Endometrial cancer: correlation of apparent diffusion coefficient (ADC) with tumor cellularity and tumour grade

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Aims and objectives

Diffusion-weighted (DW) MR imaging visualizes a random microscopic motion of molecules (Brownian motion) and thereby provides a tissue contrast different from that of conventional T1- and T2-weighted images [1]. Initially DW imaging was primarily used in imaging the central nervous system, especially diagnosing acute brain infarctions [2, 3]. Recently DW imaging is performed to detect malignant tumors and provides detailed histological characterization of focal lesions in the abdomen and pelvis [4]. DW imaging and the apparent diffusion coefficient (ADC) demonstrate the features of microstructure such as restriction of water diffusion, nuclear-to-cytoplasmic ratio and tissue cellularity which has been shown to be an important index of tumor grade [5-11]. The ADC values of malignant tumors were lower than those of normal tissue and benign lesions in various organs [8, 12, 13].

Some reports have also demonstrated the utility of ADC measurement in the differential diagnosis of the endometrial cavity lesions such as endometrial polyp, endometrial hyperplasia, submucosal myoma, and endometrial cancer [14]. Moreover, in some previous studies, the relationship between ADC values and tumor grade of endometrial cancer was investigated, and no significant relationship was found except for one study which showed a significant difference between the mean ADC value of grade 1 and grade 3 tumors [14, 15]. However, none of these studies compare the histopathological specimens including tumor cell density.

The purpose of this study is to investigate whether apparent diffusion coefficient (ADC) values of endometrial cancer vary according to histologic cancer cellularity and tumor grade.
Methods and materials

Study patients

We retrospectively reviewed 30 female patients with uterine endometrial cancer who underwent MR examination and subsequent total hysterectomy during the period of January 2010 through January 2013. The mean patient age was 57 years (range, 40-76 years). All patients were pathologically confirmed as endometrial carcinoma (n = 30; G1 in 17 patients, G2 in 7 patients, G3 in 6 patients). This study was approved by the institutional ethics committee.

MR Imaging protocol

MR imaging was performed using a 1.5T MR system (Intera 1.5T in 12 patients and Archieva 1.5T in 18 patients, Philips Healthcare Nederland, Eindhoven, Netherland), and a synergy body coil. Before MR examinations, intramuscular administration of butyl scopolamine (20mg) was performed to reduce peristalsis artifacts. Routine pelvic MR images were acquired as follows in the prone position: sagittal and axial T2-weighted fast spin echo (SE) images [repetition time (TR)/ echo time (TE) = 3800-4300/ 85-100 ms, section thickness/intersection gap = 5/5.5 mm, FOV = 25cm, matrix = 320 x 250 or 256 x 198], and axial or sagittal] T1-weighted SE images [TR/TE = 510-570/8.0-10.0 ms, section thickness/intersection gap = 5/5.5 mm, FOV = 25cm, matrix = 224 x 180]. Diffusion-weighted (DW) image was performed along the axial or sagittal plane, using a using a single-shot, multi-slice spin-echo planer diffusion pulse sequence (FOV = 25cm, matrix = 96 x 86, NEX = 4), with MPG pulse applied along three directions (x, y, z axes) with TR/TE of 3213.4-7121.6/65.9-80.0 ms and b-factors of 0 and 1,000 s/mm$^2$. ADC maps were automatically generated on a post-processing workstation.

MR image analysis

All imaging analyses were performed by a radiologist with 22 years of experience (K.K.) in MRI respectively. The ADC measurements of endometrial tumor were performed on the ADC maps in three different regions of viable tumor area, and the mean and standard deviation of the ADC values were calculated. All endometrial cancers were categorized respectively according to their respective tumor grade from G1 to G3, referring to 2008 FIGO stages of endometrial cancer [21].
Tumor cellularity analysis

The specimens were stained with Hematoxylin-Eosin, and evaluated by an expert pathologist with 10 years of experience (S.T) under the advice of a pathologist with 20 years of experience (I.M.). The number of tumor cell nuclei in high power field (x400) was determined from 3 arbitrarily selected areas where no regressive-degenerative phenomena were observed. The tumor cellularity of each resected lesion was evaluated using an optical microscope (Olympus BX 50).

