Evidence-based Rating: B

Personal Rating: 3

Early Prediction of Response to Neoadjuvant Chemotherapy Using Parametric Response Maps for MR Imaging

Neoadjuvant chemotherapy has become a commonly used treatment modality for patients diagnosed with stage II and higher breast cancers that need some form of chemotherapy in the treatment. One great benefit of giving neoadjuvant chemotherapy before surgery compared to surgery followed by adjuvant chemotherapy is the opportunity to monitor the response of each individual patient to different drug regimens, which can allow for the early termination of ineffective drugs to avoid unnecessary toxicity, and also for the earlier switch to new regimens for the effective drugs to work sooner. In order to achieve this goal, reliable imaging methods that can make accurate prediction of final treatment outcome at an early time after a regimen is administered is critically needed. Many imaging studies using different approaches have been performed; e.g. dynamic-contrast enhanced-MRI (DCE-MRI),(1) MR spectroscopy,(2) and functional optical imaging.(3) Although some promising results have been demonstrated, so far there is no method that has been validated to give accurate prediction at a very early time after 1 cycle of chemotherapy, before the tumor shrinks substantially.

In this article Cho and colleagues performed a well-designed prospective clinical study to evaluate the change of several quantitative parameters after 1 cycle of chemotherapy for predicting final treatment outcome. These parameters included the 3-dimensional tumor volume,

the tumor size (as the longest dimension), and the DCE-MRI pharmacokinetic parameters: Ktrans, kep and ve. A new method “parametric response mapping (PRM)” was also applied to measure the percentage of pixels that show increase and decrease of signal intensities after chemotherapy, and use them as response predictors. After the patient completed NAC, a careful pathological examination based on the Miller-Payne system that evaluated the distribution of residual tumor cells was performed to assign the response to scores of 1-5, with score 5 as the pathologic complete response (pCR). Two different analyses were performed: to differentiate between pCR (N=6 cases) and npCR (N=42); and to differentiate between good responders (Miller-Payne score of 3, 4, or 5, N=38) and poor responders (score of 1 and 2, N=10).

In order to measure DCE-MRI parameters accurately, a sophisticated DCE acquisition protocol with a high temporal resolution of 10 seconds was applied to measure T1 relaxation times on a pixel-by-pixel basis; also the non-contrast enhanced T10 were measured using images acquired with multiple flip angles. This is the standard method to accurately measure concentration of [Gd] contrast agents for pharmacokinetic analysis. A commercial software Tissue4D (Siemens Medical Solutions) was applied to obtain Ktrans, kep, and ve maps. This DCE protocol was pretty difficult to do, but it could yield accurate measurements of Ktrans, kep, and ve without using too much assumption. Two radiologists manually outlined the tumor margin on each imaging slice to measure the tumor volume and size. Despite the sophisticated acquisition protocol and analysis methods, none of the tumor volume, size, or DCE parameters Ktrans, kep or ve could show significant differences between different response groups. But, the PRM analysis showed that the proportion of voxels with increased signal intensity (PRMSI+) could

differentiate between pCR and npCR ($p < 0.001$), and also showed a significant difference between good and poor responders ($p=0.041$).

The PRM analysis was first proposed in Galbán et al. to evaluate the response of brain glioma to therapy based on the change of rCBV (relative cerebral blood volume), by using the CBV measured in the contralateral normal white matter as the reference.(4) Brain is confined within the skull, and the location and extent of glioma in pre- and post-treatment studies were pretty consistent, such that it allowed the corresponding pixel-by-pixel evaluation of the rCBV change for PRM analysis. In a later study by the same group, the investigators added the analysis of apparent diffusion coefficient (ADC), and showed that both rCBV and ADC could serve as early response markers.(5) The ADC is calculated based on the change of signal intensities measured using different diffusion-encoding b values, thus not based on the absolute signal intensity on the acquired images. Later another group by Bonekamp and colleagues applied the PRM method to evaluate the response of hepatocellular carcinoma to chemoembolization, and showed that the change in ADC and venous enhancement (VE) were predictive of response.(6) The liver is located deep in the body, and the presented cases also showed that the location and extent of tumors before and after therapy were pretty consistent.

In this article Cho and colleagues applied the PRM method for breast cancer. Compared to the brain and the liver, the breast is a soft organ that can easily change shape in different MRI examinations; and also the MRI is acquired by using a dedicated breast coil that is well known to generate heterogeneous signal intensities that vary substantially within the imaging field of view. In this article, the authors tried to match the tumors in soft breasts using a computer software

(MROncoTreat; Siemens Medical Solutions), and then on each matched pixel to directly calculate the change of signal intensities between pre- and post-treatment MRI studies. For locally advanced breast cancer, it is common to have a large necrotic core, and it is not clear that how the authors dealt with this problem. In the two illustrated cases, the unenhanced core in one case was excluded in the calculation, but in another case it was included. Overall, despite the finding that PRM could yield significant differences between different response groups, the effect to differentiate the poor responder group was very small, with p value of 0.041 and the area under the ROC curve of 0.716. Furthermore, based on the nature of the soft breast tissue and the heterogeneous signal intensities within field of view, the PRM analysis is very unlikely to provide robust parameters to serve as reliable markers for predicting poor responders, which is the most important clinical goal to abort the ineffective regimen for these patients.

Another problem that limited the clinical value of this work is the use of chemotherapy regimens: six cycles of docetaxel with doxorubicin, or four cycles of doxorubicin with cyclophosphamide followed by four cycles of docetaxel. Although HER2 was evaluated, the HER2-targeting drug trastuzumab was not included in the regimen for HER2-postive patients. The authors did not find different responses in different molecular biomarkers groups, which could be due to small number of patients as well as the missing of a very effective drug, trastuzumab, in the regimen for HER2-postive patients.

In summary, the low predictive value of quantitative DCE-MRI pharmacokinetic parameters that were analyzed from a sophisticated DCE-MRI acquisition protocol further supports that DCE-MRI is not capable of predicting response after 1 cycle of general chemotherapy. The tumor

volume and size carefully measured by radiologists could not predict response at such an early time either. These results were consistent with literature reports that when the evaluation was done too early after 1 cycle chemotherapy, the tumor has not had sufficient time to show substantial change yet, thus would lead to inconclusive results. In this article although the authors showed that PRM analysis of the change of signal intensities could yield significant differences between different response groups, the method based on tumor registration in the soft breasts between pre- and post-treatment MRI studies for the pixel-by-pixel analysis had fundamental problems. Many factors could affect the shape of tumor and the signal intensities, and change the measured PRM parameters substantially. In this work the authors did not demonstrate that the PRM analysis could be standardized to yield consistent and robust parameters to serve as imaging biomarkers. Many studies have evaluated the predictive ability of MRI-based parameters, but the general consensus was that tumor size shrinkage was still the most reliable predictor. When more targeted therapeutic agents become available, molecular imaging using contrast agents or tracers that are specific to the targeted molecules is the most promising approach to select candidate patients and to provide early response predictors.(7)

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