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Original contribution

Amide proton transfer imaging can predict tumor grade in rectal cancer

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ABSTRACT

Purpose: To prospectively investigate the ability of amide proton transfer (APT) imaging, in comparison with that of diffusion-weighted imaging (DWI), to predict pathological factors in rectal cancer.

Materials and methods: Twenty-two patients who underwent MR examination including APT imaging and DWI for evaluation of rectal cancer were enrolled. APT signal intensity (SI) was defined as the magnetization transfer asymmetry at 3.5 ppm and was mapped. An apparent diffusion coefficient (ADC) map was generated using b-values of 0, 500 and 1000 s/mm^2. APT SI and ADC were calculated by placing regions-of-interest in the tumors on these maps. Pathological factors including tumor size and tumor grade were also evaluated. Average APT SIs or ADCs were compared between the two groups classified based on each pathological factor using Student's *t*-test.

Results: The average APT SI of tumors with diameters of 5 cm or more (3.09 ± 1.41%) was significantly higher than that of tumors with diameters < 5 cm (1.83 ± 1.38%). In addition, the average APT SI of moderately differentiated adenocarcinoma (2.82 ± 1.51%) was significantly higher than that of well-differentiated adenocarcinoma (1.24 ± 0.57%). There was no difference in ADC between groups classified based on any pathological factor.

Conclusion: Amide proton transfer imaging can predict tumor grade in rectal cancer.

1. Introduction

Colorectal cancer has become one of the leading causes of cancer-related death, accounting for 30% to 35% of these cases [1]. The current trend in the treatment of rectal cancer is a more widespread acceptance of neoadjuvant therapies. Therefore, it is clinically important to develop noninvasive methods to select high-risk patients who need more aggressive multimodality treatment [2]. Magnetic resonance imaging (MRI) has achieved broad acceptance for local staging of primary rectal cancer prior to therapy [3]. For example, thin-section T2-weighted imaging (T2WI) can be utilized to evaluate the extramural depth of tumor invasion correctly [4]. However, new MRI techniques can provide not only morphological details of the lesions, but also functional parameters with the potential to be applied as cancer biomarkers. For example, diffusion-weighted imaging (DWI) reflects water diffusion characteristics, which are dependent on multiple factors such as cell density, vascularity, viscosity of extracellular fluid, and cell membrane integrity [5]. DWI expresses these properties as apparent diffusion coefficients (ADCs), and ADCs in turn have proven to be viable imaging biomarkers for prognostic purposes in various malignant tumors [6–11]. Although a few reports have suggested the potential of ADCs as imaging biomarkers for tumor malignancy in rectal cancer

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[12–14], the usefulness of ADCs in terms of predicting the response to chemoradiation is controversial; conflicting results have been reported [15–18]. Therefore, ADCs may not be reliable imaging biomarkers for rectal cancer given the present technologies. There is thus need of a new imaging biomarker that complements other MR methods for the clinical treatment of rectal cancer.

Chemical exchange saturation transfer (CEST) has drawn considerable attention in the field of molecular imaging as a novel contrast mechanism in MRI [19,20]. CEST contrast is achieved by applying a saturation pulse at the resonance frequency of a slow intermediate exchanging proton site (−NH, −OH, or metal-bound water molecule) of endogenous or exogenous agents, and the resulting saturated or partially saturated spin is transferred to bulk water via chemical exchange. As a result, the signal intensity of bulk water is reduced, thereby providing negative contrast in an image. Zhou et al. [21] developed amide proton transfer (APT) imaging as an endogenous CEST imaging technique. With this method, the exchange between protons of bulk water and the amide protons (−NH) of endogenous mobile proteins and peptides can be imaged. That is, the amount of proteins and peptides can be estimated with APT imaging non-invasively. Previous studies have demonstrated the usefulness of APT signal intensity (SI) to predict the tumor grade in glioma [22], the Gleason score in prostate cancer [23] and the differentiation in lung tumors [24]. Because tumor cells have a high proliferative activity and protein synthesis is also active in such tumors, the difference in amount of proteins or peptides may reflect tumor malignancy. Therefore, APT SI obtained by APT imaging, which probably reflects molecular changes in a very different manner from ADC, could be a potential imaging biomarker. We hypothesized that pretreatment APT SI could suggest tumor malignancy of rectal cancer as well.

