Outcome of Ovarian Cancer Patients Who Underwent Incomplete Surgical Staging

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Objective: To determine outcomes of patients with early stage epithelial ovarian cancer (EOC) who underwent incomplete surgical staging with those who had complete surgical staging.

Material and Method: Retrospective chart reviews were performed on early EOC (FIGO Stage I-II) patients who had registered in the Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital between 1994 and 2003. Two groups of patients were identified, patients who underwent incomplete surgical staging (n = 51) and those who had complete surgical staging (n = 50). Recurrence rate and disease free interval were demonstrated. The 5 years survival was estimated using Kaplan-Meier method.

Results: Between 1994 and 2003, 101 patients presented with early EOC. The median age at presentation was 48 years (range, 24-86). Histology distribution showed clear cell carcinoma in 35 cases (34.7%), mucinous carcinoma in 25 cases (24.8%), endometrioid carcinoma in 22 cases (21.8%), mixed epithelial cancer in 10 cases (9.9%), and serous carcinoma in nine cases (8.9%). Fifty-one cases (50.5%) underwent incomplete surgical staging initially. Recurrent rate in the incomplete surgical staging group was 11.8% compared with 14% in complete surgical staging group (p = 0.257). At the median follow up of 60 months, 50.5% of patients survived. The 5 years survival rate of incomplete surgical staged was 82.4% and 94.6%, in complete surgical staged (p = 0.404), when focused in the subgroup analysis, incomplete staging group with histology grade 3 compared to complete staging group. They had overall 5 years survival rate 81.1% vs. 88.4% (p = 0.037). Patients with stage II who underwent incomplete staging or complete staging had an overall survival rate 63% vs. 92.3% (p = 0.012).

Conclusion: In King Chulalongkorn Memorial Hospital, overall outcome of patients with early stage epithelial ovarian cancer who had incomplete staging was no different from patients who had complete staging. However, patients who had incomplete staging with grade 3 or stage II tended to have less recurrent rate and survival time.

Keywords: Early epithelial ovarian cancer, Incomplete surgical staging, Complete surgical staging

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Invasive epithelial ovarian cancer is the most lethal form of all gynecological malignancies. With an accurate system of careful surgical-pathologic assessment, however, a significant number of patients with an apparent early stage cancer of the ovary are still not staged according to the recommended surgical protocol.

The management of incomplete surgical staging patients with apparently early disease is problematic. Options include offering chemotherapy based on histopathologic factors or reoperation to obtain the necessary information needed to assign an accurate surgical stage.

In one early randomized study by the Gynecologic Oncology Group (GOG)1 no difference in survival was observed in stage I ovarian cancer patients randomized to postoperative treatment with observation, pelvic radiotherapy or melphalan, this
study identified a group of patients with early stage ovarian cancer with good prognostic factors. (i.e., stage IA or IB and grade 1 or 2) who would derive little benefit from further adjuvant cytotoxic chemotherapy. However, many gynecologic oncologists have advocated surgical staging of early stage EOC because of the frequency of microscopic disease resulting in upstaging.

The objective of the present study was to compare the outcome of patients who had complete surgical staging for early stage EOC with those who had incomplete surgery in order to determine whether the recurrence or survival rate is different in patients who are completely surgically staged.

**Material and Method**

A retrospective chart review from 1994 to 2003 of all early stage EOC patients registered at King Chulalongkorn Memorial Hospital was carried out. Patients’ demographic data, treatment modalities, tumor characteristics, and survival status at the most recent OPD visit were abstracted from initial histories, operative reports, pathology reports and follow up time were also collected. These data were then entered into a computerized database for subsequent analysis.

The term early stage ovarian cancer is used to describe disease confined to one or both ovaries (FIGO Stage I) or limited to spread to the true pelvis (FIGO Stage II).

Two cohorts of patients were identified, patients who had complete surgical staging (n = 50) and those who had incomplete surgical staging (n = 51), complete surgical staging was defined as pelvic and abdominal washing, manual exploration of all serosal surfaces, extrafascial hysterectomy, bilateral salpingo-oophorectomy, pelvic or para-aortic lymph nodes sampling, omental biopsy, and peritoneal biopsies of all suspicious lesions21. Incomplete surgical staging means lack of any of the previous-cite criteria. The patients who did not have operative record or pathological report, patients who received second exploratory laparotomy for surgical staging, or with synchronous malignancy were excluded. Patients with stage IC, II, or clear cell histological type were treated with platinum based chemotherapy. Patients without these risk factors were followed expectantly.

