EJGO European Journal of Gynaecological Oncology

Application of diffusion-weighted MRI for endometrial cancer diagnosis

Y. Zhou[1], L. Jiang[2], T. Nuerlan[1]

[1]Department of CT, The Affiliated Tumor Hospital of Xinjiang Medical University, Urumqi, Xinjiang Uygur Autonomous Region
[2]Depatrment of Radiology, the People's Hospital of Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region (China)

Summary

Objective: To investigate the usefulness of diffusion-weighted magnetic resonance imaging (DW-MRI) for the diagnosis of endometrial cancer and to verify the feasibility of apparent diffusion coefficient (ADC) values to distinguish normal and endometrial cancer. *Material and Methods:* There were 24 patients with confirmed endometrial cancer enrolled into this study and underwent preoperative MRI and total hysterectomy. Twenty-two healthy volunteers were included as control. The apparent diffusion coefficient of endometrial cancer and normal endometrium were measured on the apparent diffusion coefficient map of each diffusion-weighted image and compared. The differences among the ADC values of normal endometrium, junctional zone, and endometrium were compared as well. *Results:* The ADC values of the 22 control groups were as follows: myometrium (1.50±0.08)×10-3 mm^2/s, junctional zone (0.95±0.08)×10-3 mm^2/s, and endometrium (1.33±0.09)×10-3 mm^2/s. The ADC values of endometrial cancer (0.77±0.08)×10-3 mm^2/s was much lower than that of normal endometrium ($p < 0.001$). The mean ADC value for each histologic grade was 0.90±0.11(G1), 0.89±0.13 (G2), and 0.69±0.09 (G3). The ADC value of grade 3 tumors was significantly lower than that of grade 1 tumors ($p < 0.05$). There was a statistically significant difference among the ADC between cancer group and healthy individuals. *Conclusion:* The DW-MRI provides helpful information for evaluation of endometrial cancer.

Key words: Apparent diffusion coefficient; Cancer; Diffusion-weighted imaging; MRI; Uterus.

Introduction

In 2009, the International Federation of Gynecology and Obstetrics (FIGO) revised the new surgical staging system for endometrial cancers [1]. Precise assessment of tumor stages in uterine endometrial cancer is necessary to determine the choice of treatment. Currently, the magnetic resonance imaging (MRI) is a widely accepted option for evaluation of endometrial cancer, and the cancer lesion could be better defined at T2-weighted imaging in conventional MRI. On T2-weighted images, uterine cancers often present as a large infiltrating myometrial mass due to the intermediate or high signal intensity [2]. However, conventional MRI does not always clearly demonstrate the focus of the tumor, since the signal intensity of the endometrial cancer can range from high intensity to low intensity, and is sometimes indistinguishable from normal endometrium or adjacent myometrium [3].

Diffusion-weighted imaging (DWI) is an emerging technique used to show tissue characteristics based on the diffusion motion of water molecules that is known as Brownian motion [4]. Recently, the application of diffusion weighted magnetic resonance imaging (DW-MRI) has been reported in several studies [1, 2, 5-7]. DWI has a high potential to identify the pathologic lesions as foci of increased intensity which differentiated from suppressed background signals. The ADC value has been reported to be valuable for distinguishing malignancy from benign lesions [2, 5-8]. DWI with apparent diffusion coefficient (ADC) measurement has the capability to show the earlier abnormalities during the disease progression than the routine imaging techniques [9, 10]. Therefore, the purpose of this study was to calculate the normal and diseased ADC values of the uterine zones and to evaluate the usefulness in the diagnosis of endometrial cancers.