The purposes of this study were to prospectively investigate the ability of APT SI to predict tumor malignancy as defined by pathological findings in rectal cancer and to compare its ability with that of ADC.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board and complied with ethical committee standards. Written informed consent was obtained from all subjects before their enrollment in the study. From April of 2012 to June of 2015, 61 consecutive adult patients underwent MR examination including APT imaging and DWI for evaluation of rectal cancer, which was pathologically diagnosed as adenocarcinoma by biopsy under endoscopy. Five, three and two patients were excluded due to therapy in other hospitals, poor image quality and too small size for evaluation, respectively. Among the remaining 51 patients, 22 patients who underwent operation only were enrolled in this study. The enrolled patients consisted of 11 men and 11 women (age range, 45–79 years; mean age, 65 years). The MR examinations were performed within one month before surgery for all patients.

2.2. MRI

APT imaging was performed on a clinical whole-body 3.0-Tesla MR system equipped with dual-source parallel RF transmission technology (Achieva 3.0T TX; Philips Healthcare, Best, the Netherlands). A 32-channel torso-cardiac coil and a parallel imaging technique were used. Intramuscular injection of butylscopolamine (Buscopan 20 mg; Nippon Boehringer Ingelheim, Tokyo, Japan) was given to prevent image degradation due to bowel motion before the patient entered the MR scanner. APT imaging, in addition to T1-weighted imaging (T1WI), T2WI, DWI and contrast-enhanced T1WI, was scanned. APT imaging was acquired before administration of gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA, Bayer HealthCare, Osaka, Japan).

The acquisition software was modified to alternate the operation of the two transmission channels during the RF saturation pulse, which enables long quasi-continuous RF saturation beyond the 50% duty cycle of a single RF amplifier. Special RF shimming for the saturation homogeneity of the alternated pulse was applied, adjusting the RF amplitudes of the two transmission RF sources to equalize the B1-field [22,23]. On a single slice corresponding to the maximum cross-sectional area of the tumor, 2-dimensional (2D) axial APT imaging was performed using a saturation pulse with a duration of 0.5 s (10 × 50 ms, sinc-Gaussian-shaped elements) and a saturation power level corresponding to $B_{1,rms} = 2.0\,\mu T$. This single slice, on which the tumor appeared to be the largest, was selected as the reference in comparisons to T1WI, T2WI and DWI. For acquiring an APT Z-spectrum, the imaging was repeated at 25 saturation frequency offsets from $\omega = -6.0$ to $+6.0$ ppm with a step of 0.5 ppm as well as one far-off resonant frequency ($\omega = -1560.0$ ppm) for signal normalization. The other MR parameters of APT imaging were as follows: single-shot fast spin-echo readout with driven equilibrium refocusing; repetition time (TR)/echo time (TE), 5000 ms/6 ms; field of view (FOV), 230 × 230 mm; spatial resolution, 1.8 × 1.8 × 5.0 mm^3; slice thickness, 5 mm; echo train length (ETL), 128; sensitivity encoding (SENSE) factor, 2; total scan time, 2 min 20 s for one Z-spectrum. A ΔB_0 map for off-resonance correction was acquired separately using a 2D gradient echo with identical spatial resolution ($\Delta TE = 1.0$ ms), and it was used for pixel-by-pixel ΔB_0 correction.

The details of other MR sequences were shown in Appendix 1. An ADC map was automatically generated on a mono-exponential model by referring to SIs of DWI with b-values of 0, 500 and 1000 s/mm^2. For contrast-enhanced T1WI the amount of Gd-DTPA was based on body weight (0.2 mL/kg), and the total volume was injected intravenously before scanning.

2.3. Data analysis

APT imaging data were analyzed with the software program Image J (National Institutes of Health, Baltimore, MD, USA). We utilized the analysis method reported by Togao et al. [22]. A plug-in was created to assess the Z-spectra and magnetization transfer ratio asymmetry (MTR_{asym}) equipped with a correction function for B_0 inhomogeneity, using interpolation among the Z-spectral image data. First, rigid-body-motion correction was performed using the TurboReg algorithm [25]. The local B_0 field shift, in Hertz, was obtained from the B_0 map, which was created from dual-echo gradient-echo images (TE 1 and 2 ms) according to the following equation: $\Delta B_0(x)$ = (Phase[TE2](x) − Phase [TE1](x)) / (TE2 − TE1) ∗ 2 ∗ Pi, where phase [TEi](x) indicates the phases of the images with echo times TE1 or TE2 at position x in radians, and TE1 and TE2 are given in seconds. The ΔB0(x) is the resulting B0 map measured in Hertz. Each voxel was corrected in image intensity for the nominal saturation frequency offset by Lagrange interpolation among the neighboring Z-spectral images. This procedure corresponds to a frequency shift along the saturation frequency offset axis according to the measured B_0 shift.

The MTR was defined as $1 - S_{sat}/S_0$, where S_{sat} and S_0 are the SIs obtained with and without selective saturation, respectively [19]. To

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