SPSS version 13.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Means, medians, and standard deviations were calculated for continuous variables. Frequencies statistic was computed for categorical variables.

The Kaplan-Meier method was used to estimate survival function for complete and incomplete surgical staging patients. Stratified by whether they were treated with chemotherapy. All significant values were defined as those with p < 0.05.

**Results**

Between January 1994 and December 2003, 527 patients with epithelial ovarian cancer registered at the King Chulalongkorn Memorial Hospital. Among these patients, 215 (40.8%) were diagnosed as early stage epithelial ovarian cancer. Forty-five patients were excluded because they did not have enough data, especially operative record or pathological report (14 cases from King Chulalongkorn Memorial Hospital and 31 cases from other hospitals), 40 because they received second exploratory laparotomy for surgical staging, and 29 because they had synchronous malignancy. At the end, 101 early EOC patients were enrolled in the present study. The numbers of patients who had complete and incomplete surgical staging were 50 and 51 patients, respectively.

The median age at presentation was 48 years (range, 24-86) 55.4% of patients were premenopause and 44.6% were menopause. Histology distribution showed clear cell carcinoma in 35 patients (34.7%), mucinous in 25 patients (24.8%), endometrioid in 22 patients (21.8%), mixed epithelial in 10 patients (9.9%) and serous in nine patients (8.9%). Most of tumor grade distribution was 45 patients (44.6%) grade 3, 10 (9.9%) grade 1, 4 (3.9%) grade 2, and not report 42 (41.6%).
Table 1 outlines demographic characteristics as per initial surgical treatments. The two groups were comparable.

Histological analysis revealed that 34.7% of tumors were clear cell and 24.8% were mucinous. There were 25.5% clear cell and 27.5% mucinous tumors in the incompletely staged group compared with 44% clear cell and 22% mucinous tumor in the completely staged group (Table 1).

Adjuvant chemotherapy was given to 80 patients. In the incomplete staged group 40 patients each received six courses of Carboplatin (AUC = 5) 20 (50%), Cisplatin (70 mg/m²) 17 (42.5%), or Carboplatin (AUC = 5) with Paclitaxel (175 mg/m²) three (7.5%) based on the present high risk pathologic factors. In the complete staged group 40 patients were treated with similar chemotherapy; Carboplatin 25 (62.5%), Cisplatin 4 (10%), or Carboplatin with Paclitaxel 11 (27.5%).

The over-all survival rate of incomplete surgical staged was 82.4% and 94.6% in complete surgical staged (p = 0.404) based on the log rank test respectively (Fig. 1).

Subgroup analysis was done in grade 3 histology between both incomplete and complete surgical staged groups. There was statistically significant difference in survival time of the two groups. The over-all 5-years survival rate was 81.1% and 88.4%, respectively (p = 0.037) (Fig. 2).

The over-all 5 years survival rate was approximately 50.49% for stage I and II. There was 20 (43.5%) vs. 29 (78.4%) p = 0.354 for stage I tumor in incomplete and complete staged group, and two (63%) vs. 12 (92.3%) p = 0.012 for stage II tumor in incomplete and complete staged groups, respectively (Fig. 3).

Median time to follow up was 60 and 68 months for incomplete and complete staged group (p = 0.204) (Table 1).

The recurrence rate between incomplete and complete surgical staged groups were 11.8% vs. 14% (p = 0.257) and the median time to recurrence were 65.7 months and 57.5 months (p = 0.296) respectively.
Although when focused in the subgroup analysis, incomplete staging group with stage II compared to complete staging group had a recurrent rate of 20% vs. 28.1% (p = 0.042) or patients with histology grade 3 who underwent incomplete staging or complete staging had a recurrent rate of 10.5% vs. 26.9% respectively (p = 0.038).

There were 13 recurrences in both groups. Details of these recurrences and treatment are listed in Table 2.

**Discussion**

Although the old studies frequency than incomplete surgical staging, early stage epithelial ovarian cancer may be a threat with incomplete surgical staging due to several reasons, for example emergency condition, preserved fertility function either or inoperable surgery for complete staging. Since accurate methods of early detection are lacking, only 25-30% of these cancers are diagnosed at an early stage (3). However, the issue remains the real risk of relapse and whether the incompletely stage approach may compromise the vital prognosis of these patients.

