Role of Magnetic Resonance Imaging and Apparent Diffusion Coefficient at 3T in Distinguishing between Adenocarcinoma of the Uterine Cervix and Endometrium

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Background: To determine whether magnetic resonance imaging (MRI) and apparent diffusion coefficient (ADC) are able to distinguish between adenocarcinoma originating from the uterine cervix and endometrium.

Methods: Institutional review board approval and informed consent were obtained. From May 2006 to June 2008, 29 women 25-73 years old (mean age, 50.3 years) with a cervical biopsy yielding adenocarcinoma were enrolled for 3-T MR study with the imaging pulse-sequence protocol of T2-weighted imaging (T2WI) and dynamic contrast-enhanced (DCE) MRI and diffusion-weighted MRI (DWI, b = 0, 1000 sec/mm^2). The extent and shapes of the tumor and ADC values were evaluated by two radiologists retrospectively. Surgical histopathology served as the reference standard of the tumor origin from the cervix (n = 22) or endometrium (n = 7). The Mann-Whitney U test was used for statistical comparison and receiver operating characteristic (ROC) analysis was used to obtain optimal ADC cut off values.

Results: A longitudinal shape occurred significantly more frequently in endometrial cancer, and an oval shape was more frequently found in cervical cancer (p = 0.011). Mean ADC values were significantly lower in endometrial cancer (76.6 x 10^{-5} mm^2/sec) than in cervical cancer (96.9 x 10^{-5} mm^2/sec). Receiver operating characteristic analysis yielded an optimal ADC cutoff value of 70 x 10^{-5} mm^2/sec to distinguish cervical cancer from endometrial cancer.

Conclusion: MRI may distinguish between most uterine adenocarcinoma originating from the cervix and endometrium using distinctive characteristics found on T2WI and DCE. When tumors show an ambiguous morphology, the ADC value of the tumor may be helpful for further differentiation.

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Key words: adenocarcinoma, cervical cancer, diffusion-weighted imaging, endometrial cancer, magnetic resonance imaging

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Endometrial cancer is currently the most common gynecologic malignancy of the female pelvis in the United States and European countries and its incidence is rising in other parts of the world. Cervical cancer occurs predominantly in developing countries.[1] There are different surgical procedures for cervical adenocarcinoma and for endometrial cancer. Radical hysterectomy, which includes dissection of the bilateral cardinal ligaments and part of the upper vagina, is the standard procedure for cervical cancer while extrafascial hysterectomy and bilateral salpingo-oophorectomy is the standard for endometrial cancer with no gross cervical involvement.[2,3] The two different surgical methods imply that it is vital for clinicians to differentiate between these separate entities.

The radiologist may identify endometrial adenocarcinomas using magnetic resonance imaging (MRI) with accuracies reaching 89%, but it is not as promising for endocervical adenocarcinomas.[4] One of the main reasons is that endocervical adenocarcinoma is a great mimicker of endometrial adenocarcinoma, especially when it extends into the endometrial canal and is virtually indistinguishable from endometrial adenocarcinoma on MRI as well as clinical and pathologic studies.

The age population (mid forties) and symptoms/signs (mainly bleeding) are very similar between the two cancers.[5,6] About 30% of endocervical adenocarcinomas have endometrioid morphology on preopearative biopsies, which may be easily confused with endometrial carcinoma.[4] Biopsies can also occasionally be difficult to obtain. Positron emission tomography may accurately identify uterine adenocarcinoma, but it is still unable to discriminate these two tumors.[7]

This study was designed to search for distinctive MRI morphological characteristics in these two adenocarcinomas using T2-weighted imaging (T2WI) and dynamic contrast enhanced (DCE) MRI. The apparent diffusion coefficient (ADC) values was assessed for assistance in differentiation of cervical from endometrial adenocarcinoma.

METHODS

Patients

Data were collected retrospectively from June 2006 to June 2008. During this period, 32 women with cervical biopsies yielding adenocarcinoma were enrolled for MRI study. Three patients with tumor masses less than 1 cm in maximum diameter were excluded from our study, because the exact demarcation for ADC measurements of these tumors was extremely difficult. In total, 29 patients were included with ages ranging from 25 to 73 years (mean age, 50.3 years). Histopathological correlation with MR imaging was carried out in concordance with a gynecological pathologist. Twenty-two patients had cervical cancer and the other seven patients had endometrial cancer.

