Oncologic and reproductive outcomes of cystectomy compared with oophorectomy as a treatment for borderline ovarian tumours

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BACKGROUND: The aim of this study was to compare the oncologic and reproductive outcomes of patients with borderline ovarian tumours (BOTs) who were treated with cystectomy or unilateral salpingo-oophorectomy (USO).

METHODS: The medical records of patients with BOTs who were treated between 1997 and 2009 were reviewed retrospectively. The recurrence rates were compared between the USO and cystectomy groups. The reproductive outcomes were assessed by telephone interviews.

RESULTS: Patients with BOTs underwent a USO (n = 117) or cystectomy (n = 38). There were 12 patients who had recurrences: 1 patient had an invasive recurrence and 11 had borderline recurrences. The recurrence rate in the USO group (6.0%) was lower than in the cystectomy group (13.2%); however, this difference was not statistically significant (P = 0.110). All of the patients with recurrences were successfully treated with surgery and there was no clinical evidence of disease. Of the 116 patients contacted by telephone, 113 (97.4%) resumed menstruation following the surgery, and 45 of the 52 patients (86.5%) who attempted to conceive had successful pregnancies. USO (89.2%), like cystectomy (85.7%), resulted in excellent pregnancy rates for patients with BOTs.

CONCLUSIONS: A USO is an appropriate treatment for women with BOTs who wish to preserve fertility. However, a cystectomy is a satisfactory fertility-sparing therapy when a cystectomy is the only surgical option.

Key words: borderline ovarian tumour / fertility-sparing surgery / cystectomy / unilateral salpingo-oophorectomy / pregnancy

Introduction

Borderline tumours of the ovary (BOTs) were first described in 1929 (Taylor, 1929). BOTs have been recognized as a separate diagnostic category of epithelial ovarian tumours (Scully, 1975). Studies have consistently supported the favourable prognoses associated with BOTs. Specifically, studies have revealed an overall 10-year survival rate of 83–91% (Gershenson and Silva, 1990; Crispens, 2003). Although BOTs usually exhibit benign features, BOTs can present as metastatic disease, and can recur ≥10 years following the primary diagnosis (Crispens, 2003). BOTs often occur in women of reproductive age (Barnhill et al., 1995). Because of the generally benign behaviour of BOTs, management has become more conservative, allowing women to maintain fertility (Morice et al., 2001; Donnez et al., 2003). Fertility-sparing treatments include procedures in which the uterus and at least some functional ovarian tissue remains, which enables pregnancy to occur, even though the loss of a considerable portion of the oocyte reserve may result in reduced fertility (Donnez et al., 2003, 2006).

Although fertility-sparing surgery for BOTs has been addressed across many studies (Donnez et al., 2003; Morice et al., 2003; Fauvet et al., 2005; Morice, 2006; Kim et al., 2009; Park et al., 2009; Kane et al., 2010), only limited published data are available on the oncologic safety and reproductive outcomes associated with treatment by cystectomy. The aim of this study was to compare the recurrence and pregnancy rates for patients treated with cystectomies or unilateral salpingo-oophorectomies (USOs).
Materials and Methods

Using a computerized database and the cancer registry of the Samsung Medical Center (SMC; Seoul, Korea), patients with pathologically confirmed BOTs who were treated and followed between January 1997 and December 2009 were identified retrospectively. The study participants included those who had undergone primary surgery in our center, as well as those referred to our center for comprehensive staging following surgery at another hospital. Records were examined for information related to patient demographics, procedures associated with the surgery, surgical stage (as determined using the International Federation of Obstetrics and Gynecology system for ovarian cancer), recurrence, treatment at the time of recurrence and death. The pathologic slides were reviewed by two experienced pathologists. To evaluate reproductive outcomes, including menstrual cycles and pregnancy, telephone interviews were conducted with all patients. This study was approved by the Institutional Review Board of the SMC.