The combined analysis of ICON 1 and ACTION studies, including 925 patients, showed a 5-years disease free survival of 76% and a 5-year overall survival of 82% in the best group of patients, i.e., patients who received adjuvant chemotherapy after surgery (4). This means that some patients with early stage ovarian cancer will eventually relapse and die of the tumor, despite aggressive surgery and adjuvant chemotherapy with the limitation of an indirect comparison. It does not appear that incomplete surgical staging may worsen the prognosis of these patients. Even allowing for a selection bias, the case series here presented includes also the small number of stage II and III disease, and a fair number of stage IC tumors. Therefore, the authors may conclude from these analyses that patients with stage I and II epithelial ovarian cancer treated with conservative surgery have an excellent prognosis.

Due to the limitation of the study design, clear cell carcinoma seemed to be more frequent in complete surgical staging group. This may be caused by the selection bias.

The information of surgical pathologic factors was common missing that making treatment recommendation difficult. Occult metastasis of omentum, retroperitoneal nodes, and peritoneal or diaphragm were common.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Stage</th>
<th>Histology</th>
<th>Time to recurrence (months)</th>
<th>Site of recurrence</th>
<th>Therapy</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incompletely staged</td>
<td>IC</td>
<td>Serous</td>
<td>60</td>
<td>Liver, peritoneum</td>
<td>Reinduction chemotherapy (carboplatin x 3), hormonal therapy (Megaplex)</td>
<td>Died of disease (7 mo)</td>
</tr>
<tr>
<td>2. Incompletely staged</td>
<td>IA</td>
<td>Endometrioid</td>
<td>108</td>
<td>Vaginal cuff, sigmoid colon, liver and spleen</td>
<td>Loss to F/U</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>3. Incompletely staged</td>
<td>IC</td>
<td>Mixed (serous, mucinous)</td>
<td>34</td>
<td>Paraortic lymph nodes, IVC invasion, soft tissue at Lt.psoas area</td>
<td>Reinduction chemotherapy (carboplatin x 6)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>4. Incompletely staged</td>
<td>IC</td>
<td>Clear cell</td>
<td>31</td>
<td>Liver, vaginal cuff</td>
<td>Secondary debulking, chemotherapy (Carboplatin x 6, Cisplatin + Adriamycin x 4), hormonal therapy (Megaplex)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>5. Incompletely staged</td>
<td>IC</td>
<td>Serous</td>
<td>10</td>
<td>Cervical lymphnodes, vaginal cuff</td>
<td>Chemotherapy (Carboplatin x 6), hormonal therapy (Tamoxifen)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>6. Incompletely staged</td>
<td>IIC</td>
<td>Mixed (serous, mucinous)</td>
<td>12</td>
<td>Vaginal cuff</td>
<td>Chemotherapy (Cantomycin + Mitomycin x 4, Gemcitabine x 3), hormonal therapy (Tamoxifen)</td>
<td>Died of disease (11 mo)</td>
</tr>
<tr>
<td>7. Completely staged</td>
<td>IC</td>
<td>Clear cell</td>
<td>43</td>
<td>Peritoneum</td>
<td>Loss to F/U</td>
<td>Died of disease (2 mo)</td>
</tr>
<tr>
<td>8. Completely staged</td>
<td>IIC</td>
<td>Clear cell</td>
<td>7</td>
<td>Peritoneum</td>
<td>Chemotherapy (Carboplatin + Paclitaxel x 6)</td>
<td>Died of disease (6 mo)</td>
</tr>
<tr>
<td>9. Completely staged</td>
<td>IIC</td>
<td>Mixed (endometrioid, clear cell)</td>
<td>5</td>
<td>Peritoneum, lymphnode, liver Brain</td>
<td>Loss to F/U</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>10. Completely staged</td>
<td>IC</td>
<td>Clear cell</td>
<td>3</td>
<td>Brain</td>
<td>Radiation, chemotherapy (Carboplatin + Paclitaxel x 6)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>11. Completely staged</td>
<td>IC</td>
<td>Clear cell</td>
<td>9</td>
<td>Vaginal cuff, liver, spleen</td>
<td>Hormonal therapy (Tamoxifen)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>12. Completely staged</td>
<td>IC</td>
<td>Clear cell</td>
<td>14</td>
<td>Liver</td>
<td>Secondary debulking, chemotherapy (Carboplatin + Paclitaxel x 6), hormonal therapy (Tamoxifen)</td>
<td>Alive with disease</td>
</tr>
<tr>
<td>13. Completely stage IC</td>
<td>Endometrioid</td>
<td>27</td>
<td>Vaginal cuff, liver</td>
<td>Chemotherapy (Carboplatin x 6)</td>
<td>Alive with disease</td>
<td></td>
</tr>
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</table>
Steinberg et al(5) studies 109 omentum in 159 patients with ovarian cancers; 22% of the normal looking omentum did vary macroscopic tumor deposit with a mean tumor diameter of 6.7 mm. This emphasizes the importance of histologic evaluation of the omentum to rule out occult tumor spread. Occult retroperitoneal nodal involvement is also frequent in early stage ovarian cancer with a possible link to worsened survival if missed(6-11).

