; slice thickness, 4 mm; b-values, 50, 500, and 800 s/mm²; field of view (FOV), 380 mm. ADC maps were automatically generated with the manufacturer’s software.

Image Analysis

The diagnosis of the tumor was made when a focal lesion with altered signal intensity was visualized on T2W image, replacing the normal architecture of breast parenchyma, which showed restriction of diffusion on ADC map, as well as high-signal intensity on DWI. Fast enhancement in initial phase with washout in delayed phase was considered as an adjunct criterion, the presence of which was not deemed mandatory.

After data acquisition, all images were transferred to an independent offline workstation for analysis. The pre-NACT and post-NACT ADC values were documented. On the ADC maps, the ROIs in the tumors were manually drawn to include at least three-fourths of the solid portion of the tumor (Fig. 1). The ADC values were assessed three times at the same site and a mean was calculated. The regions showing morphology suggestive of necrotic changes in the tumors and adjacent vascular structures, on the basis of DCE MRI findings, were excluded from the ROI tracings. In cases of complete tumor regression on post-NACT images, ROIs were drawn over the projected area of previously documented tumor bulk, to avoid missing any microscopically residual tumor.

NACT Regimen

Patients were administered three cycles of CAF regimen (cyclophosphamide, 500 mg/m²; doxorubicin, 50 mg/m²; and 5-fluorouracil, 500 mg/m² body surface area), repeated every 21 days.
Histopathological Analysis (Pre-NACT and Postsurgery)

Information recorded were as follows:

- Three main molecular markers for breast cancer: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2); thus four main molecular subtypes (luminal A, luminal B, HER2-enriched, and triple-negative).
- Pathological response: Per the Food and Drug Administration of the United States (U.S. FDA) rationale and guidelines, pCR was used as the reference standard for determining response to NACT in our study and was defined as “the absence of residual invasive cancer on haematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system).”¹¹ Patients were accordingly classified into pCR and non-pCR groups.

Statistical Analysis

The statistical analysis was done using SPSS, version 20.0. All the clinical, radiological, pathological, and related parameters studied during observation period were compared using different tests for parametric and nonparametric variables. A p-value of <0.05 was considered statistically significant.

Results

Of 30 patients in our study, 19 (63.3%) showed pCR (pCR group), while 11 (36.7%) did not (non-pCR group).

Most patients in pCR group were of 40 to 60 years (17/19, 89.5%), and in non-pCR group 5 of 11 (45%) patients were below 40 years. Also, 57.9% (11/19) of pCR group and 54.5% (6/11) of non-pCR group were postmenopausal. Most tumors in pCR and non-pCR groups were right-sided (11/19 [57.9%] and 8/11 [72.7%], respectively) and presented in upper-outer quadrant of breasts (10/19 [52.6%] and 6/11 [54.5%], respectively).

The patients presented with stage IIIA and IIIB breast cancer. The pCR group had more tumors in stage IIIB (16/19, 84.2%), while non-pCR group had more tumors in stage IIIA (8/11, 72.7%). Invasive ductal carcinoma was noted in all cases of pCR group and all except one case of non-pCR group that had invasive lobular carcinoma. Most common molecular subtype in pCR group was triple-negative (8/19, 42.1%) (►Table 1). However, non-pCR group had luminal A and luminal B as the most common subtypes, which were present in equal numbers (4/11, 36.4% each).

The pCR group showed significantly lower (p < 0.001) mean prechemotherapy ADC value (mean ADCpre) but significantly higher (p < 0.05) mean postchemotherapy ADC value (mean ADCpost) than that of the non-pCR group (►Table 2).

The best ADCpre cutoff with which to differentiate pCR from non-pCR group with receiver operating characteristic (ROC) curve analysis was 0.98 × 10⁻³ mm²/s, which yielded a

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Pathological response</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pCR</td>
<td>Non-pCR</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Luminal A</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Luminal B</td>
<td>5</td>
<td>55.6</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>4</td>
<td>80.0</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>8</td>
<td>80.0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>63.3</td>
</tr>
</tbody>
</table>

Abbreviations: HER2, human epidermal growth factor receptor 2; pCR, pathological complete response.
sensitivity of 68.4% and a specificity of 63.6% (►Fig. 2). The area under the empirical ROC curve (AUC) was 0.727 (95% confidence interval: 0.539–0.916) for differentiation of pCR from non-pCR groups.