Statistical analysis:

The statistical analyses were performed using Pearson's correlation coefficient to evaluate the correlation between ADC value and cancer cellularity. High correlation was considered when the value of $r$ was between 0.5 to 1.0, or -0.5 to -1.0.
Results

The mean and standard deviation (SD) of ADC values ($\times10^{-3}\text{mm}^2/\text{s}$) endometrial cancer were 0.85 ± 0.22, and the range was 0.55 to 1.71. The mean and SD of tumor cellularity was 528.36 ± 16.89, and the range was 298.0 to 763.6. (Table.1)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Tumor Grade</th>
<th>ADC value ($\times10^{-3}\text{mm}^2/\text{s}$)</th>
<th>Tumor cellularity (mean)</th>
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**Table 1:** Table 1. The mean apparent diffusion coefficient (ADC) values and tumor cellularity in 30 patients with endometrial cancer

**References:** Radiology, St. Marianna University School of Medicine - Kanagawa/JP

The ADC values showed a significant inverse correlation with tumor cellularity. ($r = -0.74$, $P<0.01$)(Fig.1)
Fig. 1: Fig. 1. Correlation between ADC values and tumor cellularity in endometrial cancer. Scatter plots show the relationship between the mean ADC-value and the mean-tumor cell count in patients with endometrial cancer. There was a significant inverse correlation between the mean ADC-value and the mean tumor-cell count. \( r = -0.74, \ P < 0.01 \)

**References:** Radiology, St. Marianna University School of Medicine - Kanagawa/JP

ADC value was varied from 0.55 to \( 1.71 \times 10^{-3} \text{mm}^2/\text{s} \) (mean: 0.85) in all our 30 cases. Low ADC values appeared to be associated with smaller sized but pronouncedly higher cellularity of tumor cells, which we speculated to be a contributing factor to the diffusion restriction of water molecules.

The lowest ADC value in this study was \( 0.55 \times 10^{-3} \text{mm}^2/\text{s} \), as shown in Fig.2. In this case, low grade endometrial cancer (endometrioid type; G1; tumor invasion<50% of myometrial thickness) showed an exophytic mass with heterogeneously high intensity (arrow) compared with adjacent normal outer myometrium (Fig.2a). Diffusion-weighted image with a b-value of 1,000 seconds/mm² showed a high signal intensity corresponding to endometrial cancer (Fig.2b). ADC map showed
the tumor as heterogeneous hypointense area. The ADC value of the tumor was 0.55 \( \times 10^{-3} \text{mm}^2/\text{s} \) (Fig.2c). High magnification view photomicrograph (H & E stain, X400) showed high cellularity of tumor cells with glandular architecture. Mean tumor cellularity is 760 ± 21.9 (Fig.2d).

**Fig. 2**: A 60-year-old woman with histopathologically proved endometrial cancer (endometrioid type; G1; tumor invasion<50% of myometrial thickness). (a) T2-weighted image shows an exophytic mass with heterogeneously high intensity (arrow) compared with adjacent normal outer myometrium. (b) Diffusion-weighted image with a b-value of 1,000 seconds/mm\(^2\) shows a high signal intensity corresponding to endometrial cancer. (c) Apparent diffusion coefficient (ADC) map shows the tumor as heterogeneous hypointense area. The ADC value of the tumor is 0.55 \( \times 10^{-3} \text{mm}^2/\text{s} \). (d) High magnification view photomicrograph shows high cellularity of tumor cells with glandular architecture. Mean tumor cellularity is 760 ± 21.9. (H & E stain, X400)

