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Original contribution

Intravoxel incoherent motion diffusion weighted MRI of cervical cancer — Correlated with tumor differentiation and perfusion

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ABSTRACT

Objectives: To investigate the value of parameters derived from IVIM model in grading of uterine cervical cancer and the relationship between perfusion parameters derived from IVIM and that from DCE-MRI.
Methods: Parameters of DWI (ADC, D, f, D*) and semi-quantitative parameters of DCE-MRI (Slop, Maxslop, CER, Washout, AUC90) were assessed in 24 female with cervical cancers. Except for ROIs encompassed all of the area of tumors in axial plane (A_all), ROIs on tumor edge (A_peri) and tumor center (A_central) were drawn. All of the parameters were compared among three pathology grades. Perfusion parameters derived from IVIM were correlated with that from DCE-MRI.
Results: For G1, G2 and G3 tumors, on tumor edge ADC = (1.03 ± 0.11), (1.05 ± 0.10), (0.90 ± 0.05) × 10^{-3} mm^2/s, D = (0.80 ± 0.11), (0.78 ± 0.07), (0.69 ± 0.06) × 10^{-3} mm^2/s, and f = (0.19 ± 0.03), (0.22 ± 0.02), (0.24 ± 0.03). The differences among groups were significant ($P < 0.05$). On tumor center, ADC = (0.90 ± 0.10), (0.85 ± 0.03), (0.80 ± 0.07) × 10^{-3} mm^2/s with significant differences ($P = 0.027$). The other parameter, D and f of tumor center, as well as D* of all tumor areas, were of no statistic significance. Most of the DCE-MRI parameters negatively correlated with tumor volume. Although the correlation between f and slop was statistic significant, $R = 0.277$ meant a negligible correlation. f had week correlation with Maxslop, CER and AUC90 ($R = 0.361$, 0.400 and 0.405; $P < 0.001$). D* showed no statistic significant correlation with all of the DCE parameters.
Conclusion: IVIM model could possibly be used to evaluate tumor differentiation and perfusion, providing an alternative for DCE-MRI.

1. Introduction

Diffusion weighted imaging (DWI) is an MR technique which is sensitive to the Brownian motion of water molecules in a tissue and largely depends on its cell density. Apparent diffusion coefficient (ADC) derived from a mono-exponential model of DWI is one of the most widely used quantitative parameters having potentials to differentiate malignant and benign lesions and being related with tumor grading potentially in some malignancies [1]. However, the problem of the mono-exponential model is that water molecules moving within blood flow in microcirculation can be confused with water diffusion and may result in errors in quantitative analysis. Therefore some attempts have been made to separate the perfusion and diffusion part of DWI [2,3]. Intravoxel incoherent motion (IVIM) MR imaging is such a tool which was first described by Le Bihan et al. [4]. Three parameters can be evaluated in this model: (1) true diffusion coefficient (D), also named as slow diffusion coefficient, characterized the thermal diffusion, (2) perfusion-related fast diffusion coefficient (D*) characterized the blood flow of microcirculation, and (3) perfusion fraction (f) described the fraction of incoherent signal arising from the vascular compartment in each voxel.

According to published literatures, the IVIM model had been applied in numbers of different organs, like prostate, pancreas, liver, kidney, cerebrum, etc. [5,6]. These studies showed a promising

Abbreviations: ADC, apparent diffusion coefficient; DCE, dynamic contrast enhanced; DWI, diffusion weighted imaging; FIGO, International Federation of Gynecologists and Obstetricians; IVIM, intravoxel incoherent motion; MVD, micro-vessel density; ROI, regions of interest.

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future that IVIM could be used as a method to assess tissue diffusion and perfusion in vivo without employing any intravenous contrast agent. For advanced cervix cancer, tumor perfusion and its heterogeneity might be markers predicting therapeutic effect and prognosis. Also a few studies have suggested that DWI had some correlation with tumor grading and prognosis [7,8]. Thus, we supposed that IVIM might be a useful tool providing information about tumor invasiveness non-invasively. Previous studies of IVIM always focused on the perfusion part, that is the perfusion fraction f and the perfusion related fast diffusion coefficient D*, in order to differentiate lesions with hypervascular or hypovascular characters. For example, statistically significant differences had been found between the enhancing lesions and non-enhancing lesions of kidney, pancreatic neuroendocrine tumors and adenocarcinomas, breast cancers and the benign lesions [9–11]. The imaging characters of these lesions with contrast enhancement have been interpreted very well in the past, and the variation of perfusion fraction showed in these studies was consistent with that of enhancement degree. However, the correlation between perfusion parameters derived from IVIM and quantitative or semi-quantitative analysis of DCE imaging was not fully studied, and some published literatures of liver showed paradoxical results [12]. Moreover, few published study discussed the pathology basis of IVIM and found that f and microvessel density (MVD) showed positive correlation [13]. So, perfusion parameters should be further investigated both on their correlation with traditional imaging parameters of perfusion and on their pathology basis.

Therefore, the purpose of this study is to: (a) discuss the ability of IVIM perfusion parameters and semi-quantitative analysis to indicate tumor grading; and (b) study the correlation between IVIM perfusion parameters and semi-quantitative analysis of DCE-MR.