The best ADC\textsubscript{pre} cutoff with which to differentiate pCR from non-pCR group with ROC curve analysis was 1.310 $\times$ 10\textsuperscript{−3} mm\textsuperscript{2}/s, yielding a sensitivity of 68.4% and a specificity of 63.6% (►Fig. 3). The AUC was 0.734 (95% confidence interval: 0.537–0.932) for differentiation of pCR from non-pCR groups.

Overall, there was a significant increase in mean ADC values postchemotherapy. Mean ADC values for all patients (both pCR and non-pCR groups) increased significantly from 0.9977 $\pm$ 0.12489 $\times$ 10\textsuperscript{−3} mm\textsuperscript{2}/s before chemotherapy to 1.2877 $\pm$ 0.17534 $\times$ 10\textsuperscript{−3} mm\textsuperscript{2}/s after chemotherapy (p < 0.001). However, the mean $\Delta$ADC (ADC\textsubscript{post} − ADC\textsubscript{pre}) and mean $\Delta$ADC\% ($\Delta$ADC/ADC\textsubscript{pre} $\times$ 100) of the pCR group were significantly higher than those of non-pCR group (p = 0.000) (►Table 2). ROC curve analysis showed that the best mean $\Delta$ADC\% cutoff value for predicting pCR was 25%, and AUC was 0.938 (95% confidence interval: 0.850–1.000). This cutoff value showed 84.2% sensitivity, 90.9% specificity, 94.1% positive predictive value (PPV), 76.9% negative predictive value (NPV), and 86.7% accuracy (►Fig. 4).

Discussion

DWI measures the mobility of water molecules in tissues and thus reflects the cellularity and integrity of cell membranes. Tumor response to NACT results in decrease in cellularity and increase in ADC values, and thus DWI helps in assessment of tumor response.\textsuperscript{2,3,6} Our findings were in agreement with this observation made by previous studies.

Of 30 patients in our study, 63.3% showed pCR, while 36.7% did not. The mean ADC\textsubscript{pre} of the pCR group was 0.98 $\times$ 10\textsuperscript{−3} mm\textsuperscript{2}/s, and the AUC was 0.727 (95% confidence interval: 0.539–0.916). 94.1% positive predictive value (PPV), 76.9% negative predictive value (NPV), and 86.7% accuracy (►Fig. 2).

Among molecular subtypes, only HER2-enriched showed a significant difference in mean ADC\textsubscript{pre} (p = 0.045), while only triple-negative showed significant differences in mean ADC\textsubscript{post} (p = 0.032) and mean $\Delta$ADC (p = 0.019) between pCR and non-pCR groups (►Tables 3, 4, 5).

Table 2 Comparative analysis of ADC parameters between pCR and non-pCR groups of LABC

<table>
<thead>
<tr>
<th>ADC parameters</th>
<th>pCR, mean ± SD</th>
<th>Non-pCR, mean ± SD</th>
<th>t-value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ADC\textsubscript{pre}</td>
<td>0.9568 ± 0.10274</td>
<td>1.0682 ± 0.13265</td>
<td>−2.570</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean ADC\textsubscript{post}</td>
<td>1.3453 ± 0.10972</td>
<td>1.1882 ± 0.22427</td>
<td>2.586</td>
<td>0.015</td>
</tr>
<tr>
<td>Mean $\Delta$ADC</td>
<td>0.3884 ± 0.13917</td>
<td>0.1200 ± 0.13689</td>
<td>5.120</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean $\Delta$ADC%</td>
<td>41.9762 ± 18.53778</td>
<td>10.7796 ± 13.93040</td>
<td>4.833</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Abbreviations: ADC, apparent diffusion coefficient; ADC\textsubscript{post}, postchemotherapy ADC; ADC\textsubscript{pre}, prechemotherapy ADC; $\Delta$ADC, change in ADC; pCR, pathological complete response; SD, standard deviation.
latter shows poor response to cytotoxic chemotherapy due to two main reasons. First, it is poorly perfused, which reduces the delivery of chemotherapeutic agents to the tumor. Second, cancer cells near necrotic region have slower metabolism due to hypoxic environment and are thus less chemotherapy-sensitive. This indicates the potential of pre-NACT ADC to differentiate responders from nonresponders, similar to that shown by Park et al. However, few studies are not in agreement with this observation.

