Fertility-sparing surgery in patients with clear-cell carcinoma of the ovary: Is it possible?

Hiroaki Kajiyama1,*, Kiyosumi Shibata1, Mika Mizuno1, Satoyo Hosono2, Michiyasu Kawai3, Tetsuro Nagasaka4, and Fumitaka Kikkawa1

1Department of Obstetrics and Gynecology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan 2Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan 3Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Toyohashi, Japan 4Nagoya University School of Health Science, Nagoya, Japan

*Correspondence address. Tel: ++81-52-744-2261; Fax: ++81-52-744-2268; E-mail: kajiyama@med.nagoya-u.ac.jp

Submitted on March 1, 2011; resubmitted on September 6, 2011; accepted on September 20, 2011

BACKGROUND: Clear-cell carcinoma of the ovary (CCC) is often diagnosed at childbearing age, or sometimes during treatment for infertility. Therefore, most young women with early-stage CCC wish to preserve their reproductive and endocrine functions if possible.

METHODS: Clinicopathologic data collected under the central pathological review system were subjected to survival analyses. We analyzed patients with stage I CCC who underwent fertility-sparing surgery (FSS, n = 16) and compared their long-term survival with those receiving radical surgery (n = 205), or patients with non-CCC undergoing FSS (n = 64).

RESULTS: There was no difference in both the overall survival (OS) and disease-free survival (DFS) between patients with CCC who underwent FSS and those who received radical surgery [CCC/FSS (n = 16) versus CCC/radical (n = 205); OS: P = 0.519, DFS: P = 0.265]. Moreover, patients with CCC who underwent FSS did not show a poorer OS and DFS than non-CCC patients who underwent FSS (CCC/FSS versus non-CCC/FSS; OS: P = 0.584, DFS: P = 0.401), or those at the corresponding stage with no CCC. Furthermore, according to the series of patients with CCC in both the current study and four studies in the literature, there was no difference in the recurrence rate between patients with or without CCC who were treated conservatively (CCC/FSS: 13.2% versus non-CCC/FSS: 10.9%, P = 0.614).

CONCLUSIONS: Although our study did not have sufficient power to yield a definite conclusion, our data suggests that at least patients with stage IA CCC may be treated with FSS.

Key words: clear-cell carcinoma of the ovary / fertility-sparing surgery / stage / survival / recurrence rate

Introduction

Clear-cell carcinoma of the ovary (CCC) is a comparatively rare tumor, which represents <10% of all epithelial ovarian cancer (EOC) diagnosed in the USA (Kennedy et al., 1989; Russell P, 1989). In contrast, the incidence of CCC was reportedly >15% of EOC in Japan (Sugiyama et al., 2000). Patients with CCC are more likely to have early-stage tumors that are frequently associated with endometriosis with severe adhesion to neighboring organs (Czernobilsky et al., 1970; Kennedy et al., 1989; Komiya et al., 1999). In addition, a number of previous studies have suggested that their resistance to anti-neoplastic agents resulted in the poorer prognosis of patients with this tumor compared with other histological types (Sugiyama et al., 2000; Pectasides et al., 2006). Therefore, until now, maximum efforts employing radical surgery aiming at complete tumor resection have been made.

Some patients with CCC are diagnosed at childbearing age, or are sometimes identified during treatment for infertility. Thus, most young women with early-stage CCC desire to preserve their reproductive and endocrine functions if possible. Indeed, in general, fertility-sparing surgery (FSS) has been adopted in young patients with borderline, germ cell and stromal tumors, and for stage I/grade 1 invasive EOC. However, particularly in CCC, a less radical surgery to preserve fertility has been likely to be avoided owing to fear of the existence of an occult tumor. In this context, there have been very few studies reporting patients with CCC who underwent FSS to answer whether it is possible to consider FSS in patients with CCC without compromising survival. Considering the clinical courses of 10 patients...
with stage I CCC treated with conservative surgery (CCC/FSS) analyzed in our recent study, we suggest that they have a more favorable prognosis than expected, although this was based on a small number of retrospective data (Kajiyama et al., 2008). Nevertheless, our conclusion in the study was attributable not to survival analysis but to recurrence rates alone. Here, we again propose the questions of whether the prognosis of patients with CCC who undergo FSS is essentially poor, and if recurrence can be avoided if radical surgery is carried out in the initial operation.

In the present study, in an attempt to answer the above-mentioned questions, we retrospectively compared prognoses between patients with or without CCC (non-CCC patients) who underwent FSS. Furthermore, we also examined the difference in the overall survival (OS) and disease-free survival (DFS) of patients with CCC who received conservative and radical surgery. Herein, the possibility of FSS in patients with stage I CCC is proposed.

Materials and Methods

Patients
Since 1986, a variety of malignant ovarian tumors have been accumulated by the Tokai Ovarian Tumor Study Group, consisting of Nagoya University and affiliated cooperating institutions, under the central pathological review system. Up to the present, more than 1500 cases of EOC have been registered and analyzed in this group. From these cases, 285 patients with stage IA or IC EOC, including 16 with CCC and 64 patients with other histological types excluding CCC (non-CCC) who had undergone FSS, and 205 patients with a pure type clear-cell histology who had received radical surgery registered between January 1986 and February 2010 were extracted for this study. There were no patients with stage IB CCC in the current analysis.

This study was approved by the ethics committee of Nagoya University and each affiliated institution. Data were collected from the medical records and clinical follow-up visits. Patients were excluded from this study when they showed insufficient clinical data or were lost to follow-up immediately after surgery. The histological cell types were assigned according to the criteria of the World Health Organization (WHO). Tumors were classified as CCC if typical clear or hobnail cells were present in a papillary, solid or tubulocystic pattern. Histological slides immediately after surgery. The histological cell types were assigned according to the criteria of the World Health Organization (WHO).

