The utility of semi-quantitative dynamic contrast-enhanced MR imaging for differentiating type II endometrial carcinoma from type I endometrial carcinoma.

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Endometrial carcinoma is the most common gynecological malignancy and the incidence is rising. The prognosis mainly depends on three factors: histologic subtype and grade, tumor stage including depth of myometrial invasion, and lymph node status (1).

Endometrial carcinomas are typically divided into two groups with low grade type I carcinomas arising in high estrogen environments and high grade type II carcinomas arising in a background of atrophy (2,3). Type II carcinomas are comprised of the aggressive histologic subtypes such as poorly differentiated endometrioid carcinomas (grade 3), papillary serous carcinomas and clear cell carcinomas (4). The recent study by Todo et al showed that combined pelvic and para-aortic lymphadenectomy is recommended as treatment for patients with endometrial carcinoma of intermediate or high risk of recurrence including type II carcinomas (5). Therefore, preoperative prediction of type II carcinomas is important in planning the surgical procedure and determining whether to perform lymph node sampling.

Endometrial carcinomas are typically diagnosed by endometrial biopsy or dilatation and curettage. However these methods are not always helpful for the definitive diagnosis of histologic grade and subtype (6, 7). Therefore, magnetic resonance (MR) imaging may play an important role in diagnosing type II carcinomas and determining appropriate management. To our knowledge, however, few study has investigated the characterization of type II carcinomas and the usefulness of dynamic contrast-enhanced MR imaging (DCE-MRI) in the differentiation of type I and type II carcinomas.

The aim of our study was to clarify the characterization of type II endometrial carcinoma using DCE-MRI, and to evaluate the ability of semi-quantitative DCE-MRI to differentiate type II carcinomas from type I carcinomas.
Methods and Materials

Study population

From 2006 to 2012, 86 consecutive patients (mean age: 61 years; age range: 32-92 years) with histologically proven endometrial carcinoma were retrospectively evaluated with DCE-MRI.

Dynamic contrast-enhanced MRI Criteria

MR imaging were performed in 9 cases with 1.5T MR unit (Symphony; Siemens, Erlangen, Germany or Achieva; Philips Healthcare, Eindhoven, The Netherlands) and in 77 cases with 3T MR unit (Signa EXCITE HD or Discovery MR750; GE Medical Systems Milwaukee, WI, USA). A phased-array surface multicoil is used for signal reception. Conventional T2-weighted images and DCE-MRI were obtained in all cases. DCE images were obtained using three-dimensional gradient echo T1-weighted sequence (VIBE; Siemens, THRIVE; Philips and LAVA; GE) in the sagittal plane. These sequences were performed before and immediately after rapid IV injection of 0.2 mL/kg of contrast material at a rate of 2.5 mL/sec which was flushed with 15-20 mL saline, and then repeated at 25-30, 60, 90 and 120 seconds into the examination. MR data interpretation was performed on the clinical viewer (EV Insite, PSP Corporation, Tokyo, Japan). Image reading was performed by two radiologists independently, with no knowledge of the histologic findings.

Semi-quantitative analysis

In each case, a circular region of interest (ROI; at least 3 mm in diameter, avoiding partial voluming effect and spatial misregistration) was manually drawn around the most avidly enhancing part of endometrial lesion on DCE-MRI (Fig. 1). To reduce inter-MR variation, similarly sized ROI were also drawn around the area of piriformis muscle to provide an internal reference, then SI_max/SI (piriformis) ratios were also calculated (Fig 1 g).

The semi-quantitative enhancement parameters in the uterine tumor were quantified on DCE-imaging by using the following formula:

maximum absolute enhancement (SI_max)

maximum relative enhancement (SI_rel) = (SI_max-SI0) / SI0 × 100

wash-in rate (WIR) = (SI_max-S0) / SI_max × 100
Slmax was the maximum average of tissue signal intensity among each dynamic phase. SI0 was the average of tissue signal intensity on non-enhanced T1-weighted sequence. As described above, Slmax/SI(piriformis) ratios were also calculated.

**Statistics**

Interobserver variability for the ROI measurements of the two readers were analyzed by calculating interclass correlation coefficient (ICC: 0.00-0.20 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 excellent correlation). The Mann-Whitney U test was used for statistical comparison and receiver operating characteristic (ROC) analysis was used to obtain optimal cut off values. A P value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows (version 19 SPSS, Chicago, IL, USA).
Fig. 1: Regions of interest (ROI) selection. a. sagittal T2-weighted image. b, g. sagittal pre-contrast T1-weighted image. c#f. sagittal post-contrast T1-weighted image from a dynamic sequence (at 25, 60, 90 and 120 s). On one sagittal plane DCE T1-weighted images, ROI was placed around the avidly enhancing region of the uterine tumor, then manually copied to the other images including pre-contrast image (continuous yellow line = ROI). These ROIs were carefully set not to involve necrosis by referring to T2-weighted images and contrast enhanced T1-weighted images. On sagittal plane pre-contrast T1-weighted image, ROI was also drawn over the piriformis muscle. In this case, the endometrial lesion was a poorly differentiated endometroid carcinoma which corresponded to type II carcinoma (Stage IB).