The radicality of surgical management was dependent on the extent of disease, age of the patient and desire to preserve fertility. The surgical procedure was labelled as fertility-sparing when the uterus and at least part of one ovary were left in situ. Radical surgery was defined as treatment without conservation of reproductive potential. The standard radical treatments were hysterectomy and bilateral salpingo-oophorectomy. The primary surgery was considered to be a comprehensive surgical staging procedure when all of the following procedures had been completed: peritoneal washing cytology, inspection of peritoneal surfaces, omentectomy and in the case of mucinous tumours, appendectomy. Peritoneal implants were divided histologically into non-invasive and invasive implants based on the presence or absence of destructive stromal invasion into the underlying tissue. Recurrence was defined as the appearance of the same type of tumour following complete surgical resection. Recurrent tumours were subclassified into the following two forms: (i) recurrence as a BOT and (ii) recurrence as an invasive ovarian carcinoma (IOC). Patients were treated with adjuvant platinum-based chemotherapeutic regimens at the discretion of their attending physicians (Table I). Following the completion of primary treatment, patients were examined every 3 months during the first 2 years, every 6 months during the following 3 years and yearly thereafter. Post-therapy surveillance included a physical examination, assessment of tumour markers and imaging studies.

Recurrence rates and fertility outcomes for women treated with cystectomies were compared with the recurrences rates and fertility outcomes of women who were treated with USOs. The recurrence-free interval (RFI) was calculated as the number of months from the date of the initial surgery to the date of disease recurrence or the date of censor. Survival curves and rates were calculated using the Kaplan–Meier method. The differences in survival were assessed using the log-rank test. Frequency distributions were compared using chi-square and Fisher’s exact tests, and both mean and median values were compared between the two groups using Student’s t-test and the Mann–Whitney U-test. A P-value of ≤0.05 in a two-sided test indicated a significant difference. Statistical analysis was performed using SPSS software (version 12.0; Chicago, IL, USA).

Results

Clinical characteristics

There were 155 patients with BOTs who met the inclusion criteria; of these 155 patients, 117 underwent USOs and 38 underwent cystectomies. Table I shows the demographic characteristics of the study patients. The median tumour size was significantly larger in the USO group (14.9 versus 8.3 cm, P < 0.001). There were 29 patients (24.8%) in the USO group and 21 patients (55.3%) in the cystectomy group who underwent laparoscopic surgery, and the reminder underwent laparotomy surgery (P < 0.001). Comprehensive surgical staging procedures were less frequently performed among the cystectomy group (36.8 versus 15.7%). Upon completion of the primary surgery (and restaging procedure), all patients (n = 21) were shown to have no macroscopic residual tumours. The proportion of additional surgical procedures were as follows: peritoneal cytology (95.7% in the USO group).
group versus 92.1% in the cystectomy), omentectomy (36.8 versus 15.7%) and appendectomy (17.1 versus 7.9%).

The histology for all patients included 37 serous types (23.9%), 106 mucinous types (68.4%) and 12 other types (7.7%; primarily, mixed cell type). The proportion of mucinous tumours was higher in the USO group (72.6 versus 55.3%); however, this proportion was not significantly different compared with the cystectomy group ($P = 0.127$).

**Oncologic outcomes**

The median follow-up time was 56.0 months (interquartile range, 25.7–80.8 months) in the USO group and 55.6 months (interquartile range, 27.2–83.3 months) in the cystectomy group. The 5-year recurrence-free survival rates in the USO and cystectomy groups were 93.3 and 90.7%, respectively. Twelve patients had a recurrence after 10–74 months from the initial surgery (median interval, 40 months). The rate of recurrence seemed to be higher among the cystectomy group (13.2%) than among the USO group (6.0%); however, this difference was not statistically significant ($P = 0.110$; Fig. 1).

Table II shows the characteristics of patients with recurrences. Of the 12 patients, 11 had recurrent BOTs and one had a recurrence of an IOC. One patient (#3) had an magnetic resonance imaging demonstrating a large pelvic mass 26 months after the initial surgery. The final pathology report revealed a mucinous cystadenocarcinoma stage Ia of the ovary and she was successfully treated with surgery only. One patient (#1) was initially diagnosed with stage IIIb disease with non-invasive implants. This patient underwent a USO with a comprehensive staging procedure, and received adjuvant chemotherapy. This patient also experienced a recurrent borderline tumour involving the remaining ovary 27 months after delivering a baby (47 months after the primary surgery) and was treated exclusively by radical surgery.

In the USO group, the site of recurrence was the remaining ovary in all cases. In the cystectomy group, the most common site of recurrence was the ipsilateral ovary (60%; 3–5) that had been preserved at the initial surgery, followed by the contralateral ovary (40%; 2–5). All of the patients in the two groups who had an isolated ovarian recurrence, were successfully treated with surgical management, and received no additional chemotherapy. Of these patients, four underwent a second round of fertility-sparing surgery, and one (#9) had a second recurrence of a BOT in the remaining ovary, which was removed with radial surgery. At the time of analysis, all patients were alive with no evidence of disease.