In our study, the best ADC<sub>pre</sub> cutoff with which to differentiate pCR from non-pCR group with ROC curve analysis was 1.31 × 10<sup>-3</sup> mm<sup>2</sup>/s, which yielded a sensitivity of 68.4% and a specificity of 63.6%. However, higher value of 1.17 × 10<sup>-3</sup> mm<sup>2</sup>/s (94% sensitivity and 71% specificity) for the same was determined by Park et al. This discrepancy may be due to differences in the sample size, demographic characteristics of the population, chemotherapy regimens, b-values, and criteria used to determine tumor response.

Our data also showed that the mean ADC<sub>post</sub> of the pCR group was significantly higher than that of non-pCR group (p < 0.05), similar to Hu et al (p = 0.002). We also determined 1.310 × 10<sup>-3</sup> mm<sup>2</sup>/s as the best ADC<sub>post</sub> cutoff value to differentiate pCR from non-pCR group with ROC curve analysis, yielding a sensitivity of 68.4% and a specificity of 63.6%.

In our study, mean ADC values for all patients (both pCR and non-pCR groups) increased from before chemotherapy to after chemotherapy (p < 0.001). However, the change in ADC (mean ΔADC and mean ΔADC%) was significantly higher in the former (p = 0.000). This indicates the role of effective cytotoxic chemotherapy that reduces cellularity and cell membrane integrity, thus creating a less restrictive environment for the diffusing water molecules.

Our results are in concordance with the previous studies, including "The ACRIN 6698 multicenter trial" that showed that change in tumor ADC is a noninvasive and quantitative imaging biomarker of

**Table 3** Mean prechemotherapy ADC values in pCR and non-pCR groups of molecular subtypes of LABC

<table>
<thead>
<tr>
<th>Molecular subtypes</th>
<th>pCR, mean ± SD (×10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</th>
<th>Non-pCR, mean ± SD (×10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>N = 2 0.9800 ± 0.05657</td>
<td>N = 4 1.0450 ± 0.14526</td>
<td>0.592</td>
</tr>
<tr>
<td>Luminal B</td>
<td>N = 5 1.0400 ± 0.12708</td>
<td>N = 4 1.0700 ± 0.17108</td>
<td>0.771</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>N = 4 0.8825 ± 0.08261</td>
<td>N = 1 1.1900 ± 0.00000</td>
<td>0.045</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>N = 8 0.9363 ± 0.07615</td>
<td>N = 2 1.0500 ± 0.08485</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Abbreviations: HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; SD, standard deviation.

**Table 4** Mean postchemotherapy ADC values in pCR and non-pCR groups of molecular subtypes of LABC

<table>
<thead>
<tr>
<th>Molecular subtypes</th>
<th>pCR, mean ± SD (×10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</th>
<th>Non-pCR, mean ± SD (×10&lt;sup&gt;-3&lt;/sup&gt; mm&lt;sup&gt;2&lt;/sup&gt;/s)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>N = 2 1.3500 ± 0.07071</td>
<td>N = 4 1.1300 ± 0.33247</td>
<td>0.431</td>
</tr>
<tr>
<td>Luminal B</td>
<td>N = 5 1.2900 ± 0.17292</td>
<td>N = 4 1.1925 ± 0.20056</td>
<td>0.458</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>N = 4 1.3725 ± 0.13175</td>
<td>N = 1 1.3200 ± 0.00000</td>
<td>0.745</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>N = 8 1.3650 ± 0.05155</td>
<td>N = 2 1.2300 ± 0.12728</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Abbreviations: HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; SD, standard deviation.
response in women undergoing NACT for breast cancer.\textsuperscript{4,6} However, Partridge et al involved in the ACRIN trial did not observe a significant difference in change in ADC between responders and nonresponders until midtreatment (12 weeks posttreatment) due to the exclusion of patients with low-risk HR+/HER2− disease and use of a variety of treatment regimens.\textsuperscript{4}