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Results

Study population

In 86 endometrial lesions, 68 were type I endometrial carcinomas (well differentiated: grade 1 (n=52); moderately differentiated: grade 2 (n=16)) and 18 were type II endometrial carcinomas (poorly differentiated: grade 3 (n=10); papillary serous adenocarcinoma (n=4); clear-cell adenocarcinoma (n=4)).

Clinical and pathologic characteristics of the 86 patients in the study population are presented in Table 1.

Semi-quantitative analysis

Interclass correlation coefficients (ICC) were 0.93(SI_{max}) / 0.95(SI_{0}) / 0.93(SI_{piriformis}) . All the ROI measurements indicated excellent correlation. There was no significant difference in the all enhancement parameters except for SI_{max} between 1.5-T and 3-T MR (P>0.5). Each enhancement parameters for type II carcinomas were higher than for type I carcinomas (Table 2). There was a significant difference in SI_{rel} (P<0.0001), WIR (P<0.0001) and SI_{max}/SI_{piriformis} ratios (P<0.0001) between the two groups. Whereas no significant difference in SI_{max} was noted between the two groups (P>0.05).

Threshold criteria for type II tumor

Further analysis was carried out to establish optimal threshold criteria for the prediction of type II carcinomas using the parameters with significant differences between two groups. There was some overlap in the enhancement characteristics between two groups using the semi-quantitative parameters (Fig. 2a-c). ROC analysis indicated that a cut-off WIR # 43.7 as predictive of type II carcinomas produced optimal diagnostic performance providing a sensitivity of 78%, specificity of 75%, accuracy of 75%, positive predictive value (PPV) of 45% and negative predictive value (NPV) of 93% (Fig.3). In incorporating piriformis muscle enhancement as an internal reference, and therefore probably a more valuable measure when applied across different MR systems and manufacturers, regarding SI_{max}/SI_{piriformis} ratio, a threshold value # 1.54 divided the two groups was giving 67% for sensitivity, 81% for specificity, 77% for accuracy, 48% for PPV, 90% for NPV. Using relative enhancement data, a cutoff value of SI_{rel} 59% produced a sensitivity of 94%, specificity of 60%, PPV of 39%, NPV of 95% and an accuracy of 67%.
Table 1: Patients and clinicopathological characteristics.

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients n (%)</th>
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<tbody>
<tr>
<td></td>
<td>Type I</td>
<td>Type II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>68 (79)</td>
<td>18 (21)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤60 years</td>
<td>38 (56)</td>
<td>6 (33)</td>
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<tr>
<td>&gt;60 years</td>
<td>30 (44)</td>
<td>12 (67)</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
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<tr>
<td>Endometrioid</td>
<td>68 (100)</td>
<td>10 (56)*</td>
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<tr>
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<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>Clear-cell</td>
<td></td>
<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>52 (77)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>G2</td>
<td>16 (23)</td>
<td></td>
<td>-</td>
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<tr>
<td>Myometrial invasion</td>
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<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>44 (65)</td>
<td>10 (56)</td>
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<tr>
<td>≥50%</td>
<td>23 (34)</td>
<td>8 (44)</td>
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<td>unknown</td>
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* Endometrioid G3

Table 2: Comparison of type I and type II carcinomas: semi-quantitative parameters calculated on enhancing target components.

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<table>
<thead>
<tr>
<th>Group</th>
<th>SImax mean (SD)</th>
<th>SIrel mean (SD)</th>
<th>WIR mean (SD)</th>
<th>SImax/SI(piriformis) ratio mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>type I carcinomas</td>
<td>522.3 (226.7)</td>
<td>60.0 (40.5)</td>
<td>34.1 (14.4)</td>
<td>1.36 (0.3)</td>
</tr>
<tr>
<td>type II carcinomas</td>
<td>639.6 (360.2)</td>
<td>114.6 (57.2)</td>
<td>50.5 (14.9)</td>
<td>1.68 (0.3)</td>
</tr>
<tr>
<td>P value</td>
<td>0.303</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

SD = standard deviation
Fig. 2: Box and whisker plots showing a distribution of relative enhancement , b wash-in rate (WIR) and c SI_{\text{max}}(tumor)/SI(piriformis) in type I carcinomas and type II carcinomas. Box represents values from lower to upper quartiles. Central line represents median. Whiskers extend from minimum to maximal value, excluding extreme values (outliers).