**Reproductive outcomes**

Of the 155 patients, 116 (74.4%) were successfully contacted by telephone and were able to provide information related to their menstrual cycles and obstetric histories (Fig. 2). Of the 116 patients, 97 resumed regular menstruation, 5 had irregular menstruation, 12 had recurrent
Table II Oncologic outcomes of patients with relapses (n = 12).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Histology</th>
<th>Size (cm)</th>
<th>Stage</th>
<th>Surgical procedure</th>
<th>Sites of recurrence</th>
<th>Tx at recurrence</th>
<th>Surgical approach</th>
<th>Adjuvant Rx</th>
<th>RFI (mo)</th>
<th>Rx at recurrence</th>
<th>Surgical approach</th>
<th>Histology of recurrence</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>34</td>
<td>Serous</td>
<td>14.4</td>
<td>IIIb</td>
<td>USO</td>
<td>Remaining ovary</td>
<td>CP (Rad)</td>
<td>Laparotomy</td>
<td>CP, 3 cycles</td>
<td>47</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
<tr>
<td>#2</td>
<td>42</td>
<td>Serous</td>
<td>7</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>33</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
<tr>
<td>#3</td>
<td>18</td>
<td>Mucinous</td>
<td>24</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>26</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#4</td>
<td>21</td>
<td>Serous</td>
<td>15</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>18</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
<tr>
<td>#5</td>
<td>42</td>
<td>Mucinous</td>
<td>10.6</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>15</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#6</td>
<td>26</td>
<td>Serous</td>
<td>8.4</td>
<td>Ic</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>13</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
<tr>
<td>#7</td>
<td>27</td>
<td>Mucinous</td>
<td>10.6</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>21</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#8</td>
<td>36</td>
<td>Serous</td>
<td>11.2</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>20.5</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
<tr>
<td>#9</td>
<td>24</td>
<td>Mucinous</td>
<td>11.7</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>12.5</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#10</td>
<td>17</td>
<td>Mucinous</td>
<td>10.5</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>7.3</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#11</td>
<td>14</td>
<td>Mucinous</td>
<td>14</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>16.6</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Mucinous</td>
<td>NED</td>
</tr>
<tr>
<td>#12</td>
<td>28</td>
<td>Serous</td>
<td>9.3</td>
<td>IA</td>
<td>Laparoscopy</td>
<td>–</td>
<td>–</td>
<td>Laparoscopy</td>
<td>–</td>
<td>14.5</td>
<td>Remaining ovary</td>
<td>USO</td>
<td>Serous</td>
<td>NED</td>
</tr>
</tbody>
</table>

The median time between the initial operation and the attempt to conceive was 18 months. The median time between the initial operation and pregnancy was 28 months (range: 8–97 months). At the time of analysis, 54 healthy full-term babies had been born without congenital anomalies, and 4 women were in the second or third trimester of pregnancy. To date, none of the patients had undergone radical surgery after completion of childbearing, with the exception of one patient who had a stage Iic disease with invasive implants.

Discussion

Patients with BOTs are generally younger than patients with ovarian cancer (Barnhill et al., 1995; Crispens, 2003), and often wish to preserve fertility. Ovarian cystectomy may provide a better opportunity for preserving fertility than adnexectomy because the former procedure results in the removal of less ovarian tissue. However, this procedure is associated with risk in that some malignant cells may be inadvertently left in situ.

Although many studies have compared the oncologic outcomes of fertility-sparing and radical surgeries (Morice et al., 2001; Zanetta et al., 2001; Donnez et al., 2003; Fauvet et al., 2005; Park et al., 2009), only limited published data are available on the oncologic outcomes of treatments using cystectomies (Lim-Tan et al., 1988; Morris et al., 2000; Seracchioli et al., 2001; Palomba et al., 2007; Yinon et al., 2005). Furthermore, these studies have included a small number of patients and have failed to examine reproductive outcomes. To date, the current study is the largest series, including a complete reproductive report that compares cystectomy only with USO as the treatment for patients with BOTs. Several studies have compared the oncologic outcomes of USO and cystectomy (Table III). Based on the literature, the rate of recurrence tends to be higher following cystectomy (between 12 and 58% higher) than USO. Although these findings are consistent with the results of the current study that the recurrence rate was somewhat higher among the cystectomy group (13.9%) than the USO group (6.0%), although this difference was not statistically significant ($P = 0.110$). In order to reduce the risk of recurrence after cystectomy, Lim-Tan et al. (1988) recommended that a complete histologic analysis of the margins be
carried out to ensure complete resection. However, such an interpretation of section margins is very difficult, particularly if morcel-
lation or fragmentation of the tumour occurs during surgery. From a
practical point of view, analysis of surgical margins after cystectomy
does not modify the management of patients, and is therefore not
performed.

