Predicting Final Pathological Response to Neoadjuvant Chemotherapy in Breast Cancer Using Quantitative MR Spectroscopy Using Internal Reference Method at 1.5T

H-M. Baek[1], J-H. Chen[1,2], S. Bahri[1], R. S. Mehta[3], O. Nalcioglu[1], and M-Y. Su[1]

[1]Tu & Yuen Center for Functional Onco-Imaging, University of California-Irvine, Irvine, CA, United States, [2]Department of Radiology, China Medical University Hospital, Taichung 404, Taiwan, [3]Department of Medicine, University of California-Irvine, Irvine, CA, United States

Purpose:

In vivo proton MR spectroscopy (^{1}H-MRS) has been proven helpful for the diagnosis of breast cancer based on Choline-containing compounds (tCho). The presence of choline may indicate active cell replication, thus can be used for diagnosis. The role of MRS for therapy response prediction is less established. There have been several studies reporting use of ^{1}H-MRS for monitoring response of breast cancer to neoadjuvant chemotherapy (NAC) [1-2]. Bolan et al. [3] developed an internal reference method for quantification of tCho levels, and Meisamy et al. [4] found that the change in tCho level can serve as an indicator for predicting response to the treatment. As the therapeutic agents become more effective, more patients can achieve the pathological complete response (pCR), which is expected to lead to a better prognosis. In this study we applied longitudinal quantitative ^{1}H-MRS using the internal reference method to monitor the change of tCho level during the full course of NAC. The early changes were compared to the size changes, and correlated with final pathological response.

Methods:

Thirty-five patients with biopsy-confirmed breast cancer who elected to receive neoadjuvant chemotherapy were included in this study. MR imaging and ^{1}H-MRS were performed prior to treatment as the baseline, then at 2 follow-up times, F/U-1 after 1-2 cycle of AC, and F/U-2 after 4 cycles AC or 2 cycles AC followed by first cycle of taxane regimen. Then they had the F/U-3 after completing all chemotherapy. The scans were performed on a Philips Eclipse 1.5 T MR system. The single-voxel ^{1}H-MR spectra were acquired from the lesion of each patient (the voxel size, 4.8-8.0 mL). The acquisition parameters were TR/TE=2000/270 ms, with 128 averages. A fully relaxed, unsuppressed spectrum was also acquired to measure the water peak (24 averages). When a tCho peak could be clearly identifiable above the baseline noise (SNR > 2), the spectrum was analyzed by one spectroscopist to measure tCho level. The peak was quantified by fitting a Gaussian line-shape model to the data and using the unsuppressed water signal as an internal reference [5]. A radiologist determined the tumor size based on the maximum intensity projection (MIP) of the subtraction images. After completing the treatment protocol, patients received surgery. Based on the pathological examination results, they were categorized into two groups: pCR (pathological complete response, no presence of invasive tumors, N=17) and non-pCR (with minimal or bulk invasive residual disease, N=18).

Results:

17 patients achieved pathological complete response (pCR group in Table 1). 12 of 17 patients had positive tCho before treatment. The absolute tCho levels ranged from 1.40 – 5.06 (mean ± SD, 1.40 ± 1.62) mmol/kg. The mean percentage change in tCho levels after 1-2 cycle AC was -62% (-41% ~ -100 %), while the mean percentage change in lesion size was -17% (5% ~ -67%), as shown in Table 1. After completing the F/U-2, all patients did not have positive tCho. The mean change in lesion size at F/U-2 was -79% (-46% ~ -100%).

Table 1: Change in tumor size and tCho level for each follow-up study

	%Change in tumor size		%Change in tCho level			
Follow-up	pCR	Non-pCR	pCR	Non-pCR	P[1]	P[2]
ΔF/U-1	-17%	-15%	-62%	-36%	0.90	0.21
ΔF/U-2	-79%	-53%	-100%	-67%	0.008*	0.02*
ΔF/U-3	-93%	-74%	-100%	-70%	0.019*	0.29

%ΔF/U = percentage change at follow-up compared to the baseline level. P: comparison p values between pCR and Non-pCR, %Change in tumor size (P[1]) and tCho level (P[2]). * significant <0.05