Materials and Methods

From November 2005 to December 2009, there were in total 24 patients with highly suspected endometrial carcinoma enrolled in this study. There patients were admitted to the present hospital due to abnormal vaginal bleeding, and the transvaginal sonographic finding of an endometrial lesion underwent diffusion weighted imaging (DWI) in addition to routine MRI for staging purposes. All patients underwent total hysterectomy and were pathologically diagnosed for endometrial cancer by surgical resection. The control group with the normal endometrium was selected from 22 healthy volunteers who underwent preoperative MRI during the same time period. This study was conducted by closely following ethical guidelines of local authority as well as recommendations of the Declaration of Helsinki (Seoul revision, 2008). All participating patients were formally informed of the purpose of this study and a letter of consent was signed by every subject involved.

Revised manuscript accepted for publication September 19, 2016

All patients and volunteers were scanned by using a 1.5-T MRI scanner with a four-channel torso phased array coil. The sequences used for pelvic MRI were as follows: T2-weighted fast multi-shot spin echo in the sagittal and oblique axial planes (4000/109 [repetition time ms/effective echo time ms]) and T1-weighted spin echo in the oblique axial plane (520/11 [repetition time ms/effective echo time ms]). The oblique axial plane was determined by the relation to the sagittal plane and perpendicular to the uterine body to best show the relation between the endometrium and the myometrium. The pulse-sequence for DWI was a multi-section spin-echo type, single-shot echo planar imaging sequence along the axial and sagittal plane under free breathing scanning (TR/TE=3400-7500/68 ms, band width 143 Khz, slice thickness 5 mm, field of view 24×24 cm, matrix 256×256, seven excitations, water excitation with *b*-value of 0 and 1000 mm^2/s). A high *b*-value of 1000 mm^2/s was chosen because it was previously reported that a *b*-value higher than 500 mm^2/s was necessary for the precise evaluation of ADCs in the pelvic region. The ADC maps were created by signals obtained from images with two *b*-values.

Visual evaluation of the images was performed by two experienced radiologists who were blinded to the results of pathologic stage, location, and histologic grade of the tumor from resection in a consensus manner. In the endometrial cancer group, the following items were assessed: 1) the presence of the tumor on both T2-weighted images and DWIs with a *b*-value of 1000 mm^2/s, 2) the signal intensity of the tumor relative to that of the adjacent myometrium on T2-weighted images, and 3) the signal intensity of the tumor, normal endometrium, junctional zone, and myometrium on DWIs with a *b*-value of 1000 mm^2/s (whether they showed increased intensity or not). ADC maps were generated on the scanner console using *b*=0 and *b*=1000 images. The DWI data sets were transferred to an independent workstation (Leonardo console, software version 4.0) for postprocessing. MRI studies were analyzed and measurements were made by one radiologist (Z.Y), experienced in abdominal radiology. DWIs were of diagnostic quality in all cases and no cases were excluded from the study. The quality of the images was evaluated by the same radiologist, and it was determined whether the images were acceptable for further analysis or not. The ADC maps were calculated and mapped by the imaging system software. To measure normal ADC values, a circular region of interest (ROI) was placed on each uterine zone. The measurements were obtained from the same parts of each zone. The myometrium was measured from the anterior wall of the corpus uteri. The junctional zone was measured from the same level. The calculation of the endometrium was performed at the fundus level. The areas of the ROI in the control and patient groups of the myometrium, endometrium, and junctional zone were about 0.4-4.7 cm^2. For each ADC value measurement, three ROIs were placed and the average was accepted.

The data was presented as mean ± standard deviation. All results got from both patients group and health control were analyzed by student's *t*-test analysis with SPSS 13.0 software. A *p*-value less than 0.05 was considered as statistically significant.