Table III  Published studies comparing the outcome of cystectomy and USO as a treatment for BOTs.

<table>
<thead>
<tr>
<th>Author</th>
<th>F/u (mo)</th>
<th>Surgical procedure</th>
<th>Patients, n</th>
<th>Recurrence, n (%)</th>
<th>Sites of recurrence</th>
<th>Histology of recurrence</th>
<th>Interval to recurrence (mo)</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim-Tan et al.</td>
<td>90</td>
<td>Cystectomy</td>
<td>33</td>
<td>2 (6.1%)</td>
<td>1-both ovary, 1-ContOv</td>
<td>2-BOT, NR</td>
<td>2-NED</td>
<td></td>
</tr>
<tr>
<td>Zanetta et al.</td>
<td>70</td>
<td>USO</td>
<td>139</td>
<td>21 (15.1%)</td>
<td>21-RemOv, 2-pelvis, 1-both ovary, 9-IpsilOv, 2-ContOv</td>
<td>20-BOT, 1-IOC, 9-BOT, 5-IOC</td>
<td>45, 39</td>
<td>21-NED, 13-NED, 1-DOD</td>
</tr>
<tr>
<td>Morice et al.</td>
<td>109</td>
<td>USO</td>
<td>38</td>
<td>5 (13.1%)</td>
<td>5-RemOv, 1-both ovary, 1-ConOv, 2-NR</td>
<td>5-BOT, NR</td>
<td>5-NED</td>
<td></td>
</tr>
<tr>
<td>Seracchioli et al.</td>
<td>42</td>
<td>USO</td>
<td>8</td>
<td>0 (0%)</td>
<td>1-IpsilOv</td>
<td>1-BOT</td>
<td>6</td>
<td>1-NED</td>
</tr>
<tr>
<td>Beiner et al.</td>
<td>75</td>
<td>USO</td>
<td>30</td>
<td>4 (13.3%)</td>
<td>4-RemOv, 1-ConOv, 4-IpsilOv</td>
<td>4-BOT, 5-BOT</td>
<td>13, 31</td>
<td>4-NED, 5-NED</td>
</tr>
<tr>
<td>Donnez et al.</td>
<td>43</td>
<td>USO</td>
<td>14</td>
<td>3 (18.7%)</td>
<td>3-RemOv</td>
<td>3-BOT, 12</td>
<td>3-NED</td>
<td></td>
</tr>
<tr>
<td>Romagnolo et al.</td>
<td>NR</td>
<td>USO</td>
<td>32</td>
<td>4 (12.5%)</td>
<td>3-RemOv, 1-same pelvic side, 1-NR</td>
<td>3-BOT, 1-IOC</td>
<td>40, 7</td>
<td>3-NED, 1-NED, 1-DOD</td>
</tr>
<tr>
<td>Gotlieb et al.</td>
<td>57</td>
<td>USO</td>
<td>28</td>
<td>2 (7.1%)</td>
<td>2-RemOv, 1-douglas, 1-NR</td>
<td>2-BOT, 1-NR, 1-IOC</td>
<td>NR</td>
<td>1-NED, 1-NR, 2-NED</td>
</tr>
<tr>
<td>Yinon et al.</td>
<td>88</td>
<td>USO</td>
<td>40</td>
<td>11 (27.5%)</td>
<td>11-RemOv, 4-IpsilOv, 1-ContOv</td>
<td>10-BOT, 1-IOC</td>
<td>41, 23.6</td>
<td>11-NED, 5-NED</td>
</tr>
<tr>
<td>Present series</td>
<td>56</td>
<td>USO</td>
<td>117</td>
<td>7 (5.9%)</td>
<td>7-RemOv, 3-IpsilOv, 2-ContOv</td>
<td>6-BOT, 1-IOC</td>
<td>42, 28</td>
<td>7-NED, 5-NED</td>
</tr>
</tbody>
</table>

F/u, follow-up; USO, unilateral salpingo-oophorectomy; BOT, borderline ovarian tumour; IOC, invasive ovarian carcinoma; NR, not reported; NED, no evidence of disease; DOD, die of disease; ContOv, contralateral ovary; IpsilOv, ipsilateral ovary; RemOv, remaining ovary.