Dexeus et al(6) documented 15% positive pelvic nodes and 55% isolated paraaortic nodal involvement in 68 patients with early stage ovarian cancer who underwent retroperitoneal lymphadenectomy. Similarly Lang(7) studies 116 cases of stage I ovarian cancer. Eighty-two patients had a complete lymphadenectomy as part of their surgical treatment. The incidence of microscopic lymphatic metastasis was 10.3%.

Eisenkop and Spirto(11) in a recent publication studied the time during surgical cytoreductions when macroscopic nodes were detected. Even in a study patients group having advanced stage, only 31% of the macroscopically enlarged nodes were detected by palpation alone, underscoring the inaccuracy in using palpation to determine nodal status.

At present, it is not clear from the current literature, whether these patients should be reoperated to collect data that will accurately stage their cancer followed by chemotherapy if needed or whether they should be treated based on a number of already established histopathologic risk factors for recurrences.

As demonstrated in our retrospective review, the differentiation of the complete and incomplete surgical staging cohorts, such as stage and histology, that may be affected to the recurrence rate and survival time. Most of incomplete staged group had characterized by stage I 90.2% and stage II 9.8%. On the part of complete staged group was stage I 74% and stage II 26%. Histology of incomplete staged group was mucinous type 27.5%, clear cell type 25.5% and complete staged group was clear cell type 44%. In multivariate analysis, clear cell histology both in early and in advanced stages has been associated with a higher recurrence rate and poorer prognosis than with other epithelial subtypes(12-15).

The recurrence and survival rates were not significantly different between incomplete surgical staged and complete surgical staged patients who had surgery for early stage epithelial ovarian cancer. It may be from the patients of the complete staged group trend to have clear cell histology and stage II more than the incomplete staged group.

Subgroup analysis between stage I and II had demonstrated the significant difference of time to recurrence in stage II patients who had complete surgical staging 77.4 months, 32.5 months in the incomplete surgical staged group (p = 0.05). However, stage I who had complete and incomplete surgical staging were not significantly different in time to recurrence, 56.75 and 69.80 months respectively. Thus, complete surgical staging may serve as a benefit in stage II more than stage I.

There was a significant difference of overall survival rate in stage II (p = 0.012) between complete staged group and incomplete staged groups. Although complete surgical staging did not significantly improve the survival for the stage I patients, it is important to note that stage I patients who had incomplete surgical staging had more no histological grading report than those who received complete surgical staging (47.1% vs. 36%). It may be the disturbing survival time cause of inaccuracy grading histology.

At 5 years follow up, the surviving patients of the incomplete surgical staged group were all stage I, no patients in stage II survived. However, all the patients of the completed surgical staged group were alive with stage II 13.63% and stage I 86.63%. This support the assumption that the stage of tumor influenced the survival rate. Additionally, the grade 3 EOC were significantly improved in the overall survival rate (p = 0.037) between the complete staged group and incomplete staged groups.

In summary, complete surgical staging can predict outcome for patients with stage II, grade 3 of epithelial ovarian cancer. However, this may be of little benefit for stage I patients. Patients with clear cell histology are at a significant risk for recurrence. Consideration may be given to treating these patients aggressively regardless of the disease stage.