Results

Representative cases are shown in Figures 1, 2, and 3. Endometrial cancer was demonstrated in all patients on both T2-weighted images and DWIs with a *b*-value of 1000 s/mm^2. On DWIs all endometrial cancers were clearly depicted as an increased intensity area corresponding to the tumor on T2-weighted images, with the myometrium hypointense in 21 cases. In three case with the isointense tumor compared with the myometrium, the border between the tumor and the adjacent myometrium could not be clearly identified on T2-weighted images. DWIs could accurately depict the precise extent of the tumor. On ADC map images, endometrial cancers and all the normal endometrium could be clearly identified. In the control group, all the normal endometrium appeared hyperintense on both T2-weighted images and DWIs (Figure 4). The mean and the standard deviation of the ADC values of the 22 control groups were as follows: myometrium (1.65±0.08)×10-3 s/mm^2, junctional zone (0.95±0.08)×10-3 mm^2/s, endometrium (1.33±0.09)×10-3 mm^2/s. There were statistically significant differences among the ADC values of the myometrium and endometrium ($p < 0.05$), the myometrium, and junctional zone ($p < 0.001$), and the endometrium and junctional zone ($p < 0.001$). The mean and the standard deviation of the ADC values of the endometrial cancers were (0.77±0.09)×10-3 mm^2/s. There was a statistically significant difference among the ADC values of normal endometrium and endometrial cancer ($p < 0.001$). The histopathological results proved adenocarcinoma in all of the 24 patients. The histologic grade of endometrial cancer were grade 1 (n=14), grade 2 (n =7), and grade 3 (n=3). The mean ADC value for each histologic grade was (0.90±0.11)×10-3 mm^2/s (grade 1), (0.89±0.13)×10-3 mm^2/s (grade 2), and (0.69±0.09)×10-3 mm^2/s (grade 3), respectively. The ADC value of grade 3 tumors was significantly lower than that of grade 1 tumors ($p < 0.05$).

Discussion

DW-MRI is the thermally induced motion of water molecules in biological tissues, called Brownian motion. It is a functional imaging technique whose contrast derives from the random motion of water molecules within tissues [11]. Because image contrast is derived from inherent differences in the restriction of the movement of water molecules, diffusion-weighted sequence is able to highlight both oncological and non-oncological lesions throughout the entire body. Improvements in MRI pelvic coils, software have allowed for greater speed of data acquisition and superior image quality, all accounting for the widespread use of DWI in gynecological cancers. In clinical practice, DW-MRI is usually performed at two or more *b*-values, which always include one or more low *b*-values (0 or 50 mm^2/s) and a very high *b*-value (usually -1000 mm^2/s). The use of a high *b*-value makes images more sensitive to water diffusion; hence, it increases contrast enhancement between normal and cancerous tissue [12]. DWI with high *b*-value in the present study showed the advantages of higher signal-to-noise ratio and better image contrast at 1.5T. On high *b*-value DWIs, endometrial cancers were clearly depicted as a hyperintense areas, whereas normal myometrial signals were effectively suppressed. Histologically, normal en-

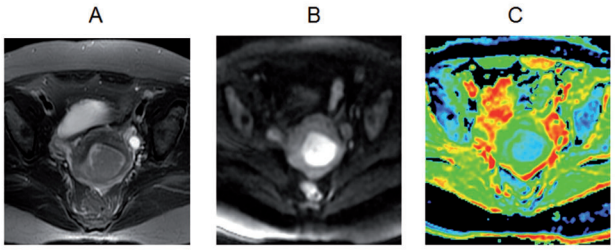

Figure 1. — Endometrial cancer imaging. (a) T2-weighted axial image shows an ill-defined hypointense mass in the posterior myometrium. (b) Axial DWI shows marked heterogeneous hyperintense area corresponding to the tumor. (c) ADC map image shows hypointensity (restricted diffusion) compared with normal parenchyma.

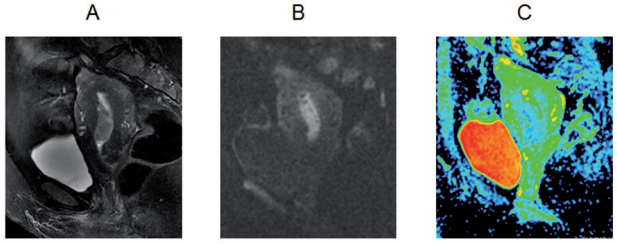

Figure 2. — Well-differentiated endometrioid adenocarcinoma (grade 1). (a) Sagittal T2-weighted image shows a tumor in the endometrial cavity. (b) DWI shows an increased signal intensity corresponding to the endometrial tumor. (c) ADC map image shows the tumor as a slightly hypointense area compared with normal parenchyma.

