Surface-epithelial ovarian carcinoma: imaging and clinical characteristics of each subtype

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Aims and objectives

To clarify the clinical and imaging characteristics of each subtype of ovarian carcinoma, as the prognosis is different from one another.

[Background]

Primary ovarian carcinoma is divided into surface-epithelial stromal, sex-cord stromal and germ cell origin. Most of malignant surface-epithelial stromal tumor is adenocarcinoma, which is sub-classified into serous, mucinous, endometrioid and clear cell subtypes(1). All of them are classified as malignant epithelial ovarian tumors, however, their biological behavior and patients' prognosis, especially sensitivity to chemotherapy, are quite different from one another (2). Serous adenocarcinoma is the most common subtype of the epithelial ovarian cancer and also known for sensitive to platinum based chemotherapy. On the other hand, the 5-year survival rate of the mucinous adenocarcinoma(2) and clear cell adenocarcinoma is significantly poorer than those of serous adenocarcinoma (3,4,5). Current standard treatment against epithelial ovarian cancer is primary debulking surgery followed by chemotherapy (6,7,8). The clinicians can know the subtypes of ovarian cancer before starting chemotherapy in this scenario. However, neoadjuvant chemotherapy followed by interval debulking surgery has been more commonly performed as an alternative treatment option past several years (9,10). In this scenario, clinician should often start chemotherapy only based upon the cytological diagnosis, in which pathologist hard to diagnose subtype of the adenocarcinoma. Therefore, it may be meaningful to estimate subtype of ovarian carcinoma using imaging modality.

[Objectives]

• To clarify the imaging characteristics of each subtype of epithelial ovarian cancer
• To study whether the ancillary findings such as endometriosis or thrombosis is useful for differentiating each subtype or not.
• To study whether the tumor marker is helpful in distinguishing each subtypes or not.

[Aims]

Our goal is to clarify the clinical and imaging characteristics of each subtype of ovarian carcinoma, as the prognosis is different from one another.
Methods and materials

Imaging and clinical findings of 125 consecutive patients with primary ovarian carcinoma were retrospectively analyzed. The numbers of serous, mucinous, clear cell and endometrioid adenocarcinomas were 44, 13, 53 and 15, respectively. We studied the bilateralism, morphological type, tumor diameter, ratio of solid part, relative signal intensity on T2WI and DWI, contrast ratio, existence of endometriosis on MR, calcification, the degree of peritoneal dissemination and lymph node metastasis, clinical staging, and the existence of thromboembolism on CT. We also studied CA125, CA 19-9, CEA, and serum calcium concentration on medical records. Each parameter was statistically analyzed with Mann-Whitney U, chi-square, and Kruskal-Wallis test.

[Patients]

From 2008 to 2012, 185 consecutive patients with suspected primary ovarian cancer were treated in our institute. Seventeen cases without enough imaging or clinical information were given and 43 cases with inappropriate pathological diagnosis for this study were excluded (Figure 1). Therefore, 125 cases were included into this study.
Table 1 Histopathologic Subtypes of the Patients

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>44</td>
</tr>
<tr>
<td>Mucinous</td>
<td>13</td>
</tr>
<tr>
<td>Clear cell</td>
<td>53</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>125</strong></td>
</tr>
</tbody>
</table>

Table 2 Treatment of the Patients

| Treatment                                                      | Number of Cases |
|                                                               |                 |
| Primary debulking surgery with and without postoperative chemotherapy (PDS) | 102             |
| Neoadjuvant chemotherapy followed by interval debulking surgery (NAC/IDS) | 23              |
| **Total**                                                      | **125**         |

[CT & MR examination]

Contrast CT and MR are obtained in our institute in all cases.

CT examination

- 16 or 64 multi detector-row scanner (Brilliance 16 or Brilliance 64, Philips Medical Systems, Best the Netherlands)
- 800ml of diluted oral contrast agent (Gastrografin®, Bayer-Schering Pharma, Berlin, Germany) for oral contrast agent
- 100ml of 370mgI Iopamidol or 300mgI Iohexol or 240mgI Ioversol were administered for intravenous contrast agent optimized for each patients' body weight
- Non contrast study covered whole primary lesion in adnexa
• Contrast study covered whole abdomen and pelvis

