Quantification of Cervical Tumor Choline Concentration by Proton MR Spectroscopy at 3 Tesla: a Pilot Study

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Introduction: *In vivo* ^{1}H-MRS is a non-invasive technique that provides information on tumor metabolism, which may be used in tumor diagnosis and tumor response to therapy[1,2]. Recently, several studies have demonstrated that choline (Cho) can be detected in human cervical tumors using ^{1}H-MRS with endovaginal coil at 1.5 T[3,4,5]. However, in some of these studies, Cho signals were also detected in post-treatment residual tissue and in normal cervix tissues. Thus, a quantitative method is necessary to accurately determine levels of Cho to segregate different pathologies. The current study applied an internal water reference method to provideabsolute quantification of Cho levels in the tumor. We want to show that ^{1}H MRS can be used to improve diagnostic accuracy and monitor cervical cancer response to therapy.

Methods: The internal reference method for quantifying Cho concentration in *in vivo* study was utilized in multiple other studies[1,2]. The current work is an implementation of the technique for cervical cancer MRS studies. In the present study, all acquisitions were recorded at the constant receiver gain. Hence, the absolute Cho concentration was calculated by the equation (1)[1]:

$$[\mathrm{Cho}] = \frac{n_{H_2O}}{n_{Cho} MW_{H_2O}} \times \frac{S_{Cho}}{S_{H_2O}} \times \frac{f_{T_{1H_2O}}}{f_{T_{1Cho}}} \times \frac{f_{T_{2H_2O}}}{f_{T_{2Cho}}} \times CF_{H2O} \times CF_{Lipid} \quad (1); \quad f_{T_1} = 1 - \exp\left(-\frac{TR}{T_1}\right) \quad (2); \quad f_{T_2} = \exp\left(-\frac{TE}{T_2}\right) \quad (3).$$

where [Cho] = the concentration of the Cho in units of mmol/kg; S_{Cho} = integral value of Cho peak at 3.2 ppm; S_{H2O} = integral value of the unsuppressed water signal at 4.7 ppm; n_{Cho} and n_{H2O} (the numbers of ^{1}H nuclei for each molecule) = 9 (3*CH_3)and 2, respectively; MW_{H2O} = 18 × 10^{-6} kg/mmol, CF_{H2O} = 0.77 / 1.0 (i.e. 77% water content of muscle), which is believed to be relatively constant between tumors and normal tissues; $CF_{Lipid} = S_{H2O} / (S_{H2O} + S_{Lipid})$, accounting for the lipid content within each voxel. The $f_{T1}$and f_{T2} relaxation time correction factors were calculated by using equations 2 and 3.

Six patients (mean age = 48 ± 7 years) with biopsy-proven cervical cancer (Stage II to IVa) were included in this study. A baseline scan was done prior to the start of radiotherapy. Patients were re-evaluated within a few weeks after completion of the treatment. The examinations were undertaken on a clinical 3.0 T MR system (Achieva Philips Medical Systems, Best, Netherlands) in combination with a 6-element SENSE cardiac surface coil. Water-suppressed single-voxel proton MRS (SVS) of the cervical lesion was performed with PRESS localization. An experienced radiologist placed the MRS-voxel on the same region of the tumor in pre- and post-therapy measurements with care taken to avoid inclusion of adjacent fat or obvious tumor necrosis zones.. Consequently, the voxel size (volume size 6-15 ml) depended on the dimension of the tumor under examination. Spectroscopic data were obtained with the following parameters: TE 135ms, TR 2000ms, spectral width 2000Hz, sample points 1024, 160 signal averages. The internal referencing strategy requires T_1 and T_2 corrections of the Cho and water. T_1 and T_2 relaxation times of Cho and water were measured in the cervix of four healthy subjects (age = 32 ± 4 years). The average T_1 values of water and T_1 and T_2 values of Cho from all subjects were calculated and would be used for correction of Cho level in cervical tumors. T_2 relaxation time of water was measured in tumor/cervix of each patient during MR exams. All spectroscopic data were analyzed utilizing AdvancedViewer software (Philips Medical Systems, Best, Netherlands). Cho levels before and after radiotherapy and compared using a paired t-test.