*One patient who initially had been diagnosed with mucinous BOT underwent reoperation due to suspected local recurrence on the remaining ovary 9 months following the surgery. However, the pathology report revealed an endometrioid ovarian carcinoma.
In the present series, all but one relapse had a borderline histology, which is in agreement with other studies (Lim-Tan et al., 1988; Morris et al., 2000; Morice et al., 2001; Seracchioli et al., 2001; Zanetta et al., 2001; Donnez et al., 2003; Morice et al., 2003; Morice, 2006; Palomba et al., 2007; Yinon et al., 2007; Kane et al., 2010). All patients, including one patient who relapsed with invasive cancer, had an isolated ovarian recurrence and could thus be treated successfully with surgery; none of the patients died as a result of the tumour. Furthermore, all recurrent diseases were diagnosed using a follow-up procedure based on clinical examination, ultrasonography and/or the blood markers CA-125 or CA-19.9 levels (Engelen procedure based on clinical examination, ultrasonography and/or the blood markers CA-125 or CA-19.9 levels (Engelen et al., 2000). For young patients expecting long and normal lives, optimization of the follow-up modalities becomes critically important. Given the inolent behaviour of local recurrences of BOTs and the usual occurrence in the spared ovaries, we suggest that ultrasound, particularly using a vaginal probe, is the optimal mode of follow-up, and this procedure reduces the invasiveness and hazard of repeated computed tomography scans (Zanetta et al., 1994). We also suggest that, even though the risk of relapse is substantial after cystectomy of a BOT, patient survival is not altered with the use of this approach.

According to telephone interviews, 113 of the 116 patients (97.4%) resumed menstruation following the fertility-sparing surgery, and 45 of the 51 patients (88.2%) who attempted to conceive had successful pregnancies. Generally, a unilateral cystectomy is associated with an increased likelihood of preserving a woman’s fertility compared with adnexitomy because of the removal of less ovarian tissue. However, the pregnancy rates in the two groups in the current study were 89.2% (33 of 37) in the USO group and 85.7% (12 of 14) in the cystectomy group. Although three patients had miscarriages, the majority of patients had successful term pregnancies with no congenital anomalies. These findings suggest that the reproductive outcomes after USO or cystectomy are promising.

Our study had several limitations. First, comprehensive surgical staging was not considered beforehand for all cases; thus our data may be biased. Although, Camatte et al. (2004) reported that the absence of surgical staging in patients with an ‘apparent stage I’ does not modify survival, even if the recurrence rate is increased, further studies involving a much larger number of patients with BOTs should be carried out in order to confirm this issue. Second, our study used a retrospective design, introducing some degree of bias. Thus, there was an unequal distribution of several variables, such as tumour size and surgical approach, between the two study groups. Prospective randomized trials are needed to clarify the roles of cystectomy and USO for women with BOTs. Third, given that the median time to recurrence for BOTs has been reported to be 5–7 years (Crispens et al., 2002) and given the rare recurrence of stage I BOTs, our sample size and follow-up period may weaken our results. Nevertheless, our series is the largest study of its kind to date.

In conclusion, recurrence rates among patients with BOTs treated with USO (6.0%) are lower than among patients with BOTs treated with cystectomy (13.2%), although this difference was not statistically significant (P = 0.110). Furthermore, USO (89.2%), like cystectomy (85.7%), results in excellent reproductive outcomes for patients with BOTs. Therefore, USO is an appropriate treatment for women with BOTs who wish to preserve fertility. However, when cystectomy is the only viable option (e.g. previous history of unilateral oophorectomy or salpingo-oophorectomy or bilateral involvement of BOTs), cystectomy is a satisfactory therapy for women who are willing to undergo careful and prolonged follow-up examinations.

Authors’ roles

T.S. and C.C.H. carried out the analysis of all data and drafted the manuscript. Y.-Y. L., T.-J.K., J.-W.L., D.-S.B. and B.-G.K. contributed to summarizing medical records and the statistical analysis and revising the manuscript for important intellectual content. B.-G.K. participated in the study design and coordination.

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