MRI

All scans were performed on a 3-T MR scanner (Tim Trio, Siemens, Erlangen, Germany), using the lower 9 elements of the integrated spine coil and lower 6 elements of the body-phased array coil to cover the entire pelvis. Diffusion weighted imaging was obtained in the coronal, sagittal and axial planes using a single-shot spin-echo echo-planar with chemical-shift-selective fat- suppression technique (repetition time of 3300 ms, echo time of 79 ms, average number of signals: 4; section thickness: 4 mm; gap 1 mm; matrix: 128 x 128; field of view (FOV) 20 x 20 cm). The b-value was chosen to be 0 and 1000 s/mm^2 to optimize the signal-to-noise ratio. Diffusion-weighting gradients were applied in all three orthogonal directions, which were coincident with the slice-selective, phase encoding and read out directions of the gradient. After T2-weighted MRI (T2WI, 5630/87; average, 3; matrix, 256 x 320; FOV, 20 cm), dynamic contrast-enhanced T1-weighted MRI was acquired at 0, 30, 60, 90, 120 sec (80/3; average, 1; matrix, 256 x 320; FOV, 20 cm) and 180 sec (567/10; flip angle, 150°; average, 2; matrix, 256 x 320; FOV, 20 cm), after a rapid intravenous bolus injection of 0.1 mmol / kg body weight of contrast medium (Gadopentetate dimeglumine, Magnevist, Schering, Berlin, Germany) followed by a 20-mL saline flush.[8] Sequences were obtained in identical slice thicknesses and gaps in the axial and sagittal planes to cover the entire true pelvis. The study was acquired during normal respiration. No pre-medication was utilized.

Imaging analysis

The evaluation and measurements of the uterine adenocarcinoma were based on the following: (1)

The largest tumor dimension was defined as the measurement of its anteroposterior (AP), cranio-caudal (CC) and lateral length (L). The ratios of CC/L and AP/CC were further calculated and analyzed. (2) The ADC values of each primary tumor were measured as follows: (A) Sagittal T2-weighted images showing the largest tumor diameter were selected, (B) Irregular regions of interest were manually placed in the tumor, (C) Necrotic areas from regions of interest on the basis of T1 enhanced and T2-weighted MR images were excluded, and (D) The regions of interest were copied to the ADC map.[9] The tumor diameters and ADC values were measured by two readers independently and were averaged to be the representative value for each tumor.

T2WI and DCE were used together for the exact demarcation of the tumor diameter, especially when the tumor extended into associated anatomic structures such as the following: (1) The myometrium, with disruption of the juctional zone on T2WI and subendometrial enhancement on DCE.[10,11] (2) The cervical stroma, with increased signal intensity on T2-weighted imaging and/or early contrast enhancement compared with that in fibrous cervical stroma.[4,12] (3) The vagina and parametrium, with the tumor less intensely enhanced than other normal structures in the delay phase.[11,13]

Statistical analysis

The Mann-Whitney U test was used for the two arm comparison and *p* value acquisition. Receiver operating characteristic analysis and the area under the ROC curve (AUC) were applied to compare the ADC values of cervical and endometrial adenocarcinoma and also to calculate the optimal cut off value for the ADC value. The sensitivity, specificity, and diagnostic accuracy of selected ADC values were calculated.

RESULTS

There were 22 primary cervical and 7 primary endometrial cancers. All calculated results are summarized in the Table 1. Morphological features shown on T2WI and DCE images, endometrial adenocarcinoma (Fig. 1) was more frequently found to extend in the cranio-caudal direction in the endometrial cavity, forming a longitudinal shaped mass with a mean length and width of 50.67 x 38.09 mm. In contrast, cervical adenocarcinoma (Fig. 2) was more frequently found to form an oval/round mass with a mean length and width of 28.92 x 31.16 mm. The characteristics were further confirmed by high ratio values for the CC/L diameter (p = 0.001) and low values for the AP/CC diameter (p = 0.004) in endometrial cancer compared with those in cervical cancer.

