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Value of normalized apparent diffusion coefficient for estimating histological grade of vesical urothelial carcinoma

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AIM: To compare the efficacy of apparent diffusion coefficient (ADC) and normalized ADC (nADC) for estimating the histological grade of vesical urothelial carcinoma and to identify an optimal reference for nADC calculation.

MATERIALS AND METHODS: Thirty patients with histologically confirmed vesical urothelial carcinomas underwent preoperative diffusion-weighted magnetic resonance imaging (DW-MRI) of the pelvis. nADC of the tumour was calculated as ADC (tumour)/ADC (reference) using urine in the bladder lumen, and the obturator internus and gluteus maximus muscles as reference. Receiver operating characteristic (ROC) curves were constructed and compared to identify an optimal reference for nADC calculation.

RESULTS: Both ADC and nADC of low-grade tumours ($1.112 \pm 0.159 \times 10^{-3}$ mm^2/s, $0.403 \pm 0.047 \times 10^{-3}$ mm^2/s) were significantly ($p < 0.001$) higher than those of high-grade tumours ($0.772 \pm 0.091 \times 10^{-3}$ mm^2/s, $0.276 \pm 0.033 \times 10^{-3}$ mm^2/s). The area under the nADC ROC curve using urine as reference was significantly ($p = 0.000$) larger (0.995) than those using obturator internus (0.960) and gluteus maximus (0.945).

CONCLUSIONS: nADC is superior to ADC for estimating the histological grade of bladder carcinoma using urine in the bladder lumen as an optimal reference for nADC calculation.

Introduction

Urothelial carcinoma of the bladder is the most common malignancy of the urinary tract, accounting for 90% of all bladder cancers.[1] Although the 5-year survival rate can be as high as 81%, it is significantly reduced to 36% and 6% in the presence of local and distant metastasis, respectively.[2] Treatment and prognosis depend on the clinical stage and histological grade. Biopsy of the tumour reflects only the histological grade of the focal lesion rather than that of the entire tumour. Imprecise preoperative histological grading may cause incomplete resection or overtreatment, higher risk of recurrent or metastatic tumour, and poor quality of life. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a functional imaging tool that provides qualitative and quantitative information about the diffusion of water

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molecules within tissues. The apparent diffusion coefficient (ADC) is lower in malignancy with high cell density and disrupted tissue organization reducing the extracellular space. DW-MRI is useful as a biomarker for the diagnosis, treatment follow-up, and predicting the prognosis of various tumours.[3] Previous studies have shown that high-grade vesical urothelial carcinoma has a significantly lower ADC and higher frequency of metastasis than low-grade tumour.[2,4] However, comparing ADC values between studies is difficult because of variation of ADC with different equipment, scanning protocols, and b-values, as well as age and body temperature of patients. Normalized ADC (nADC) has been beneficial in evaluating brain, liver, pancreas, prostate, bone, and lymph node lesions.[5–10] The objective of the present study was to compare the efficacy of ADC and nADC for estimating the histological grade of vesical urothelial carcinoma and to identify an optimal reference standard for nADC calculation.

Materials and methods

From November 2011 through May 2013, 30 patients (26 men, four women; age range 31–77 years, mean 60.4 ± 2.6 years) with 44 histologically confirmed vesical urothelial carcinomas underwent preoperative DW-MRI of the pelvis before transurethral resection of the bladder tumour (21), radical cystectomy (7), or partial cystectomy (2). Five patients had multifocal disease and the remaining 25 patients had solitary lesions. The study was approved by the institutional medical ethics committee. Written informed consent was obtained from all patients.