**MR examination**

• 1.5T superconducting unit (Intera or Achieva, Philips Medical Systems, Best the Netherlands)
• Intramuscular injection of hyoscine butylbromide (Buscopan®, Boehringer Ingelheim GmbH, Ingelheim, Germany) to reduce bowel peristalsis
• 5mmol of gadopentetate dimeglumine (Magnevist®, Bayer-Schering Pharma, Berlin, Germany) for intravenous contrast agent
• 8cm - 36cm Field of View, 4-6mm slice thickness/0.4-0.6mm gap
• 320x320 - 512x512 matrix for T1-, T2- and fat-saturated T1WI
• 256x256 matrix size for DWI

**T1WI: Spine Echo**

• TR/TE = 353-575/11-14 ms
• 2-4 excitations

**T2WI: Fast Spin-Echo**

• TR/TE = 1600-2100/100 ms;
• 16-echo train length
• 2 excitations

**Fat-saturated T1WI: spectral presaturation with inversion recovery**

• TR/TE = 600-650/10-13 ms
• 2-4 excitations

**Diffusion weighted images: Echo Planner Images**

• Available only in 98 cases
• TR/TE=5000/55 msec
• b value = 1000sec/mm2
• 19-echo train length
• 2 excitations

**[Image analysis]**

• Retrospective review
• One trained radiologist with more than ten years experience in gynecologic MR
• Blind reading

**Nature of the primary lesion**
• Morphological subtypes
  · Multilocular cyst 1
  · Unilocular cyst with solitary mural nodule 2
  · Unilocular cyst with multiple mural nodules 3
  · Multilocular cysts with mural nodules 4
  · Predominantly solid 5

  • Unilateral or bilateral

  · Unilateral 0, bilateral 1

  • Maximum diameter of the larger adnexal mass
  • Maximum diameter of the largest mural nodule
  • Ratio of the solid part
  • Signal intensity of the solid part on T2WI (compared to skeletal muscles)
  • Signal intensity of the solid part on DWI (compared to endometrium)*
  • Contrast ratio compared to myometrium*
  • Calcification

  · Negative:0, Positive 1

Ancillary findings
  • Intraperitoneal Dissemination

  · None:0, Pelvis only 1, Pelvis and Upper Abdomen 2

  • Lymph node metastasis

  · Evaluated as positive if

  Solitary and larger than 10mm in minimal diameter
  Multiple and larger than 6mm in minimal diameter

  · None 0, Only regional LNs** 1, More than regional 2

  • FIGO staging diagnosed by CT & MR
  • Endometriosis

  · Evaluated as positive if there are

  # Multilocular cystic adnexal mass with hemorrhagic contents and thick capsule and septa
  # Adhesion in the pelvic floor

  • Thrombosis
Evaluated as positive if there are

- Filling defect in veins or pulmonary arteries
- Splenic or renal infarction

* Signal intensity on DWI and contrast ratio could not be measured as total hysterectomy had been performed before present illness in 6 cases.

** Regional LNs include intrapelvic and paraaortic LNs. Non-regional LNs include Retrocrural, cardiophrenic.

[Clinical Information]

- Retrospective review of medical record
- Tumor markers

- CA125
- CA19-9
- CEA

  - Hypercalcemia

- Evaluated as positive if 10.4mg/dl or higher

[Statistical analysis]

- All the parameter of the serous adenocarcinoma were compared to those of CCC and all other three subtypes
- Numerical value was analyzed with Mann-Whitney U test and Mann-Whitney U test Kruskal-Wallis test
- Non-parametric value was analyzed with Chi-square test and Mann-Whitney U test Kruskal-Wallis test
Results

Serous adenocarcinoma showed significantly higher serum CA125 level, more common bilateral disease and intraperitoneal dissemination, smaller tumor size, larger solid part, higher signal intensity on DWI. CA19-9 level was significantly higher in mucinous adenocarcinoma, in 12 of 13 of which appeared as multilocular cystic. Clear cell adenocarcinoma showed larger tumor size and higher contrast ratio. Endometriosis was significantly commonly complicated with clear cell and endometrioid adenocarcinoma. Hypercalcemia was also commonly seen in clear cell adenocarcinoma.

Morphological type, relative signal intensity on T2WI, incidence of lymph node metastasis, clinical staging, serum level of CEA, and incidence of thromboembolism was not significantly different from one another.

