Improving accuracy in measurement of choline as a predictor of early response to neoadjuvant chemotherapy: correction of internal reference using external reference

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Introduction: The principal indication of Neoadjucant chemotherapy (NAC) is the treatment of unresectable breast cancers to reduce tumor to a size that allows resection. However, because of its benefits, NAC is also used for stage II and III tumor to improve the possibility of breast-conservation surgery. Meanwhile, toxicity of chemotherapy drugs are severe, therefore early and accurate assessment of response to NAC is important for optimizing the chemotherapy regime. Recently, in vivo proton MR spectroscopy of breast is demonstrating promising results in early assessment of response to NAC, using internal reference [1] and external reference [2]. With internal reference method, however, change of tissue water content (internal reference) during chemotherapy was observed, and with external reference method, coil sensitivity difference between tumor and reference phantom becomes issue. The aim of our study was (a) to correct the internal reference using external reference and take into account the actual tissue water content, and (b) to examine whether the difference of changes in tCho between two groups (responder and non-responder) assesses the pathological response early and accurately.

Methods: 21 patients with histopathologically confirmed breast cancer, who underwent NAC and scanned with the MRI/MRS protocol, were included in this study. The first MRI/MRS was performed before the start of NAC, second MRI/MRS was performed when approximately half of the course of NAC, and the third MRI/MRS was performed after final course of NAC, using a 1.5 T MR scanner (Philips Healthcare, Best, the Netherlands). Proton density image was acquired before contrast-enhanced dynamic study (Fig.[a]). After MRI examination including dynamic study was completed, single-voxel 1H-MRS was performed using a point-resolved spin-echo sequence (PRESS). The voxel was carefully positioned to maximize the coverage of the contrast-enhanced lesions while minimizing the inclusion of adipose tissue. The voxel size was 1.5cm x 1.5cm x 1.5cm. The tCho concentration was calculated using the tissue water from the unsuppressed spectrum using the following equation, slightly modified from the equation previously presented in [3], to take into account the tissue water content percentage:

$$[Cho] = [Tissue\ Water] \times \frac{n_{H2O}}{n_{Cho}} \times \frac{S_{H2O}}{S_{Cho}} \times \frac{\left(1-exp\left(-\frac{TR}{T1_{H2O}}\right)\right)}{\left(1-exp\left(-\frac{TR}{T1_{Cho}}\right)\right)} \times \frac{exp\left(-\frac{TE}{T2_{H2O}}\right)}{exp\left(-\frac{TE}{T2_{Cho}}\right)} \qquad * [\text{Tissue Water}] = tissue\ water\ content(\%) \times \frac{1}{MW_{H2O}}$$

here, tissue water concentration was obtained by signal intensity ratio of tumor and external reference phantom in the proton density image. The percentage of changes in tCho between first and second MRS was compared between responders and non-responders by using the two-way Mann-Whitney non-parametric test.

Results: Out of 21 patients, 8 and 13 were histopathologically comfirmed responders (grade 2 and 3, with criteria of Japanese Breast Cancer Society) and non-responders (grade 0 and 1) respectively. Fig.[b] shows contrast enhanced lesion of first, second and third MRI of a patient in responder group, and Fig.[c] is corresponding spectra. The change of tCho showed earlier disappearance than tumor. Whereas, spectra of a patient in non-responder group did not show significant decrease in tCho following NAC (Fig.[d]). Two graphs show the changes (%) of tCho between first MRS and second, third MRS in responder and non-responder group respectively (Fig.[e] and [f]). In responder group, most of patients showed immediate disappearance of tCho peak, and in non-responder group, they did not. There is significant difference between two groups of two groups (P<0.001).

Conclusion: In this study, we presented a method to correct the internal reference by using external reference for more accurate assessment of tCho concentration. Accurate method is preferred, but it should be done within acceptable examination time and easiness in clinical situation. This method is simple and easy to implement, and further our data showed that tCho is a better predictor of early response to NAC.

Fig.[a]

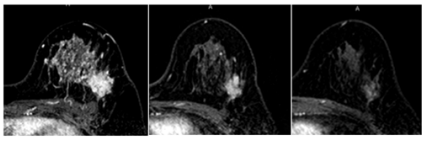

Fig.[b]

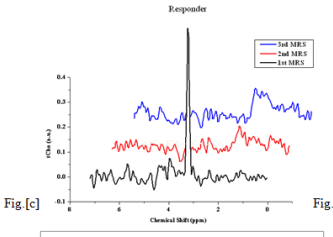

Fig.[c]

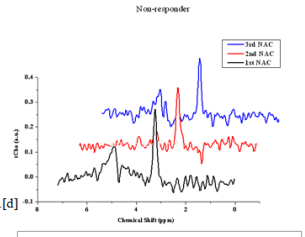

Fig.[d]

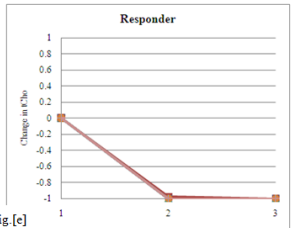

Fig.[e]

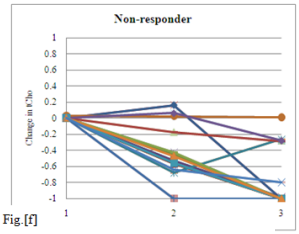

Fig.[f]

Reference:

[1] Baek et al., Radiology 251: 653-662 (2009)

[2] Tozaki et al., J Magn Reson Imaging 31: 895-902 (2010)

[3] Baik et al., Magn Reson Mater Phy 19: 96-104 (2006)