Table 1. Mean Values for Endometrial and Cervical Adenocarcinoma

	Endometrium adenocarcinoma (n = 22)	Cervical adenocarcinoma (n = 7)	*p* value
Age, yr	52.57 ± 4.65	50.45 ± 13.07	0.86
Anteroposterior diameter, mm	33.36 ± 18.77	29.34 ± 12.06	0.71
Lateral diameter, mm	28.09 ± 11.12	31.16 ± 11.87	0.6
Craniocaudal diameter, mm	50.67 ± 20.17	28.92 ± 12.06	0.01*
Craniocaudal/Lateral diameter	1.86 ± 0.51	0.94 ± 0.4	0.001*
Anteroposterior/ Craniocaudal diameter	0.67 ± 0.26	1.13 ± 0.36	0.004*
ADC value x 10^{-5} mm^2/sec	79.57 ± 13.25	96.91 ± 21.13	0.048*

*: Significant *p* value.

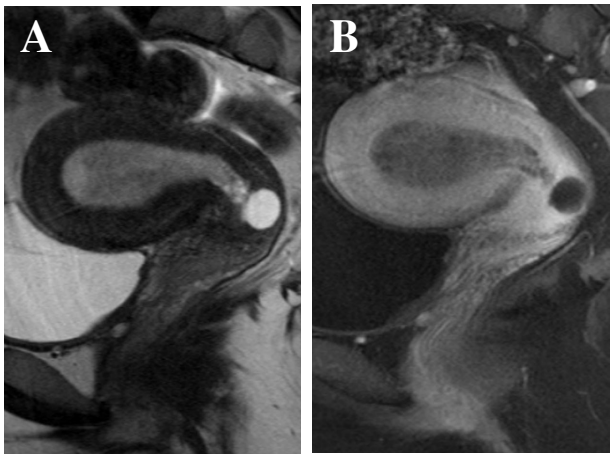

Fig. 1 Endometrial adenocarcinoma in a 61 year-old woman. Sagittal (A) preoperative T2-weighted (B) and contrast enhanced T1 weighted MRI show a large, elongated, homogenous tumor located in the endometrial canal with mild disruption of the ventral endometrium, suggesting a tumor with superficial myometrial invasion (< 50%). This is a classic image of endometrial adenocarcinoma, which biopsy also proved to be an endometrial adenocarcinoma with myometrial invasion. Beside the tumor, there is a nabothian cyst located at the posterior cervix.

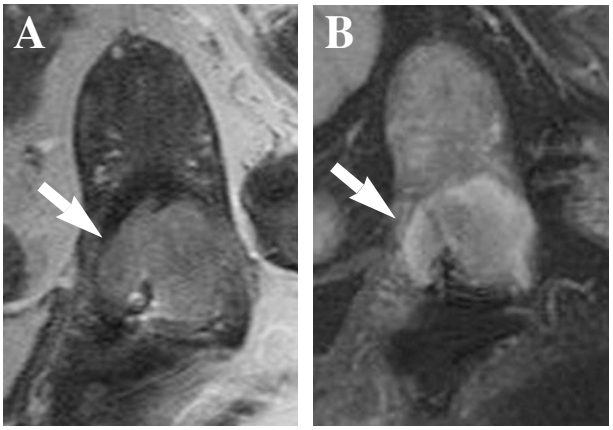

Fig. 2 Cervical adenocarcinoma in a 61 year-old woman. Sagittal (A) preoperative T2-weighted (B) and contrast enhanced T1 weighted MR images show an ovoid, heterogeneous tumor (arrow) distending the cervical canal with stromal involvement. This is a classic image of cervical adenocarcinoma, which biopsy also proved to be cervical adenocarcinoma with stromal invasion.