[Result 1 The Result of the each parameter in each subtype]

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Mucinous</th>
<th>Clear cell</th>
<th>Endometrioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>44</td>
<td>13</td>
<td>53</td>
<td>15</td>
</tr>
<tr>
<td>Largest tumor diameter (mean, mm)</td>
<td>79.5</td>
<td>193.3</td>
<td>138.328</td>
<td>126.9</td>
</tr>
<tr>
<td>Largest solid part diameter (mean, mm)</td>
<td>50.4</td>
<td>24.6</td>
<td>63.3</td>
<td>57.2</td>
</tr>
<tr>
<td>Ratio of the solid part (mean)</td>
<td>0.70</td>
<td>0.14</td>
<td>0.48</td>
<td>0.47</td>
</tr>
<tr>
<td>T2 signal ratio (mean)</td>
<td>4.16</td>
<td>5.30</td>
<td>4.86</td>
<td>4.08</td>
</tr>
<tr>
<td>DWI signal ratio (mean)</td>
<td>1.84</td>
<td>1.18</td>
<td>1.37</td>
<td>1.56</td>
</tr>
<tr>
<td>Contrast Ratio (mean)</td>
<td>0.84</td>
<td>1.18</td>
<td>1.14</td>
<td>0.92</td>
</tr>
<tr>
<td>Bilaterality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>13</td>
<td>11</td>
<td>48</td>
<td>14</td>
</tr>
<tr>
<td>Bilateral</td>
<td>31</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multilocular cystic</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unilocular with single nodule</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Unilocular with multiple nodule</td>
<td>Multilocular with solid</td>
<td>Solid</td>
<td>Calcification</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------</td>
<td>-------------------------</td>
<td>-------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>6</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 The Result of the each parameter in each subtype

[Result 2 serous vs clear cell adenocarcinoma, statistical analysis]
<table>
<thead>
<tr>
<th></th>
<th>P value</th>
<th>Statistics Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest tumor diameter</td>
<td>&lt; 0.0001</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>Largest solid part diameter</td>
<td>0.0451</td>
<td></td>
</tr>
<tr>
<td>Ratio of the solid part</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>T2 signal ratio</td>
<td>0.0292</td>
<td></td>
</tr>
<tr>
<td>DWI signal ratio</td>
<td>0.0028</td>
<td></td>
</tr>
<tr>
<td>Contrast Ratio</td>
<td>0.0193</td>
<td></td>
</tr>
<tr>
<td>Bilaterality</td>
<td>&lt; 0.0001</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Morphology</td>
<td>N.S.</td>
<td>Kruskal-Wallis test</td>
</tr>
<tr>
<td>Calcification</td>
<td>N.S.</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Dissemination</td>
<td>&lt; 0.0001</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>LNs mets</td>
<td>0.0024</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Staging</td>
<td>N.S.</td>
<td>Kruskal-Wallis test</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.0217</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>N.S.</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>CA125</td>
<td>&lt; 0.0001</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0.0017</td>
<td>Chi-square test</td>
</tr>
</tbody>
</table>

**Table 4 serous vs clear cell adenocarcinoma**, statistical analysis

**[Result 2 serous vs three other subtypes, statistical analysis]**

<table>
<thead>
<tr>
<th></th>
<th>P value</th>
<th>Statistics Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest tumor diameter</td>
<td>&lt; 0.0001</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>Largest solid part diameter</td>
<td>0.0016</td>
<td></td>
</tr>
<tr>
<td>Ratio of the solid part</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>T2 signal ratio</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>DWI signal ratio</td>
<td>0.0100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td></td>
<td>Contrast Ratio</td>
<td>0.0263</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>N.S.</td>
<td>Kruskal-Wallis test</td>
</tr>
<tr>
<td>Calcification</td>
<td>N.S.</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Dissemination</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>LNs mets</td>
<td>N.S.</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Staging</td>
<td>N.S</td>
<td>Kruskal-Wallis test</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.0063</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>N.S.</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>CA125</td>
<td>&lt; 0.0001</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0.0073</td>
<td>Chi-square test</td>
</tr>
</tbody>
</table>

*Table 5 serous vs three other subtypes, statistical analysis*
Conclusion

Ovarian cancer subtypes could be partly predicted with CT, MR and clinical findings.