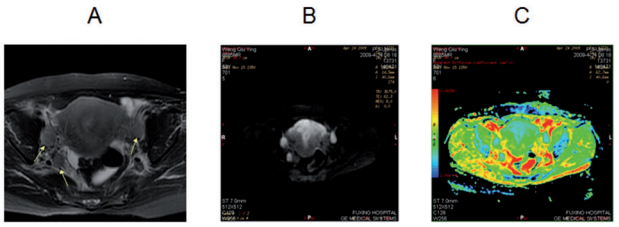

Figure 3. — Poorly-differentiated endometrioid adenocarcinoma (grade 3). (a) Axial T2-weighted image shows a mass of intermediate signal intensity in the endometrial cavity and the whole myometrium with reactive lymph nodes (arrow).The exact extent of the tumor is not clearly recognized in this image due to poor contrast between the tumor and the adjacent myometrium.(b) DWI shows the extent of the tumor more clearly. (c) ADC map image demonstrates the tumor as a prominent hypointense area compared with normal parenchyma.

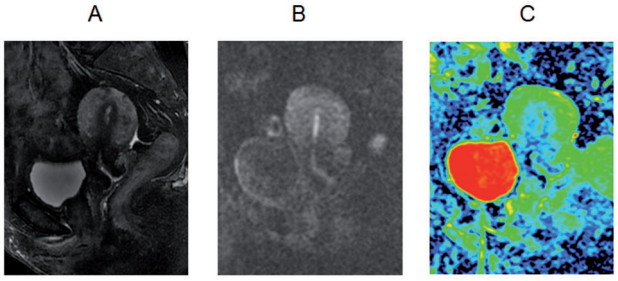

Figure 4. — A 47-year-old pre-menopausal woman with normal endometrium and normal myometrium. (a) T2-weighted sagittal image shows high signal intensity in the endometrium and low signal intensity in the myometrium. (b) Sagittal DWI shows high signal intensity in the endometrium and low signal intensity in the myometrium. (c) ADC map image demonstrates the normal endometrium as a hyperintense area.

dometrium in women of reproductive age is composed of endometrial glands and endometrial stromal cells, which are highly cellular and contain abundant cytoplasm. Accordingly, high intensity on DWIs may be attributable to abundant water molecules confined within intracellular space of endometrial stromal cells. In solid tumors of high cellularity, there are additional significant reductions in extracellular space, resulting in further restrictions to free water movement. The ADC relates to the molecular translational movement of water molecules. This movement is limited in an environment that contains structures such as cell membranes [11-13]. Decreased ADC values therefore correlate with increased tumor cellularity and total nuclear area, which act to restrict water diffusion [14, 15].