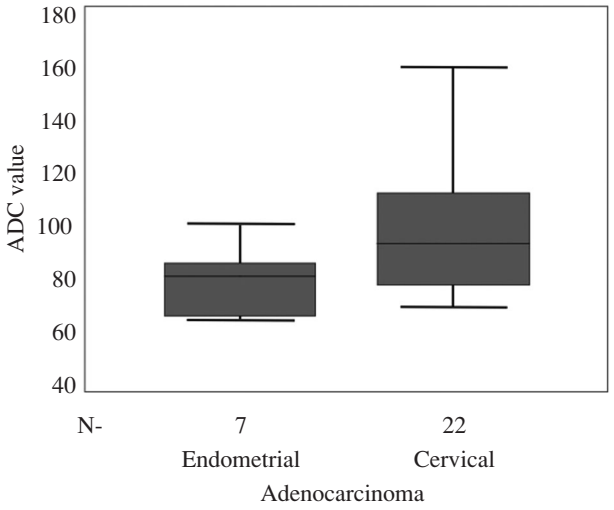

Fig. 3 Box plot displays the full range of variation of apparent diffusion coefficient (ADC) values for both endometrial and cervical adenocarcinoma. Both the distribution and median value of the cervical adenocarcinoma ADC are greater than those for endometrial adenocarcinoma.

Besides the distinctive morphological characteristic findings on T2WI and DCE, endometrial tumors had lower ADC values (mean 79.57 $\pm$ 13.25 x 10^{-5} mm^2/sec) than that of cervical cancer (mean 96.91 $\pm$ 21.13 x 10^{-5} mm^2/sec). These mean values had a statistically significant difference ($p = 0.048$) (Fig. 3).

The ROC curve was plotted from two sets of ADC data, with an AUC of 0.748 (95% CI. 0.539-0.958). This AUC value was greater than 0.5 with $p = 0.056$, which indicated significance (Fig. 4). The optimized cut-off value of 70 x 10^{-5} mm^2/sec was acquired from the values which had a maximum summation of specificity and sensitivity. With an ADC $\geqq$ 70 x 10^{-5} mm^2/sec for cervical cancer, the diagnostic accuracy for cervical cancer was 79.3% (95% CI 60.3-92%) with a sensitivity of 100% (95% CI 83.2-100%) and specificity of 11.5% (95% CI 7.5-70.1%).

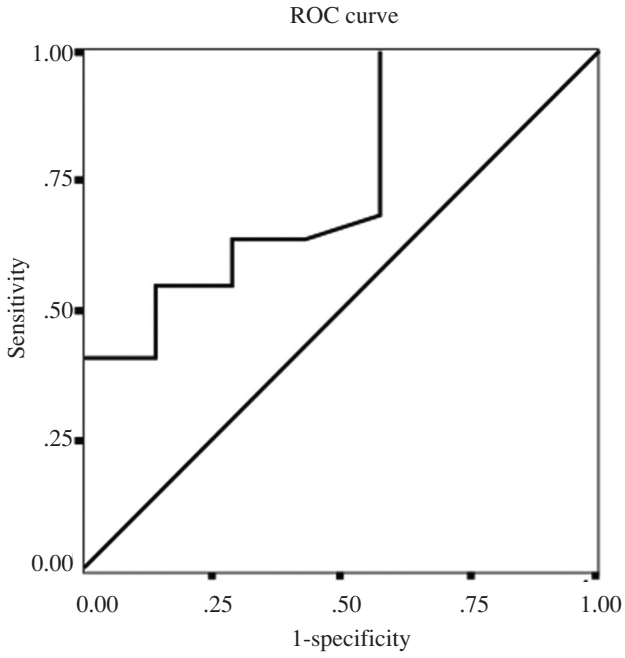

Fig. 4 A receiver operating characteristic curve is plotted from two sets of apparent diffusion coefficient data and the area under curve reaches up to 0.748, which is relatively significant ($p = 0.056$).

DISCUSSION

Gynecologists are becoming more dependent on MRI for the surveillance of gynecological malignancies. MRI enables the evaluation of the full extension of uterine tumors and is also capable of assessing their response to chemotherapy.[14,15]

The results of the present study show that mor-

phological patterns (on T2WI and DCE images) are helpful in distinguishing endometrial and cervical adenocarcinomas. Endometrial cancer appears more elongated than cervical cancer and tends to form a longitudinal shape while cervical cancer tends to appear round or ovoid. We postulate that it is difficult for a tumor mass in the endometrium to expand in a lateral or anteroposterior direction because it is sandwiched by the strong uterine muscular wall. Therefore endometrial cancer is forced to migrate in a cranio-caudal direction rather than a lateral direction, thus resulting in an elongated configuration.