18 patients had residual disease after completing all chemo, and were classified as non-pCR. 17 of them had a positive tCho at the baseline. There is no significant difference in tCho level at the baseline between pCR and non-pCR groups (1.40 ± 1.62 vs. 2.35 ± 1.64, p = 0.09). In F/U-1 after 1-2 cycle AC, the mean percentage change in tCho levels was -36% (43% ~ -100%), while the mean percentage change in lesion size was -15% (9% ~ -93%), as shown in Table 1. In F/U-2, 2 patients showed increased tCho, 5 decreased but still positive, and the remaining 10 patients did not have detectable tCho. The mean percentage change in lesion size in F/U-2 study was -53% (-26% ~ -100%). The percentage change in lesions size and tCho level in F/U-2 was significantly different between pCR and non-pCR groups (P = 0.008, P = 0.02), respectively.

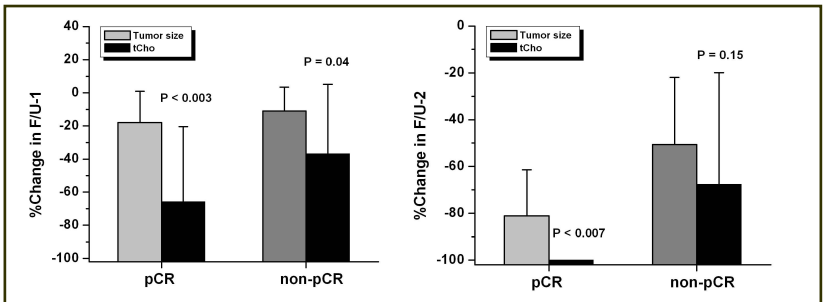

Figure 1: comparison of %change of lesion size and tCho after 1-2 cycle AC (Left, F/U-1) and after 4 cycles AC or 2 cycles AC+taxane (Right, F/U-2) in pCR vs. non-pCR groups.

The metabolic changes and volumetric changes in F/U-1 and F/U-2 are shown in Figure 1. In pCR group there was a significant reduction in tCho level compared to that of tumor size (P < 0.003, P < 0.007). In non-pCR group, there was a significant difference between changes in tCho and tumor size in F/U-1 (P = 0.04), but not significant in F/U-2 (P = 0.15).

Discussion:

In this study, 17/35 (49%) patients achieved a pathologic complete response after all treatments. Of them, 12 had baseline tCho, and non had detectable tCho peak at F/U-2. 18/35 (51%) patients did not achieve pCR. Of them 17 had baseline tCho, and 6 had residual tCho in F/U-2. The change in tCho level in F/U-1 was greater in the pCR group (-62%) than in the non-pCR group (-36%), but not reaching significant level (P = 0.21). Later in F/U-2, both the change in lesion size (-79% vs. -53%, p = 0.008) and Cho level (-100% vs. -67%, p = 0.02) was significantly greater in the pCR than the non-pCR group. The result suggests that a greater reduction in both tCho and size at F/U-2 may be associated with a final complete response, so they may help to predict pCR. Our finding is consistent with results reported by Meisamy et al. [4]. As shown in Fig. 1, the metabolic changes were greater than the size changes, suggesting that they might have occurred before gross morphological changes. A reduction of tCho level can be interpreted as reflecting the inhibition of cellular proliferation and the cytotoxic effect of chemotherapy. In patients who did not achieve pCR, they also showed Cho reduction, and in fact all patients were showing a substantial lesion shrinkage (mean -74% at F/U-3), some even done to minimal tumor burden only with scattered cells. Therefore, since all tumors were responding, it might be difficult to find reliable indicator for predicting pCR. Our results showed that MRS may provide useful information that might be more sensitive than tumor size changes, which warrants further investigation.

References: [1]. Jagannathan et al. Br J Cancer 84(8): 1016-1022 (2001). [2]. Manton et al. Br J Cancer 94: 427-435 (2006). [3]. Bolan et al. MRM 50: 1134-1143 (2003). [4]. Meisamy et al. Radiology 233:424-431 (2004). [5]. Baek et al., MAGMA 19:96-104 (2006).

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