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Urologic Oncology: Seminars and Original Investigations 33 (2015) 337.e15–337.e24

UROLOGIC ONCOLOGY

Original article

Histogram analysis of diffusion kurtosis magnetic resonance imaging in differentiation of pathologic Gleason grade of prostate cancer

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Received 10 April 2015; received in revised form 2 May 2015; accepted 3 May 2015

Abstract

Objective: To investigate diagnostic performance of diffusion kurtosis imaging with histogram analysis for stratifying pathologic Gleason grade of prostate cancer (PCa).

Materials and methods: This retrospective study was approved by the institutional review board, and written informed consent was waived. A total of 110 patients pathologically confirmed as having PCa (diameter >0.5 cm) underwent preoperative diffusion-weighted magnetic resonance imaging (*b* value of 0–2,100 s/mm^2) at 3 T. Data were postprocessed by monoexponential and diffusion kurtosis models for quantitation of apparent diffusion coefficients (ADCs), apparent diffusion for Gaussian distribution (D_{app}), and apparent kurtosis coefficient (K_{app}). The measurement was based on an entire-tumor histogram analysis approach. The ability of imaging indices for differentiating low-grade (LG) PCa (Gleason score [GS] $\leq$ 6) from intermediate-/high-grade (HG: GS $>$ 6) PCa was analyzed by receiver operating characteristic regression.

Results: There were 49 LG tumors and 77 HG tumors at pathologic findings. HG-PCa had significantly lower ADCs, lower diffusion kurtosis diffusivity (D_{app}), and higher kurtosis coefficient (K_{app}) in mean, median, 10th, and 90th percentile, with higher D_{app} in skewness and kurtosis than LG-PCa ($P < 0.05$). The 10th ADCs, the 10th D_{app}, and the 90th K_{app} showed relatively higher area under receiver operating characteristic curve (Az), Youden index, and positive likelihood ratio in stratifying aggressiveness of PCa against other indices. The 90th K_{app} showed relatively higher correlation ($\rho > 0.6$) with ordinal GS of PCa; significantly higher Az, sensitivity, and specificity (0.889, 74.1%, and 93.9%, respectively) than the 10th D_{app} did (0.765, 61.0%, and 79.6%, respectively; $P < 0.05$); and higher Az and specificity than the 10th ADCs did (0.738 and 71.4%, respectively; $P < 0.05$) in differentiating LG-PCa from HG-PCa.

Conclusions: It demonstrated a good reliability of histogram diffusion kurtosis imaging for stratifying pathologic GS of PCa. The 90th K_{app} had better diagnostic performance in differentiating LG-PCa from HG-PCa.

Keywords: Prostate cancer; DKI; Histogram analysis; D_{app}; K_{app}

1. Introduction

Prostate cancer (PCa) is one of the most primary malignant tumors worldwide. A patient newly diagnosed with PCa faces a variety of treatment options depending on an accurate assessment of the aggressiveness and stage of the disease and the likelihood of recurrence [1,2]. Preoperatively determining tumor aggressiveness of PCa is vital for selecting the optimal therapy, and it is thus helpful for the improvement of active surveillance. Pathologic Gleason score (GS) is one of the most useful markers for prediction of biological aggressiveness, disease outcome, and risk of mortality in PCa [3]. However, determination of GS is based on invasive biopsy or radical prostatectomy (RP), which can be associated with severe adverse effects [4]. Therefore, to preoperatively distinguish low GS from high GS cancer would be a major advance and would have a significant benefit for individualized treatment options.

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http://dx.doi.org/10.1016/j.urolonc.2015.05.005
1078-1439/