Beside the above mentioned morphology, additional information on associated anatomic involvement by uterine adenocarcinoma may also assist radiologists in differentiating the origin of the tumor. One study showed that endometrial primary cancer often invades the myometrium from the endometrium (up to 60% in the study population). As for cervical cancer, there was a higher prevalence of cervical stromal involvement (96% of the study population).[4]

In this study, we used 3T MRI which may provide better image quality, finer detection of anatomic details, and a shorter acquisition time compared with 1.5T.[16,17] The spatial resolution and acquisition time of the whole pelvis ranges between 2 and 3 mm^3 and 4-5 minutes using 1.5T and 0.83 mm^3 and 38 seconds using 3T.[17] The shorter acquisition time suggests less motion artifacts, better image quality, and more diagnostic accuracy.[16]

When the tumor is located crossing both the endometrial and endocervical canals (Fig. 5) or at the transitional zone between two canals, it poses a great challenge for the radiologist to determine the origin of the adenocarcinoma using T2WI and DCE alone. On the other hand, concurrent endometrial and endocervical adenocarcinoma is extremely rare.[18] Since the morphological MRI features may not be useful for the definitive differentiation of ambiguous cases, the application of the ADC may be helpful.

Diffusion-weighted MRI is the prevailing technique used to depict uterine malignant tumors with high conspicuity. DWI also provides the ADC value of the tissues, which is considered to be influenced by the nuclear-to-cytoplasm ratio and cellular density.[19,20] From our study, there was a significant difference in the ADC value in cervical and endometrial cancers. The present study shows that endometrial

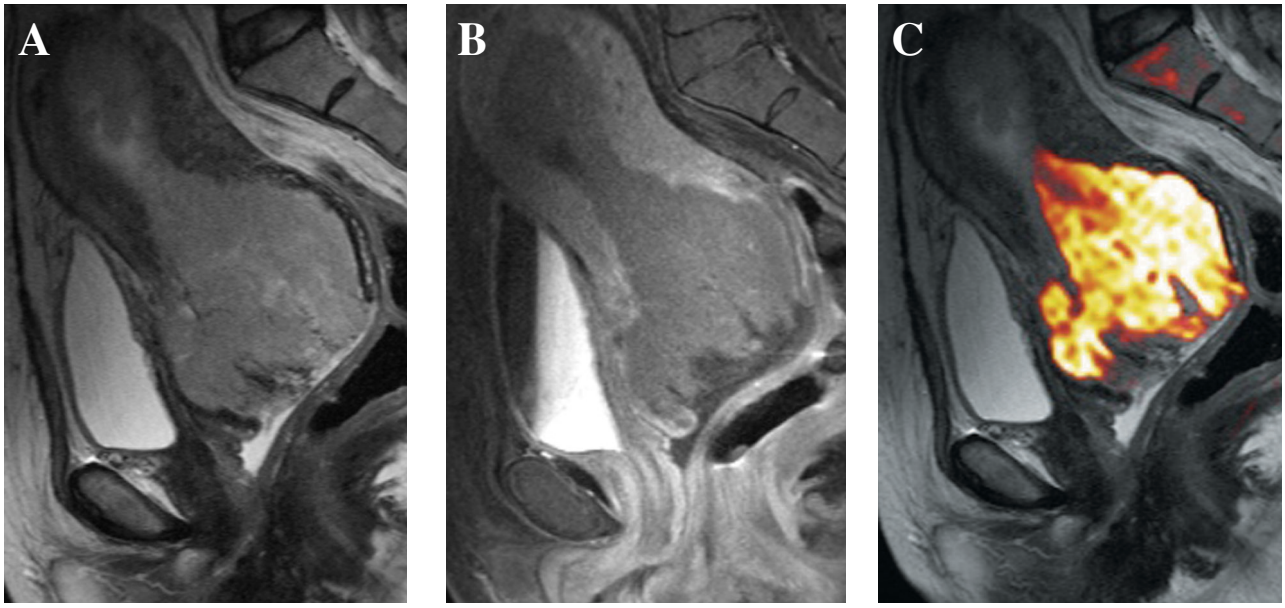

Fig. 5 Endometrial adenocarcinoma in a 51 year-old woman. Sagittal (A) preoperative T2-weighted, (B) contrast enhanced T1 weighted, (C) and fused T2-weighted and diffusion-weighted MRI show a large, heterogeneous tumor situated primarily at the endocervical canal and extending to the endometrial canal. There is tumor invasion of the myometrium and cervical stroma. Differentiation of the tumor origin using T2WI and DCE may be difficult. The ADC value of this tumor measures 67.8 x 10^{-5} mm^2/sec, suggesting an endometrial origin. Biopsy confirmed the diagnosis of endometrial adenocarcinoma.