Results and Discussion: Cho metabolite was detected in all healthy subjects and patients before and after the radiotherapy treatments. For the volunteer studies, the average T1 and T2 relaxation times of Cho were 1369±35ms and 131±12ms respectively. The average T1 relaxation times of water were 1490±45ms. Utilizing the calculated average relaxation times for Cho and water, the absolute Cho concentrations within tumor and residual treated tissues of 6 patients were calculated and shown in Table 1 and Figure 1a. The relative changes (([Cho]pre-[Cho]post)/[Cho]pre*100%) in Cho concentration between pre- and post- radiotherapy showed significant difference (P = 0.04) between responders (4 of 6) and non-responders (2 of 6), although the absolute changes ([Cho]pre-[Cho]post) in Cho concentration were not significantly different between responders and non-responders (p = 0.1829). Figure 1b show a representative MRS measurement from patient #1 before and after radiotherapy. It can be noted that the cervical tumor (Figure 1b(C)) was substantially reduced even disappeared compared to the dimension in the baseline study (Figure 1b(A)). Meanwhile, a significant reduction in Cho concentration was also noted (Figure 1b(B) and 1b(D)).The observation of decreased Cho in this study is consistent with other studies where reduced levels of Cho have been reported after cancer treatment[5].

Conclusion: The preliminary results of our pilot study indicate that Cho level with absolute quantification can be used as a biomarker for evaluating treatment response in patients with cervical cancer using external surface coil at 3T. A larger study is being undertaken to confirm this hypothesis and determine whether absolute Cho levels have any correlation with subsequent tumor response or if early (prior to completion of radiotherapy) MRS-Cho evaluation will be predictive.

References: 1. Bolan PJ, *et al. MRM* 2003; 50:1134–1143. 2. Baik HM, *et al. MAGMA* 2006; 19:96–104. 3. Mahon, M. M., *et al., NMR Biomed,* 2004. 17: 1-9. 4. DeSouza NM, *et al. Br J Cancer* 2004; 90:2326–31. 5. Allen JR, *et al., Am J Clin Oncol* 2001;24:522–9. Research supported in part by the Mary Kay Ash Foundation.

(a) (b)

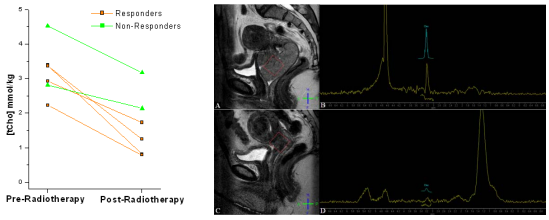

Figure 1. Monitoring cervical tumor response to therapy using quantitative MRS. These data included 6 patients measured with 3T cervix MRI/MRS before the start of radiotherapy and after the complete course of treatment (2-3 months later). The Cho concentration measurements were shown for the pre- and post-radiotherapy measurements in (a): both responders and non-responders showed a decrease in Cho concentration after treatments, but non-responders had relatively higher levels of Cho remaining after the treatments. (b): An example of a responder, showing decreased Cho concentration after radiotherapy, and a clear anatomical response by the end of treatment. MRI and MRS measurement of a 52-year-old patient with biopsy-proven invasive squamous cell carcinoma of the cervix. A, Sagittal non-fat-suppressed T2-weighted image shows an invasive squamous cell carcinoma located in the cervix. This image also demonstrates the voxel placement. B, Magnified spectrum illustrates a high Cho resonance peak is visible at 3.2 ppm, and the fitting produces a measurement of [Cho] = 3.39 ± 0.23 mmol/kg. C, Sagittal non-fat-suppressed T_2-weighted image obtained 3 months later, after completion of treatment with radiotherapy. D, There is resolution of the peak centered around Cho ([Cho] = 0.81± 0.69 mmol/kg), which is indicative of significant positive response.

Table 1: Quantification of [Cho] in 6cervical cancer patients (*/**: Pre-/post-treatment tumor dimension)

Patient	Age (year)	Pre-TD* (cm)	Post-TD** (cm)	Pre-[Cho] (mmol/kg)	Post-[Cho] (mmol/kg)	Rel. [Cho] change %	Comments
1	52	8.1	3.3	3.39	0.81	76	Responder
2	41	4.4	2.1	2.23	0.79	65	Responder
3	38	6.6	5.3	2.81	2.14	24	Non-responder
4	56	6.1	5.1	4.52	3.18	30	Non-responder
5	48	7.5	2.2	3.37	1.25	63	Responder
6	50	3.5	1.5	2.93	1.73	41	Responder
Ave±STD	48±7	6.0 ± 1.8	3.3 ± 1.6	3.21±1.77	1.65 ± 0.92		