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**Fig. 3:** Receiver operating characteristic curves show results of interpretation of SIrel, WIR and SImax/SI(piriformis). AUC= area under the receiver operating characteristic curve.

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Fig. 4: 65-year-old woman with poorly-differentiated (G3) endometrioid adenocarcinoma (Stage IVB). a. T2-weighted image shows heterogeneous hyperintense lesion distending the endometrial cavity. Dynamic enhanced T1-weighted images before (b), at 60 s (c) show rapid and strong, heterogeneous enhancement. A ROI was drawn (red circle) and quantitative enhancement characteristics were calculated. Value of $\text{SI}_{\text{rel}}=150.1$, $\text{WIR}=60.0$, and $\text{SI}_{\text{max}}/\text{SI(piriformis)}$ ratio $= 1.5$ suggest type II carcinoma.

Fig. 5: 81-year-old woman with uterine papillary serous carcinoma (Stage IB). a. T2-weighted image shows heterogeneous hyperintense lesion distending the endometrial cavity. Dynamic enhanced T1-weighted images before (b), at 25 s (c) show small and focal enhancement region in the tumor. A ROI was drawn (red circle) and quantitative enhancement characteristics were calculated. Value of $\text{SI}_{\text{rel}}=141.3$, $\text{WIR}=58.5$, and $\text{SI}_{\text{max}}/\text{SI(piriformis)}$ ratio $= 1.8$ are suggestive of a type II carcinoma.
**Fig. 6:** 80-year-old woman with clear cell carcinoma (Stage IA). a. T2-weighted image shows heterogeneous hyperintense lesion distending the endometrial cavity. Dynamic enhanced T1-weighted images before (b), at 25 s (c) show rapid and strong, heterogeneous enhancement. A ROI was drawn (red circle) and quantitative enhancement characteristics were calculated. Value of $SI_{rel}=238.1$, $WIR=70.4$, and $SI_{max}/SI_{(piriformis)}$ ratio $= 2.1$ strongly suggested type II carcinoma.
Conclusion

Our results demonstrate that type II endometrial carcinomas show strongly enhancement than type I endometrial carcinomas. Moreover semi-quantitative evaluation of DCE-MRI is useful in differentiating type II carcinomas from type I carcinomas and is associated with substantially high interobserver agreement.

In a series of 53 patients, Hirano et al reported that six of nine patients with type II endometrial carcinomas showed irregular, early enhancement compared with that of the myometrium on dynamic images (8). We also confirm that type II carcinomas exhibited greater early enhancement than the type I carcinomas. Semi-quantitative DCE-MRI with enhancement curves have been reported for breast, head and neck, prostate, ovary, and soft tissue tumors (9-12). However, no data exist regarding the performance of DCE-MRI for the assessment of uterine endometrial carcinomas. In present study, we have shown that semi-quantitative DCE-MRI can aid in the discrimination between type I carcinomas and type II carcinomas.

Dynamic contrast-enhanced MRI is a well-established method for detecting and quantifying tumor angiogenesis, which is often assessed in terms of microvessel density (MVD), and vascular endothelial growth factor (VEGF)(13-15). VEGF plays a key role in tumor angiogenesis, and the degree of VEGF expression correlates with dynamic MR imaging enhancement in various tumors (16, 17). Thomassin-Naggara et al showed the early enhancement patterns of ovarian epithelial tumors on DCE-MRI were found to correlate with tumoral angiogenic status such as VEGF and its receptors (16). On the other hand, the recent study by Dobrzycka et al showed type II carcinomas demonstrated higher serum levels of VEGF than type I carcinomas (18). Therefore, we considered that early enhancement of type II carcinomas are attributed to these angiogenic factors.

Our study had several limitations. First, our study is the retrospective nature and the number of patients is relatively small, in particular papillary serous and clear cell adenocarcinoma. Prospective studies with larger populations are needed to support our results. Second, our study population did not include patients with benign endometrial abnormalities, such as endometrial hyperplasia and endometrial polyp, and other malignant tumor, such as carcinosarcoma. Thus, the ability of DCE-MRI to distinguish between endometrial carcinomas and these endometrial lesions was not assessed. Third, different MR systems were used in this study. However, the imaging parameters had no significant difference between 1.5T and 3T.
In conclusion, endometrial carcinoma with strong enhancement on DCE-MRI is suggestive for type II endometrial carcinoma. Semi-quantitative evaluation of DCE-MRI is useful for differentiating type II carcinomas from type I carcinomas.
References


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