**References**: Radiology, St. Marianna University School of Medicine - Kanagawa/JP
Of all 30 patients, only one showed ADC value greater than $1.15 \times 10^{-3}$ mm$^2$/s, and whom also exhibited prominent inflammatory cell infiltration. The highest ADC value of this study was $1.71 \times 10^{-3}$ mm$^2$/s, as shown in Fig.3. In this case, low grade endometrial cancer (endometrioid type; G1; tumor invasion<50% of myometrial thickness) showed an exophytic mass with heterogeneously high intensity (arrow) compared with adjacent normal outer myometrium on T2-weighted image (Fig.3a). Diffusion-weighted image with a b-value of 1,000 seconds/mm$^2$ showed a high signal intensity corresponding to endometrial cancer (Fig.3b). ADC map showed the tumor as heterogeneous hypointense area. The ADC value of the tumor is $1.71 \times 10^{-3}$ mm$^2$/s (Fig.3c). High magnification view photomicrograph (H & E stain, X400) showed low cellularity of tumor cells with glandular architecture. Prominent inflammatory cell infiltration is demonstrated. Mean tumor cellularity is $360 \pm 29.4$ (Fig.3d).

Fig. 3: A 43-year-old woman with histopathologically proved endometrial cancer (endometrioid type; G1; tumor invasion<50% of myometrial thickness). (a) T2-weighted image shows an exophytic mass with heterogeneously high intensity (arrow) compared with adjacent normal outer myometrium. (b) Diffusion-weighted image
with a b-value of 1,000 seconds/mm² shows a high signal intensity corresponding to endometrial cancer. (c) Apparent diffusion coefficient (ADC) map shows the tumor as heterogeneous hypointense area. The ADC value of the tumor is 1.71 × 10⁻³ mm²/s. (d) High magnification view photomicrograph shows low cellularity of tumor cells with glandular architecture. Prominent inflammatory cell infiltration is demonstrated. Mean tumor cellularity is 360 ± 29.4. (H & E stain, X400)

**References:** Radiology, St. Marianna University School of Medicine - Kanagawa/JP

In our study, no significant relationship was observed between ADC values and tumor grade, consistent with a considerable overlap between ADC values and tumor grade referring to different histologic tumor grades (mean ADC values: G1, 0.88 ± 0.265 10⁻³ mm²/s; G2, 0.80 ± 0.178 10⁻³ mm²/s; G3, 0.81 ± 0.117 10⁻³ mm²/s). As for the average of the ADC value, there were no significant difference among G1, G2, and G3. However the lower grade of the tumor showed the wider width of standard deviation. (Fig.4)

![Relation between ADC value and tumor grade](image)

**Fig. 4:** Fig.4. Comparison of the ADC values in the G1, G2, and G3 endometrial cancer groups. There was no significant difference in the mean ADC value among G1, G2, and G3 endometrial cancer (G1, 0.88 ± 0.265 10⁻³ mm²/s; G2, 0.80 ± 0.178 10⁻³ mm²/s; G3, 0.81 ± 0.117 10⁻³ mm²/s).
In higher grade cancer, more of the cancer cells are arranged in a disorganized way and do not form glands, and also the size of tumor cell is bigger, which could cause the restriction of the diffusion of water molecules. A case of High grade endometrial cancer (endometrioid type; G3; tumor invasion>50% of myometrial thickness) can be seen in Fig.5. T2-weighted image showed an exophytic mass growing into the uterine cervix with heterogeneously high intensity compared with adjacent normal outer myometrium (Fig.5a).

Diffusion-weighted image with a b-value of 1,000 seconds/mm$^2$ showed high signal intensity corresponding to endometrial cancer (Fig.5b). ADC map shows the tumor as heterogeneous hypointense area. The ADC value of the tumor was 0.738 X10$^{-3}$mm$^2$/s (Fig.5c). High magnification view photomicrograph (H & E stain, X400) showed high cellularity of tumor cells without glandular architecture. The tumor cells were larger than those of lower grade tumor, and also showed prominent nuclear atypia. Mean tumor cellularity is 518.6 ± 6.60 (Fig.5d).
**Fig. 5:** A 50-year-old woman with histopathologically proved endometrial cancer (endometrioid type; G3; tumor invasion>50% of myometrial thickness). (a) T2-weighted image shows an exophytic mass growing into the uterine cervix with heterogeneously high intensity compared with adjacent normal outer myometrium. (b) Diffusion-weighted image with a b-value of 1,000 seconds/mm² shows a high signal intensity corresponding to endometrial cancer. (c) Apparent diffusion coefficient (ADC) map shows the tumor as heterogeneous hypointense area. The ADC value of the tumor is 0.738 X 10⁻³ mm²/s. (d) High magnification view photomicrograph shows high cellularity of tumor cells without glandular architecture. The tumor cells are larger than those of lower grade tumor, and also show prominent nuclear atypia. Mean tumor cellularity is 518.6 ± 6.60. (H & E stain, X400)