Since an endometrial biopsy may usually not be helpful for the definitive diagnosis of endometrial cancer, MRI may play an important role for diagnosing these tumors and determining appropriate management. By providing information on extracellular-space tortuosity, tissue cellularity, and the integrity of cellular membranes, DWI has potential roles in distinguishing cancerous from normal tissues, determining lesion aggressiveness, and monitoring response to therapy [16]. Regarding myometrial invasion, Shen *et al.*[10] reported a diagnostic accuracy of 0.62 using 1.5-T DWI. Lin *et al*. [5] showed an even higher accuracy of 0.88 by using fused T2-weighted and DW imaging at 3 T. Recent studies [2, 6, 8] used 1.5T DWI for patients with endometrial cancer, focusing on differentiating various endometrial disease by using the ADC value. Tamai *et al*. [9] evaluated 18 endometrial cancers and 12 normal endometrium by DWI (b=500 and 1000 s/mm2), and the ADC values in endometrial cancers and normal endometrium were 0.88±0.16×10-3 mm^2/s and 1.53±0.10×10-3 mm^2/s, respectively ($p < 0.01$). Inada *et al.* [17] evaluated 22 endometrial cancers and 31 normal endometrium by DWI (b=800 mm^2/s). The ADC values in endometrial cancers and normal endometrium were 0.97±0.19×10-3 mm^2/s, and 1.52±0.20×10-3 mm^2/s, respectively ($p < 0.0001$). Takeuchi *et al.* [6] evaluated 45 endometrial cancers and 22 benign lesions (hyperplasia and polyps) by DWI (b = 800 mm^2/s). The ADC values in endometrial cancers and benign lesions were 0.84±0.19×10-3 mm^2/s and 1.58±0.36×10-3 mm^2/s, respectively ($p < 0.0001$). Kilickesmez *et al*. [18] evaluated 107 benign and malignant uterine pathologies and 50 healthy controls by DWI (b=0.500,1000 mm^2/s) with ADC values. The mean and the standard deviation of the ADC

values of the control group were as follows: myometrium 1.76±0.19x10-3 mm^2/s, junctional zone 0.99±0.18)×10-3 mm^2/s, endometrium 1.65±0.33×10-3 mm^2/s, and cervix 1.71±0.17×10-3 mm^2/s. The ADC values in endometrial cancers was 0.86±0.13×10-3 mm^2/s. Fujii *et al.* [7] reported that endometrial polyps and submucosal leiomyomas revealed increased ADC values when compared with endometrial carcinomas. The ADC values in the malignant and benign endometrial cavity lesions were 0.98±0.19×10-3 mm^2/s and 1.44±0.34×10-3 mm^2/s, respectively. In the present series, the authors obtained high *b*-value (b=1000 mm^2/s) DWI to evaluate water diffusion in the pathological lesions more precisely, with ADC values in 24 endometrial cancers of (0.77±0.08)×10-3 mm^2/s and 22 normal controls of (1.33±0.09)×10-3 mm^2/s, respectively ($p < 0.01$). The mean ADC value of endometrial cancers (0.77) was lower than those of the normal myometrium without any overlap, which corresponds to the above published literatures reporting on decreased ADC values of various malignant tumors.

In endometrial cancer, the vast majority of histologic subtype is endometrioid adenocarcinoma, which is histologically further classified into three grades (grade 1, 2, and 3) based on architectural features. This histologic grade, as well as depth of myometrial invasion, is one of the important prognostic factors, which is highly predictive of the extent of the disease and correlates strongly with the risk of lymph node metastasis and patient survival [8]. In the present study the mean ADC value for each histologic grade for endometrial cancer was 0.90±0.11 (G1), 0.89±0.13 (G2), and 0.69±0.09 (G3), respectively. The ADC value of grade 3 tumors was significantly lower than that of grade 1 tumors ($p < 0.05$). There are some reasons for above results. First, the sample sizes of endometrial cancer were small. Larger series must be conducted to verify our results. Second, the estimation of histologic grade based on ADC values is difficult because of considerable overlap. Third, menstrual phase of the patients was not taken into account in the assessment of the ADC values of the normal myometrium.

In conclusion, DWI has potential as method of differentiating normal and endometrial cancers. It is not time-consuming and is easy to perform. As an adjunct sequence for preoperative evaluation, DWI is sensitive for detecting lesion foci in the examination field and can help to assess myometrial invasion. The present authors believe that DWI should be considered part of routine preoperative MRI evaluation for endometrial cancer.

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Corresponding Author:
T. NUERLAN, M.D.
Department of CT, The Affiliated Tumor Hospital
of Xinjiang Medical University
137 South Liyushan Road
Urumqi, Xinjiang Uygur Autonomous Region
830011 (China)
e-mail: nuerlantuerxun@sina.com