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Variation in apparent diffusion coefficient measurements among women with locally advanced cervical cancer

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ABSTRACT

ADC variability from mixed data sets acquired from women with locally advanced cervical cancer appears to be predominantly of biologic origin. Intra-histology ADC variance was similar when pooled across technical factors. Inter-histology pooling increased ADC variance. Normalization to urine ADC improved intra-histology variance and receiver-operator curve test performance.

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More than 40% of women with locally advanced cervical cancer develop relapse following radical chemoradiation [1]. Non-invasive functional imaging techniques including diffusion-weighted magnetic resonance imaging (DWI-MRI) may identify high risk patients prior to treatment [2]. Most often, the DWI-MRI signal is calculated at low and high sensitivities to diffusive motion, characterized by the b-values (units of s/mm^2). The apparent diffusion coefficient (ADC, units of mm^2/s) is quantified from the slope of the linear regression of the logarithmically-transformed DWI-MRI signal and b-values, of which a minimum of 2 are required.

For cervical cancer, ADC improves detection and characterization of cancerous lesions for routine staging, and may also provide a predictive and prognostic biomarker [3–7]. Lower ADC indicates increased cellularity and differentiates malignant from benign tissues [8–11], and the extent of ADC change following chemoradiation has correlated with tumor response and disease-free survival [7,12,13]. However, the measured ADC can depend on technical factors, including field strength, region-of-interest (ROI), and b-value selection [14–19]. For example, linear regression may not hold when b is very low or high [15,16], plus b-value sets are not standardized across anatomic sites or institutions [20]. Multiple studies report that ADC is variable between field strengths and vendors [13,14,21]. Standardization efforts are further complicated by system upgrades and changes in departmental scanning protocols.

This work measures variability in ADC for locally advanced cervical cancer patients imaged under heterogeneous DWI conditions. Thereby, we hope to enable single and multi-center comparisons and to improve clinical trial design. Three aspects of the ADC measurement are considered: (1) Model accuracy – to investigate the linearity of the logarithmically-transformed DWI signal with b-value across pelvic structures; (2) Variance analysis and normalization – to evaluate ADC variance within pelvic structures according to histology, field strength, and protocol, and to identify potential internal reference structures; and (3) Histologic classification – to assess discriminatory abilities of absolute and normalized ADC between squamous cell carcinoma (SCC) and adenocarcinoma (ADE).

Materials and methods

This study was approved by the institutional research ethics board.

Patient selection

Eighty consecutive women with locally advanced cervical cancer (FIGO stage 1B2-IVa) treated with definitive chemoradiation at Princess Margaret Cancer Centre between 2009 and 2013 were identified from a prospective database. The median age of the entire cohort was 54 years (range 25–85). The majority of cases were FIGO stage 1B2 or 2, (35/80; 36/80) and squamous cell carcinomas (55/80). There were no statistical differences in patient age ($p > 0.8$, student's *t*-test), FIGO stage, and histology between protocols ($p > 0.4$, Fisher's Exact Test). Patients were required to have pre-treatment MRI imaging including axial T2-weighted MRI and DWI. Seven patients were excluded because of poor DWI image quality following inadequate fat suppression.

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MRI methods

Diffusion-weighted acquisition used a single-shot spin-echo echo-planar imaging (EPI), based on 2 protocols on 1.5 Tesla Avanto or 3 Tesla Verio systems (Siemens Medical Systems, Erlangen, DE) equipped with equivalent gradient sets (peak gradient amplitude 45 mT/m; peak slew rate 200 T/m/s). Protocol A was an investigational sequence (511 Works-in-Progress Package, Siemens Medical Systems), which was implemented with improved fat suppression and image reconstruction options. Protocol B was the standard-of-care DW-EPI package. Details of the imaging protocols are summarized in Table 1 of the Supplemental content.

Prospective phantom characterization of these methods was not acquired, however contemporary quality assurance testing was performed using the ice water standardization phantom [22] on 1.5T Espree and 3T Verio Siemens MRI systems with equivalent gradient performance (45 mT/m peak amplitude; 200 T/m/s peak slew rate). A 50 cc tube filled with distilled water was positioned within a wide-mouth 500 ml container filled with ice, and insulated within 2 insulating pads. At 2 h, the water temperature was less than 0.3 degrees Celsius. On each system, the tube was positioned within 0.5 cm of the magnet isocenter, and 5 repetitions of protocols A and B were interleaved using the spine array and an anteriorly positioned 6 coil body array coil for data acquisition. ADC values were measured from the in-line processed images using MIPAV software (National Institutes of Health, Bethesda, MD), and means were compared.

For clinical scanning, a 16-element spine coil was placed posteriorly, and two 6-channel torso coils were placed anteriorly. Each patient was scanned once only, with 40 at 1.5 T and 33 at 3 T; 33 with Protocol A; 40 with Protocol B.