**References:** Radiology, St. Marianna University School of Medicine - Kanagawa/JP
Conclusion

ADC value was varied from 0.55 to $1.71 \times 10^{-3}$ mm$^2$/s (mean: 0.85) in all our 30 cases. Fujii et al. [14] reported that the ADC value less than $1.15 \times 10^{-3}$ mm$^2$/s showed the highest accuracy for the diagnosis of uterine endometrial malignant tumors, which was almost concordant with our study. Of all 30 patients, only one showed ADC value greater than $1.15 \times 10^{-3}$ mm$^2$/s, and whom also exhibited prominent inflammatory cell infiltration and in addition to tumor cell density, the nuclear/cytoplasm ratio and large nuclei, we presume that DW imaging can be affected by many other conditions such as tumor proliferation, perfusion, extracellular space relative to normal tissue, and the state of the stroma [17, 18]. In our study, a possible explanation for the variation of ADC value is that endometrial cancer may be associated with inflammation, hemorrhage, and necrosis, which can affect DW imaging and ADC values, but the growth of the stroma is not prominent.

Low-grade endometrial carcinomas are sometimes composed of ‘normal-appearing’ glands resembling morphologically normal endometrium and may also be associated with, or preceded by endometrial hyperplasia. Low-grade endometrial carcinomas (G1) show low cellularity and high motion of water molecules, therefore they are expected to have a lower ADC values; conversely high-grade endometrial carcinomas (G3) typically have high cellular density and so would be expected to have lower ADC values [19]. In previous studies, no significant relationship between ADC values and tumor grade was found except one study suggesting a trend toward lower ADC values in higher-grade endometrial cancers by Tamai et al [15]. In our study, no significant relationship was observed between ADC values and tumor grade, consistent with a considerable overlap between ADC values and tumor grade referring to different histologic tumor grades (mean ADC values: G1, $0.88 \pm 0.265 \times 10^{-3}$ mm$^2$/s; G2, $0.80 \pm 0.178 \times 10^{-3}$ mm$^2$/s; G3, $0.81 \pm 0.117 \times 10^{-3}$ mm$^2$/s). As for the average of the ADC value, there were no significant difference among G1, G2, and G3. However the lower grade of the tumor showed the wider width of standard deviation. This result might be because in lower grade cancer more of the carcinoma tissue forms glands which free water of the outside of the cells increases and could cause vary the ADC values. Moreover, in higher grade cancer, more of the cancer cells are arranged in a disorganized way and do not form glands, and also the size of tumor cell is bigger, which could cause the restriction of the diffusion of water molecules. If tumor cells are large, extracellular space become small, and a motion of water is restricted, but since the number of tumor cells per unit area is also restricted, we are conjectured that the range of ADC in grade 3 is small. Moreover, there is a possibility that the abnormalities of a cell membrane, nuclear atypia [19] the state of cell division, and the difference of the pathological proteins [20] produced might also participate in the movement of water molecules.
In conclusion, the ADC values for endometrial cancer significantly correlated with tumor cellularity, therefore the ADC value might be an important clue of diagnosis for endometrial cancer. However, they do not correlate with histologic tumor grade.

Limitations: We investigate only endometrioid adenocarcinoma and do not include other histological types such as serous carcinoma and clear cell carcinoma. The second, the study population was small. Further studies are required to validate the present results in a larger population and other histological subtypes.