cancer has a lower ADC value (mean 76.6 x 10^{-5} mm^2/sec) than cervical cancer (mean 96.9 x 10^{-5} mm^2/sec). Based on ROC curve analysis, an ADC value of 70 x 10^{-5} mm^2/sec is an optimal cutoff point. In our sample, all cervical adenocarcinomas had ADC values greater than 70 x 10^{-5} mm^2/sec and the overall accuracy for diagnosing cervical adenocarcinoma may reach up to 84.6%.

Eleven tumors in our series crossed both the endometrial and endocervical canals and the origin of the tumors was not easily determined using T2WI and DCE alone. Nine cases were cervical adenocarcinoma and 2 cases were endometrial adenocarcinoma. The ADC values of all nine cervical adenocarcinoma cases were above 70 x 10^{-5} mm^2/sec (mean ADC value of 94.22 x 10^{-5} mm^2/sec), whereas one of the two endometrial adenocarcinoma cases had an ADC value above 70 x 10^{-5} mm^2/sec. Therefore we believe that an ADC value < 70 x 10^{-5} mm^2/sec suggests that the uterine adenocarcinoma originates from the endometrium rather than the uterine cervix.

Furthermore, cervical adenocarcinoma exhibits a smaller range of ADC values compared with endometrial adenocarcinomas, reflecting that cervical adenocarcinomas are less likely to be influenced by the menstrual cycle and thus the cellular quantity of the tumor varies less. The limitations of this study are first, the small sample size with an uneven distribution of sample numbers (22 primary cervical and 7 primary endometrial cancers). Second, heterogeneous tumor may cause a measurement error but all study parameters were objectively measured, and therefore the potential for retrospective bias should be considered non-influential. The last limitation is that this study could only be performed on patients whose tumor masses were grossly visible on MRI images (maximal diameter greater than 1 cm).

Conclusions

MRI is useful for differentiating uterine adenocarcinoma originating from the cervix and the endometrium. In cases of ambiguous findings, the application of the ADC value may provide additional helpful information for treatment decisions.

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MRI 與擴散加權成像可否區分出子宮腺癌源於子宮頸或子宮內膜

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目 的： 核子共振 (MRI) 和擴散加權成像可否區分出子宮腺癌是源自於子宮頸或子宮內膜。

方 法： 從 2006 至 2008 共收集 29 例病理證實子宮腺癌的病患，年齡分布爲 25 歲至 73 歲。所有病患接受 3 Telsa 核子共振檢查，分別組出子宮腺癌 MRI 常規成像、動態增強成像和擴散加權成像 (DWI, b = 0, 1000 sec/mm^2)。兩位放射科醫師以回朔性的方式判讀所有的影像，特別針對兩種不同部位的子宮腺癌在影像學上做分析。其中，29 個病患裡包含了 22 個子宮頸腺癌和 7 個子宮內膜腺癌並運用了 Mann-Whitney U 和 Reciver operating characteristic (ROC) 統計方式加以分析。

結 果： 由 MRI 常規成像、動態增強成像上可觀察到子宮內膜腺癌比子宮頸腺癌較瘦長 (p = 0.011)。表面擴散係數 (apparent diffusion coefficient) 之平均值在子宮頸腺癌 (mean 96.9 x 10^{-5} mm^2/sec) 高於子宮內膜腺癌 (mean 76.6 x 10^{-5} mm^2/sec) 並且 p 值達 0.042。

結 論： MRI 常規成像、動態增強成像可區分出大部份子宮腺癌是源於子宮頸或子宮內膜。但當遇到困難時必須合併擴散加權成像協助區分。

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關鍵詞： 子宮腺癌，子宮頸腺癌，擴散加權成像，子宮內膜腺癌，核子共振

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