Pelvic MRI was performed using a 3 T MRI system (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany) with an eight-channel phased-array pelvic coil after a 4–6 h fast and voiding 1 h before the examination. The entire pelvis was scanned in the supine position from the aortic bifurcation to the inferior margin of the pubic symphysis. In addition to axial spin-echo T1-weighted [600 ms repetition time (TR)/21 ms echo time (TE)] and fast spin-echo T2-weighted (3500–4500 ms TR/91–131 ms TE) imaging, high spatial resolution (320 × 320 matrix, 20 × 20 cm field of view) fast spin-echo T2-weighted imaging (3500–4650 ms TR/95–102 ms TE) was performed in three orthogonal planes with three excitations. Dynamic contrast-enhanced axial fat-suppressed three-dimensional volumetric spoiled gradient-echo images (3D VIBE; 3.31 ms TR/1.22 ms TE, 13° flip angle, 2 mm section thickness, 0.4 mm intersection gap, two excitations) were acquired before, 20, 45, 70, 95, and 131 s after intravenous injection of 0.2 ml/kg Gd-DTPA (Magnevist, Bayer Healthcare Pharmaceuticals, Leverkusen, Germany) at 2 ml/s up to a total volume of 20 ml. Two minute-delayed axial spin-echo T1-weighted images were also obtained. Unenhanced DW-MRI was performed with free-breathing, water-excited single-shot spin-echo echo-planar imaging (4000 ms TR/78 ms TE, 4 mm section thickness, 0.4 mm intersection gap, eight excitations) in an oblique axial plane perpendicular to the bladder wall inferior to the tumour using b-values of 0 and 1000 s/mm^2. Oval regions of interest (ROI) were manually drawn and the ADCs were measured by a uroradiologist (W.H.J.) on the automatically generated ADC map without knowledge of the clinical staging and histological grading of the tumours. To ensure accuracy of the ADC measurements, lesions <1 cm in diameter, necrosis, tumour stalk, small blood vessels, and areas containing artefacts were excluded. Three ROI >20 mm^2 were drawn in different areas of the tumour and an average ADC was obtained. To select an optimal reference for nADC calculation, ADC values were obtained from urine in the bladder lumen and the obturator internus and gluteus maximus muscles. To avoid partial volume effects generated by bowel peristalsis, the ROI were placed in the centre of bladder lumen and areas of muscles with homogeneous signal intensities (Fig 1). nADC was calculated as ADC (tumour)/ADC (reference).

Student's *t*-test was used to compare the ADC and nADC values of high- and low-grade malignancy. Receiver operating characteristic (ROC) curves for the nADC values of the three references were drawn using SPSS 13.0 and the areas under the ROC curves were compared. Additional ROC curves for ADC and nADC were constructed using the largest areas under the ROC curves for the three references in order to differentiate between high- and low-grade tumours. Statistical significance was defined as $p < 0.05$.

Results

Of 44 confirmed bladder tumours in 30 patients, 13 lesions <1 cm in diameter were excluded from the analysis to avoid error caused by partial volume effect. Of the 31 evaluated lesions, 11 were low-grade and 20 were high-grade carcinomas. The ADC and nADC values of the high-grade tumours were significantly ($p < 0.001$) lower than those of low-grade malignancy (Table 1). The area under the ROC curve of nADC of urine (0.995 ± 0.038) was significantly ($p < 0.001$) larger than those of gluteus maximus (0.945 ± 0.039) and obturator internus (0.960 ± 0.034). The area under the ROC curve of nADC (0.995 ± 0.038) using urine as a reference was significantly ($p < 0.001$) larger than that of ADC (0.985 ± 0.018) for differentiating high- and low-grade urothelial carcinomas (Fig 2) with 100% sensitivity and 95% specificity, indicating that the former is more efficient than the latter in differentiating high- from low-grade urothelial carcinomas of bladder.

Discussion

The lack of standardized DW-MRI protocols reduces the reliability of ADC comparisons between studies because of inherent variations in the equipment, including different vendors, coils, pulse sequences, scanning parameters, and magnetic susceptibility artefacts. These variables can result in inter-study ADC differences of 5–15%.[11–13] Sasaki et al.[12] reported 4–9% variation in ADC values of grey and white matter of the brain in 12 healthy volunteers using eight 1.5 T and two 3 T scanners from four vendors. The ADC variation