ROC curve analysis in this study showed that the best mean ΔADC\% cutoff value for predicting pCR after three cycles of NACT was 25%, and the AUC was 0.938 (95% confidence interval: 0.850–1.000). This cutoff value showed 84.2% sensitivity, 90.9% specificity, 94.1% PPV, 76.9% NPV, and 86.7% accuracy. Pereira et al also reported ΔADC\% cutoff value as 25% for predicting pCR with AUC of 0.840 (95% confidence interval: 0.728–0.953).\textsuperscript{3} Their cutoff value that showed 83% sensitivity, 84% specificity, 77% PPV, and 89% NPV was calculated after the first cycle of NACT, and there was considerable heterogeneity among the NACT regimens.

In our study, only HER2-enriched showed a significant difference in mean ADC\textsubscript{pre} (p = 0.045), while only triple-negative showed significant differences in mean ADC\textsubscript{post} (p = 0.032) and mean ΔADC (p = 0.019) between pCR and non-pCR groups. The exploratory analysis by Partridge et al suggested higher predictive performance of ΔADC in HR+/HER2− tumors.\textsuperscript{4} They highlighted the clinical importance of their observation as these tumors less often achieve pCR. Pereira et al found no statistically significant difference between the ADC\textsubscript{pre} values in relation to histological grade and molecular subtypes but showed that expression of PR and ER contributed to lower ADC (p = 0.02), while expression of HER-2 had no effect on ADC.\textsuperscript{3}

Our study had several limitations. First, ADC values were measured manually. However, compound parametric maps would have been more accurate. Second, we did not perform MRI after each cycle of chemotherapy, which could have evaluated the role of DWI in early response prediction and timely alteration of ongoing NACT regimen. Third, a small sample size was used; studies with larger sample size are needed for validation of our results. Fourth, it was a tertiary hospital-based study and therefore results cannot be generalized at the community level.

However, the key strengths of our study were the homogeneity of the clinical, radiological, and pathological assessments, uniform chemotherapeutic regimen, and use of pCR as the reference standard for determining tumor response to NACT that avoided any potential bias while measuring ADC values.

An individual-based “tumor response prediction tool” using ADC, molecular subtype, genetic markers (Ki67), type of NACT regimen, and timing of response assessment after NACT cycle is the need of the hour for tailored management of LABC. Timely detection of tumor resistance to a particular NACT regimen will allow timely alteration in the treatment protocol. This would not only save the patient from unnecessary side effects of a drug but also help in adequate debulking or downstaging of the tumor, thus allowing less radical surgery and maximum post-surgery response.

### Conclusion

We conclude that ADC\textsubscript{pre}, ADC\textsubscript{post}, and ΔADC can predict pCR to NACT in LABC. Among molecular subtypes, ADC\textsubscript{pre} was predictive only in HER2-enriched subtype, while ADC\textsubscript{post} and ΔADC were predictive only in triple-negative one.

### Funding

None.

### Conflicts of Interest

There are no conflicts of interest.

### References

5. Sharma U, Danishad KKA, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging

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**Table 5** Mean ΔADC values in pCR and non-pCR groups of molecular subtypes of LABC

<table>
<thead>
<tr>
<th>Molecular subtypes</th>
<th>pCR, mean ± SD (× 10^{-3} mm²/s)</th>
<th>Non-pCR, mean ± SD (× 10^{-3} mm²/s)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>N = 2 0.3700 ± 0.01414</td>
<td>N = 4 0.0850 ± 0.19157</td>
<td>0.119</td>
</tr>
<tr>
<td>Luminal B</td>
<td>N = 5 0.2500 ± 0.06595</td>
<td>N = 4 0.1225 ± 0.14523</td>
<td>0.120</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>N = 4 0.4900 ± 0.17301</td>
<td>N = 1 0.1300 ± 0.00000</td>
<td>0.160</td>
</tr>
<tr>
<td>Triple-negative subtype</td>
<td>N = 8 0.4288 ± 0.11370</td>
<td>N = 2 0.1800 ± 0.04243</td>
<td>0.019</td>
</tr>
</tbody>
</table>
of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. NMR Biomed 2009;22 (01):104–113