Evaluation of Magnetic Resonance Diffusion and Spectroscopy Measurements as Predictive Biomarkers in Stage 1 Cervical Cancer

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Introduction

In stage 1 cervical cancer, treatment and outcome are critically dependent on the histological characteristics of the tumor. Functional magnetic resonance techniques enable interrogation of tissue structure and provide metabolic information from within a primary tumor, with the advantage of informing on the whole tumor pre-operatively without the effects of sampling error. The purpose of this study therefore was to determine whether ADC and tCho were significantly different in cervical tumors with different histological characteristics (type, degree of differentiation and presence or absence of lymphovascular invasion) in order to investigate their potential as predictive biomarkers.

Materials and Methods

This single-institution study was approved by the Local Research Ethics Committee. Written informed consent was obtained from all subjects: 62 women (median age 38 years, range 24 to 74 years) who presented invasive disease on smear, punch or cone biopsy, staged as FIGO 1a or 1b1 disease were studied.

MR Imaging: MRI was performed at 1.5T (Philips Intera, Best, The Netherlands) with a 37 mm diameter endovaginal coil [1]. Air in the vagina was aspirated to minimise susceptibility-related field inhomogeneity. T2-W fast spin-echo images were obtained in three orthogonal planes (TR/TE of 4500/80 ms, 3 mm slice thickness). Single-shot echo-planar diffusion-weighted (EPI-DW) images were acquired over the lesion (TR/TE = 2500/69 ms, b-values 0, 100, 300, 500 and 800 s/mm^2 and a 96 x 95 data acquisition matrix, reconstructed to 128 x 128, slice thickness 3-4 mm). The ADC map was calculated using in-house software (IDL 6.1, RSI, Boulder CO, USA) by fitting a mono-exponential to the data. Regions of interest (ROIs) encompassing the whole tumour were drawn by a radiologist by visual correlation of the ADC maps with anatomical information on the T2-W image. The radiologist was blinded to tumour characteristics on histology. When internal receiver coils are used the confidence levels on the calculated pixel ADC values are expected to depend on their position in relation to the coil, and for this reason a threshold on the χ^2 goodness-of-fit coefficient was used to exclude excessively noisy pixels from the drawn ROI.

In vivo MR Spectroscopy: MR spectroscopic imaging (MRSI) used a 15 mm slice, 16 x 16 grid, 120 mm FOV, 4 averages, TR 888 ms, TE 135 ms, a Press volume of ~ 25 x 18 x 15 mm, BASING water suppression and an automated shim. A water line width within the PRESS box of < 15Hz was deemed acceptable. Signal from unsuppressed water as a concentration reference was also acquired with identical scan parameters except only 2 averages and with TR of 650 ms. Metabolite peaks were fitted using LCMODEL [2], with the full basis set supplied, including choline, creatine, N-Acetyl Aspartate (NAA) and lipids. No correction for relaxation was included. Spectra were omitted when the Cramer-Rao Lower Bound estimate on the metabolite concentration > 20%, the water width > 0.3 ppm, or visually the fit to data or baseline was poor. The tissue type for each voxel was identified using the corresponding T2-W images as non-tumor (predominantly epithelium or stroma) or tumor (>30% tumor). One voxel contained a benign cyst and so was excluded. To avoid bias, statistical comparisons were made between the average tCho from voxels of each histological type for each patient, rather than assuming all voxels were independent.

Histology: After trachelectomy and hysterectomy sectioning, tumours were classified as squamous or adenocarcinomas; well, moderately or poorly differentiated; and as showing presence or absence of lymphovascular invasion. Excised pelvic nodes were scored as being positive or negative for metastasis.

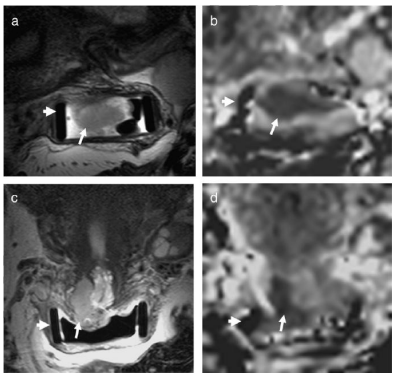

Figure 1 - T2-weighted images (left) and ADC maps (right) in well differentiated squamous (top) and poorly differentiated adenocarcinoma (bottom). Large arrow indicates coil position.

Results and Discussion

Patient cohort: Fifty-eight of 62 patients underwent surgery (6 knife cone surgery procedures, 23 trachelectomies, and 29 hysterectomies) and the remaining four patients had chemoradiotherapy as primary treatment modality. There were 41 squamous carcinomas, 20 adenocarcinomas and 1 adenosquamous carcinoma. Sixty-one patients had pelvic lymph node dissection; the remaining patient had no disease in their treatment cone biopsy, and therefore did not have lymph-node dissection. Five adenocarcinomas and 19 squamous carcinomas had lymphovascular invasion while 8 and 2 respectively (and 1 adenosquamous carcinoma) had lymph node metastases

Apparent Diffusion Coefficients (ADCs): Figure 1 shows T2-W and ADC maps in a well differentiated squamous and in a poorly differentiated adenocarcinoma (above and below, respectively). There was a statistically significant difference between the ADC of tumors that were well/moderately differentiated (1196±181x10^{-6} mm^2/s) compared with those that were poorly differentiated (1038±153x10^{-6} mm^2/s; p = 0.016, Figure 2). There was no significant difference between the ADCs of the tumors when separated by other characteristics (tumor type, lymphovascular invasion, lymph-node metastases).

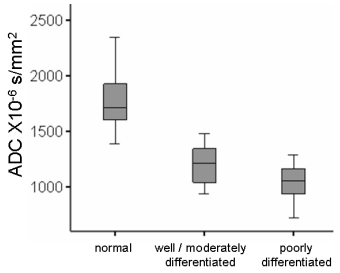

Figure 2 – Comparison of ADC values in different tissue types.

Total Choline (tCho): An example MR spectrum with the LCmodel fit is shown in Fig 3. There was no significant difference in tCho between any of the tumor categories investigated. There was no correlation between tumor ADC and tCho (r = -0.23; p = 0.4).

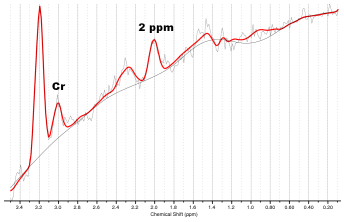

Figure 3 – Cervix MR Spectrum.

Conclusions

ADCs may be used to indicate the degree of differentiation of a tumor, though not other histological characteristics such as lymphovascular invasion and lymph node metastasis. tCho on the other hand did not differentiate between histological features of tumors. Use of ADC as a prognostic biomarker in cervical cancer warrants investigation in larger scale clinical trials.

References 1. deSouza NM et al. Am J Roentgenol 1996 Mar;166(3):553-9. **2.** Provencher SW. NMR Biomed 2001 Jun;14(4):260-4.

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