References


ผลการศึกษาผู้ป่วยมะเร็งรังไข่ที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์

พราวชี บ้านทรัพย์, เรืองศักดิ์ เลิศขจรสุข

วัตถุประสงค์: เพื่อเรียบเทียบผลการรักษาในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวระยะเริ่มต้นที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์และแบบสมบูรณ์

ชนิดของการวิจัย: การวิจัยเชิงวิเคราะห์แบบย้อนหลัง (retrospective analytical study)

สถานที่ที่ทำวิจัย: ภาควิชาสูติศาสตร์ นรีเวชวิทยา โรงพยาบาลจุฬาลงกรณ์

กลุ่มตัวอย่าง: ผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวระยะเริ่มต้นทั้งหมดที่ได้รับการตรวจรักษาที่ภาควิชาสูติศาสตร์ นรีเวชวิทยา โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ปี พ.ศ. 2537 ถึง พ.ศ. 2546

วัสดุและวิธีการ: การศึกษาเวชระเบียนย้อนหลังในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวระยะเริ่มต้น (FIGO stage I-II) ที่ได้รับการตรวจรักษาที่ภาควิชาสูติศาสตร์ นรีเวชวิทยา โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ปี พ.ศ. 2537 ถึง พ.ศ. 2546 โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มแรก คือผู้ป่วยที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์จำนวน 51 ราย และกลุ่มที่ 2 คือผู้ป่วยที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบสมบูรณ์จำนวน 50 ราย เพื่อเรียบเทียบคุณลักษณะการติดตามและอัตราการรอดชีวิตของทั้งสองกลุ่มโดยใช้สถิติวิธี Kaplan Meier

ผลการศึกษา: ผลการศึกษาจาก พ.ศ. 2537 ถึง พ.ศ. 2546 มีผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวระยะเริ่มต้นที่มีคุณสมบัติตามเกณฑ์การศึกษาจำนวน 101 ราย แบ่งเป็น 51 ราย (ร้อยละ 50.5) ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์ และ 50 ราย (ร้อยละ 49.5) ได้รับการผ่าตัดแบ่งระยะของโรคแบบสมบูรณ์ ค่ามัธยฐานอายุอยู่ที่ 48 ปี (ช่วงอายุ 24-86 ปี) ชนิดชองเซลล์ที่พบเป็น clear cell 35 ราย (ร้อยละ 34.7), mucinous 25 ราย (ร้อยละ 24.8), endometrioid 22 ราย (ร้อยละ 21.8), mixed epithelial 10 ราย (ร้อยละ 9.9) และ serous 9 (ร้อยละ 8.9) อัตราการกลับเป็นซ้ำในกลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์เทียบกลับแบบสมบูรณ์ คิดเป็นร้อยละ 11.8 และ 14 ตามลำดับ (p = 0.257) และค่ามัธยฐานการตรวจติดตามอยู่ที่ 60 เดือน พบว่าผู้ป่วยในกลุ่มโดยรวมระยะเวลา 50.49 ตีตราการตรวจชิด 5 ปี ที่กลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์เทียบกลับแบบสมบูรณ์ ระยะเวลา 82.4 และ 94.6 ตามลำดับ (p = 0.404) และเมื่อเรียบเทียบกลุ่ม grade 3 กลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์มีอัตราการตรวจชิด 5 ปี ที่กลุ่ม 81.1 ส่วนกลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบสมบูรณ์ระยะเวลา 88.4 (p = 0.037) เข้าใจกับกลุ่มระยะ 2 (FIGO stage II) กลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์ มีอัตราการตรวจชิด 5 ปี ที่กลุ่ม 83.3 ส่วนกลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบสมบูรณ์ระยะเวลา 92.3 (p = 0.012)

สรุป: ผลการรักษาในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวระยะเริ่มต้นที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์ไม่แตกต่างกันกับแบบสมบูรณ์ อย่างไรก็ตามถ้ารอดชีวิตของผู้ป่วยแบ่งระยะของโรคแบบไม่สมบูรณ์ไม่แตกต่างกันกับแบบสมบูรณ์ อย่างไรก็ตามผลการติดตามเป็นช่วงและอัตราการตรวจชิด ในกลุ่ม grade 3 หรือกลุ่มระยะ 2 ที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบไม่สมบูรณ์มีแนวโน้มน้อยกว่ากลุ่มที่ได้รับการผ่าตัดแบ่งระยะของโรคแบบสมบูรณ์