2. Materials and methods

2.1. Patients

This study was approved by our institutional review board and informed consent was obtained from all patients. Between June 2012 and July 2013, 27 consecutive female patients with biopsy proven uterine cervical squamous cell cancers had undergone MR imaging. 3 of them were excluded, because the diameter of each of the lesions was less than 1 cm. It was too small to be measured accurately. The other 24 patients were enrolled in this study. All of the patients were with no medical or radiation treatment for uterine cervical cancer before their MR examinations.

2.2. MR examination

In order to reduce bowel peristalsis, patients were recommended to fast for 4–6 h before imaging and 20 mg of the spasmolytic agent Scopolamine Butylbromide was given intramuscularly to all patients immediately prior to MR examination. All MR examinations were performed using a 3.0-T unit (Discovery MR750, GE Healthcare, USA) and an 8-channel phased array cardiac coil. Patients were in the supine position throughout the examination.

Before DWI, conventional T_2-weighted fast recovery fast spin-echo (FRFSE) imaging was performed in the sagittal, transverse and coronal planes (TR = 4368–6688 ms, TE = 98–105 ms, bandwidth (BW) = 62.5 kHz/pixel, echo chain length (ECL) = 24, number of excitations (NEX) = 2, matrix size = 288 × 288, field of view (FOV) = 22 cm, slice thickness = 4 mm, gap = 0.4 mm). T_1-weighted fast spin-echo imaging was performed in the transverse plane (TR = 484 ms, TE = 6.72 ms, BW = 62.5 Hz/pixel, ECL = 4, NEX = 2, matrix size = 320 × 224, FOV = 32 cm, slice thickness = 5 mm, gap = 1 mm).

Diffusion-weighted MR images were acquired using a non-breath-hold single-shot spin-echo echo-planar imaging (EPI) sequence in the transverse plane, 10 b values of 0, 30, 50, 100, 150, 200, 400, 800, 1000 and 1500 s/mm^2 were used (TR = 2600 ms, TE = 71.5 ms, BW = 250 kHz/pixel, matrix = 160 × 160, FOV = 34cm, slice thickness = 5.0 mm, gap = 1 mm).

During the dynamic enhancement imaging, T_1-weighted LAVA in the axial plane was obtained (TR = 3.1 ms, TE = 1.4 ms, BW = 166.67 kHz/pixel, flip angle = 12°, NEX = 1, matrix = 260 × 224, FOV = 30 × 27 cm, slice thickness = 3 mm, gap = −1.5 mm). Right after the first phase was finished as the baseline non-enhanced images, the bolus injection of Gadopentate Dimeglumine (Gd-DTPA) (0.1 mmol/kg at a rate of 2 ml/s) started and immediately followed by a flush of 20 ml of 0.9% sodium chloride solution at the same rate. Acquisition of following 20 phases with no interval of DCE images began with the start of bolos injection and was completed in 196 s.

2.3. Imaging analysis

Images were transferred to a GE AW4.5 Workstation. Analysis was accomplished by a radiologist with 5 years of experience of diagnostic imaging in gynecology, who was unaware of the surgical and pathological results of the patients. Analysis of DWI was performed with the build-in software (AW4.5 Functool, GE Healthcare). D, D*, f maps of bi-exponential model as well as ADC maps of mono-exponential model were calculated on a pixel-by-pixel basis. The bi-exponential model was fitted with the equation: $S_b/S_0 = (1 - f)\exp(-b\cdot D) + f\cdot\exp(-b(D + D^*))$, where S_b represents the signal intensities (SI) with different b values and S_0 represents the SI without diffusion sensitive gradient. Analysis of DCE-MRI was carried out using a GE Cinetools software. Functional maps of the following semi-quantitative parameters were calculated: the slope (Slop; second^{-1}) and maximum slope of contrast uptake (Maxslop; second^{-1}), contrast enhancement ratio (CER; ratio of the average signal within the ROI after the arrival of contrast to the average signal in the pre-contrast images), the washout curve (Washout; second^{-1}) and the areas under the curve within initial 90 s (AUC90).

All of measurements were obtained by using different regions of interest (ROIs) from each slice contained tumor area and the number of each slice was recorded. To avoid partial volume effect, the first and the last slices were excluded. For every tumor, three kinds of ROIs were defined by tracing a line freehand on the DW images with b value equaling to 1000 s/mm^2 at first and were copied to all of the functional maps: (a) an irregular ROI encompassed the whole tumor area of hyper intensity (recorded as A_total_n, n: the slice number), (b) an irregular ROI at the tumor edge, which encompassed the peripheral area within 5 mm of the edge of hyperintense region (recorded as A_peri_n), and (c) an irregular ROI at the tumor center, which encompassed the hyperintense region located 5–10 mm away from the edge (recorded as $A\_central_n$).

For each of the tumors, mean values of these parameters were calculated (e.g. $A\_peri = \Sigma_{i=1}^{n}(A\_peri_n)$) and recorded as A_peri, A_central and A_total respectively. Tumor volume was calculated by multiplying A_total on each section by slice thickness plus gap. Examples of ROI placement were shown in Fig. 1.

2.4. Histopathological evaluation

All of the tissue samples with hematoxylin–eosin staining were reviewed by two gynecology pathologist together (one of them was with 5 years of experiences in gynecology pathology and the other