Data analysis

An axial DWI slice which presented all pertinent regions of interest (tumor, bladder, muscle) was segmented using MIPAV. Cranio-caudal displacement from the selected slice to the magnet isocenter was recorded. ROIs of 100.0 ± 50 mm^2 were generated within visually homogeneous areas of tumor, skeletal muscle (gluteus maximus) and bladder (urine) (Fig. 1). Areas of obvious necrosis or cysts were avoided. ROIs were generated on the $b = 0$ s/mm^2 image and propagated to the remaining b-value images to ensure geometric consistency and visualize signal uniformity. Per pixel signal values for each b-value and ROI were exported to MATLAB (Mathworks, Natick, MA).

Model Accuracy

ADC value for each ROI was calculated by data fitting to a mono-exponential decay (Eq. (1)) via logarithmically-transformed linear regression analysis:

$$S(b) = S_0 e^{-b \cdot ADC} \quad (1)$$

where $S(b)$ is the signal magnitude for diffusion weighting b, and S_0 is the signal magnitude for the reference diffusion weighting. ADC values were calculated, with and without exclusion of perfusion-sensitive $b < 100$ s/mm^2 images [23], considering b-values of 100 and 800 s/mm^2 for protocol A, and b-values of 400 and 800 or 1000 s/mm^2 for protocol B. Coefficients of determination (R^2) and standard error were obtained.

Variance analysis and normalization

Patients were grouped according to histology, field strength, protocol, and b-values; and ADC mean, standard deviation and coefficient of variation (CV) were recorded. Tumor ADC was

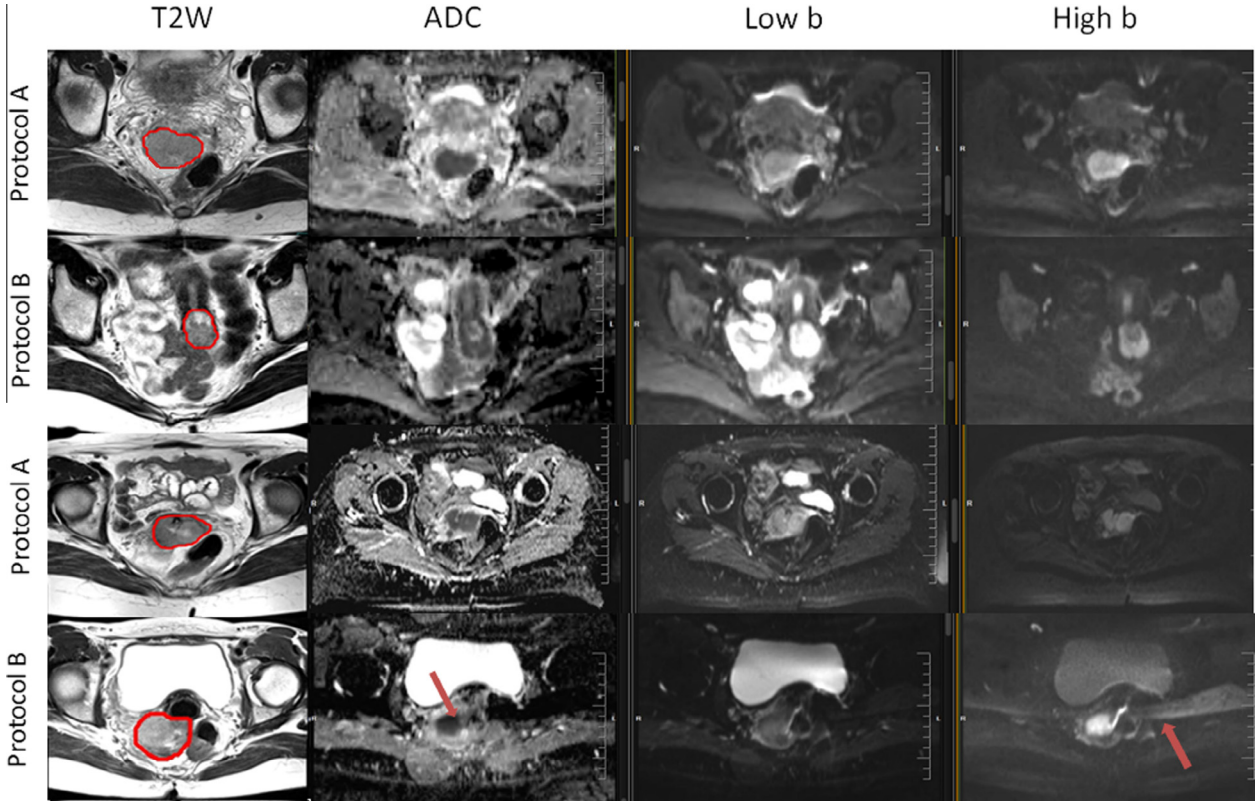

Fig. 1. Representative acquisitions from each protocol, including T_2-weighted, ADC, $b = 0$ s/mm^2 DWI, and $b = 800$ or 1000) s/mm^2 DWI images: (Row 1) Protocol A at 1.5 T; (Row 2) Protocol B at 1.5 T; (Row 3) Protocol A at 3 T; and (Row 4) Protocol B at 3 T. The tumor volumes are contoured in red in the T_2-weighted image. Red arrows highlight residual fat artifact for protocol B data acquired at 3 T.

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