[Discussion]

Primary debulking surgery followed by chemotherapy is an established standard treatment against epithelial ovarian cancer, as it has achieved excellent therapeutic results using cytotoxic agent (6,7,8). It may be owing to the vast majority of the ovarian cancer is serous adenocarcinoma especially in United States and Europe. On the other hand, the number of primary ovarian cancer accompanied with endometriosis has come to the front, past a couple of decades (11,12). It is well known that clear cell and endometrioid adenocarcinoma is the common subtypes arising from the endometriotic cysts of the ovary (11,12). As the incidence of the ovarian cancer accompanied with endometriosis is higher in Japan compared to U.S. and Europa, the incidence of clear cell adenocarcinoma is much higher. Clear cell adenocarcinoma is also known as the chemotherapy resistant subtype (3,4,5). Therefore, clinicians want to avoid neoadjuvant chemotherapy (NAC) in patients with this tumor.

The imaging findings of ovarian adenocarcinoma have been rarely reported, although, we can speculate their morphological characteristics based upon macroscopic findings reported in pathological literatures. Serous adenocarcinoma has been characterized by psammomatous calcification on CT (13), peritoneal carcinomatosis, relatively normal-sized ovaries, and a highly elevated serum CA-125 level (14). Our result also revealed these tendency and the bilateral diseases are also common in the serous adenocarcinoma. Recently, the serous adenocarcinoma is subdivided into low-grade and high-grade subtype (15,16,17,18). Low-grade serous adenocarcinoma is considered arising from serous borderline tumors. Serous surface papillary borderline tumors (SSPBTs) are characterized by papillary architecture and internal branching pattern, like sea anemone (19,20,21). Therefore, low-grade serous adenocarcinoma may resemble the SSPBTs that tend to make larger tumors (Fig. 2 on page 14). Our results included a few such tumors, although, vast majority of the tumor showed marked peritoneal carcinomatosis with relatively small primary lesions (Fig. 3 on page 14).

Mucinous adenocarcinoma is also a chemo-resistive subtype (2). However, Intestinal subtype of mucinous adenocarcinoma appears as a large stained-glass tumor on MR (22,23,24) and it maybe a hallmark of the tumor. Therefore, we may easily predict the possibility of this tumor with MR (Fig. 4 on page 15). On the other hand, the Mullerian subtype of the mucinous tumor may arising from the endometriotic cyst (1). Our results also revealed high incidence of endometriosis in this subtype. It may suggest that it may be difficult to differentiate it from clear cell or endometrioid adenocarcinoma.
Clear cell and endometrioid adenocarcinoma are commonly complicated with endometriosis (11,12). Therefore, co-existing endometriosis maybe the key finding of these tumors (25,26,27,28). Despite clear cell adenocarcinoma has been reported to appear as larger unilocular cystic mass with eccentric mural nodules (29,30), there were large number of clear cell adenocarcinoma with multilocular cysts in our study. Clear cell adenocarcinoma also appeared in earlier stage of the disease, however, it seemed impossible differentiating clear cell from endometrioid adenocarcinoma only with imaging findings, especially in stage I diseases (Fig. 5 on page 16, Fig. 6 on page 16 Fig. 5 on page 16). Co-existing thrombosis (31,32) and hypercalcemia (33,34,35,36,37) are more commonly seen in clear cell adenocarcinoma as previously reported, that may help the differential diagnosis.

[Limitation]

First, we could only analyzed the morphological characteristics of adenocarcinomas, although, there are numerous histological types of tumors affecting ovaries. Therefore, the process of differential diagnosis in daily practice maybe more complex.

The second, the number of the tumor that we analyzed was limited and we could not perform multivariate analysis.
Images for this section:

Fig. 2: Fig. 2 Low-grade serous adenocarcinoma A: Axial T2WI, B: Axial fat-saturated enhanced T1WI, C: Non-contrast CT, D: Enhanced CT.

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Fig. 3: High-grade serous adenocarcinoma A: Axial T2WI, B: Axial fat-saturated enhanced T1WI.
**Fig. 4:** Fig.4 Mucinous adenocarcinoma A: Sagittal T2WI, B: Sagittal T1WI, C: Sagittal fat-saturated enhanced T1WI.

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**Fig. 5:** Fig.5 Clear cell adenocarcinoma A: Sagittal T2WI, B: Sagittal fat-saturated T1WI, C: Sagittal fat-saturated enhanced T1WI.

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Fig. 6: Endometrioid adenocarcinoma A: Sagittal T2WI, B: Sagittal fat-saturated T1WI, C: Sagittal fat-saturated enhanced T1WI.

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