Recently, advances in magnetic resonance imaging (MRI) of prostate with diffusion-weighted imaging (DWI) have resulted in greater ability in determination of localized PCa and prediction of its pathologic Gleason grade [5–9]. The correlations between GS of PCa and apparent diffusion coefficients (ADCs) obtained from DWI have been strongly shown by histopathologic-radiologic studies, and the studies have explained it as a result of increased cellularity in high GS tumor [10–12]. However, actually in intravital tissues, ADC reflects the ability of water molecules to move freely and is influenced by a number of factors, e.g., cellularity, cell membrane integrity, viscosity, and microcirculation. In a conventional diffusion theory, the displacement of freely mobile water molecules diffusing from one location to another in a certain time is considered to have a Gaussian distribution. Based on this Gaussian diffusion behavior, a monoexponential decay model with equally spaced semi-permeable barriers and biexponential intravoxel incoherent motion imaging model with water exchange in different tissues and intracellular and extracellular spaces have been adopted for diffusion analysis in clinical study [13–15]. Recently, Jensen et al. [16,17] argued that the water diffusion probability distribution function can be referred to as non-Gaussian because of the presence of barriers (e.g., cell membrane) and compartments (e.g., intracellular and extracellular spaces) in many biological tissues. So the non-Gaussian distribution may be a true condition in tissue, and a diffusion kurtosis (DK) model was established to provide a more complete characterization of water diffusion in the brain, head and neck [18,19], breast [20], and even for the whole body [21]. Rosenkrantz et al. [22] used the DK model to assess the aggressiveness of peripheral zone (PZ) cancer of the prostate, and an increased value of DK imaging was demonstrated in cancer assessment against standard DWI . However, the study was limited by the lack of a precise histological reference standard to define regions of cancer. Suo et al. [23] and Tamura et al. [24] also conducted a similar study about PCa, but the patient population size was relatively small. Moreover, the existing studies are limited by the performance with a region of interest (ROI)–based measurement. Such method (e.g., placed regional ROIs on a representative section of the tumor) has been pointed out as a limitation of many studies [25,26] in which the overlap of a single measurement may lead to interobserver variability in ROI placement, and inappropriate ROI placement may not accurately reflect various biological features of the tumor (e.g., in distinguishing foci with high cellularity from these with low cellularity). A histogram analysis approach has been shown a promising way in discriminating tumor grade, differentiating their subtypes, and assessing therapeutic effect of cancer [15,27–29].

Accordingly, the purpose of this study was to primarily investigate diagnostic performance of DK imaging with an entire-tumor histogram analysis approach for stratifying Gleason grade of PCa, by using postoperatively pathologic results as the reference standard.

2. Materials and methods

2.1. Patients

Our institutional review board approved this retrospective study and waived the informed consent requirement for it. Between August 2013 and January 2015, 139 consecutive patients with clinically localized PCa (proved by biopsy examination) underwent standard pelvic MRI examination before RP treatment. Patients with the following criteria were included: (a) not undergone prior hormonal or radiation treatment, (b) DWI performed on one 3.0-T MRI scanner and with unified sequence parameters, (c) the diagnosis of "primary" PCa, and (d) performance of detailed histopathology where at least one tumor focus with a diameter of 0.5 cm or more is available for multiparametric DW-MRI calculation. A total of 110 patients met all inclusion criteria and were included in this study. The other 29 patients were excluded because parameters of DWI were not unified (n = 5), the tumor was too small (n = 14), or neoadjuvant therapy was administered before the MRI examination (n = 10).

2.2. MRI Protocols

MRI examinations were performed with a 3.0-T MRI scanner (Trio Tim; Siemens, Erlangen, Germany) and a pelvic phased-array coil. As per the standard clinical prostate MRI examination at our institution, the images obtained included transverse T1-weighted turbo spin-echo images (repetition time ms/echo time ms, 700/14; section thickness, 3.5 mm; intersection gap, 0.5 mm; field of view, 25 cm; and matrix, 384 × 336) and transverse, coronal, and sagittal T2-weighted turbo spin-echo images (repetition time ms/effective echo time ms, 6,000/124; section thickness, 3.5 mm; intersection gap, 0.3 mm; field of view, 25 cm; and matrix, 384 × 336) of the prostate and seminal vesicles. Then, single-shot echo-planar imaging (repetition time ms/echo time ms, 6,800/98; field of view, 25 cm; matrix, 192 × 130; section thickness, 3.5 mm; intersection gap, 0.3 mm; a parallel imaging factor of 2; and 13 sections) was performed with diffusion-module and fat-suppression pulses. Diffusion in 3 directions was measured by using b values of 0; 700; 1,400; and 2,100 s/mm^2. Dynamic contrast material–enhanced imaging was also performed but not assessed in this study.

2.3. Imaging and histological correlation

After RP, the prostatic specimens were uniformly processed and submitted for histological investigation. The prostatectomy specimens were fixed in 10% neutral buffered formalin and stored overnight after surgical resection. Prostatectomy specimens were fixed in 5% buffered formalin, processed, and cut serially into 3.5-mm-thick blocks from apex to base in transverse planes. Each block was then halved or quartered (depending on its size), and microtome slices measuring 7 to 8-μm thick were