In principle, patients in the FSS group were eligible if they: (i) had histologically confirmed stage I CCC or non-CCC, (ii) were ≤40 years of age at the time of the initial diagnosis, (iii) strongly desired to retain fertility and (iv) underwent salpingo-oophorectomy on the side of the ovarian tumor with at least a full peritoneal staging (cytology of peritoneal washing or ascites, careful palpation and inspection throughout the peritoneal cavity and, if necessary, multiple peritoneal biopsies). Systemic retroperitoneal lymphadenectomy, wedge resection of the remaining ovary and omentectomy were optional. In cases in which systemic retroperitoneal lymphadenectomy or sampling was omitted, the absence of swelling lymph nodes of >1 cm in diameter was confirmed by a preoperative computed tomography (CT) scan. In a preoperative counseling session, these women were informed of the possible risks and benefits of FSS, and signed a consent form. In patients who underwent conventional radical surgery, the following were carried out in principle: hysterectomy and bilateral salpingo-oophorectomy with peri toneal staging (peritoneal washing, omentectomy, multiple peritoneal biopsies and the removal of peritoneal implants) with retroperitoneal lymphadenectomy or sampling. In some patients at too advanced an age (e.g. over 80 years old) or with severe complications, retroperitoneal lymphadenectomy was exceptionally omitted. If retroperitoneal lymphadenectomy was omitted, the absence of a swollen lymph node ≥1 cm in diameter was confirmed by preoperative CT scan; however, if present, palpable nodes were appropriately sampled.

Of all patients, 222 patients (77.9%) were treated postoperatively with 3–6 cycles of adjuvant platinum-based chemotherapy. Forty-two (14.7%) did not receive adjuvant chemotherapy owing to severe complications, the patients’ wishes, within the criterion of omission (stage IA/grade 1), and the decision of each institution. In 21 patients (7.4%), specific information on chemotherapy was not available. Details of the chemotherapy regimen in each period were described previously (Suzuki et al., 2008).

Follow-up and analysis
At the end of treatment all patients underwent a strict follow-up consisting of clinical checkups such as a pelvic examination, ultrasonographic scan, cancer antigen-125 evaluation and periodic CT scan. The OS was defined as the time between the date of surgery and the last date of follow-up or death owing to EOC. DFS was defined as the time interval between the date of surgery and that of recurrence or the last follow-up. The distributions of clinicopathologic events were evaluated using the $\chi^2$ or Fisher’s exact tests. Univariate survival analysis was based on the Kaplan–Meier method. Comparison between the survival curves was conducted using the Log-rank test. A $P$-value of $<0.05$ was considered significant.

Results

Clinical outcome
Patients’ characteristics are summarized in Table I. The median follow-up for all surviving patients was 58.8 (4.8–256.5) months. All patients were divided into three groups: (i) patients with CCC who had undergone FSS ($n = 16$) (CCC/FSS group), (ii) patients with CCC who had undergone radical surgery ($n = 205$) (CCC/Radical group) and (iii) non-CCC patients who had undergone FSS ($n = 64$) (non-CCC/FSS group). The median age at the time of the diagnosis of patients in the CCC/FSS group was 35 years, ranging from 31 to 39, while that of the non-CCC/FSS group was 28 years, ranging from 12 to 40 and that of the CCC/Radical group was 54 years, ranging from 30 to 78. The age of the CCC/FSS group was higher than that of the non-CCC/FSS group ($P < 0.0001$). Among the CCC/FSS group, seven patients had FIGO IA disease, and nine had IC disease.

Consequently, in all patients undergoing FSS (with or without CCC), nine (IA: 2, IC: 7) and one (IC) patient experienced recurrence, respectively. We compared the OS between the CCC/FSS and CCC/Radical groups. The 5-year OS rates were 90.5% (CCC/FSS) and 88.2% (CCC/Radical), respectively. The patients with CCC with FSS did not show a poorer prognosis than those with radical surgery ($P = 0.519$). In addition, the 5-year DFS rates were 92.9% (CCC/ FSS) and 81.9% (CCC/Radical), respectively. On statistical analysis, the difference in DFS between the two groups was also non-significant (Fig. 1B, $P = 0.265$). Moreover, confining analysis to patients with stage IC CCC, there was no difference in the OS and DFS between the two groups (OS: $P = 0.783$, DFS: $P = 0.484$).

Moreover, patients in the CCC/FSS group are obviously younger than those in the CCC/Radical group. To examine whether age
difference has any impact on the outcome, CCC/Radical group was further stratified to two subgroups: ≤40 (n = 17) and over 40 (n = 188). As shown in Fig. 1C and D, the differences in OS (C) and DFS (D) among these three groups were also non-significant (OS: P = 0.684, DFS: P = 0.495).

We subsequently compared the prognosis of CCC with that of non-CCC patients who both underwent FSS. The 5-year OS and DFS rates of the non-CCC/FSS group were 89.3 and 85.5%, respectively. On statistical analysis, there was also no significant difference in the OS and DFS between the two groups (Fig. 2A and B: OS: P = 0.584, DFS: P = 0.401).

### Series in the literature of stage I CCC or non-CCC patients treated conservatively

Reports of patients with CCC treated conservatively are extremely limited. Series of stage I CCC or non-CCC patients in both the current study and the literature are summarized in Table II (Zanetta et al., 1997; Schilder et al., 2002; Morice et al., 2005; Satoh et al., 2010). Patients that could not to be discriminated as stage IA or IC in the literature were categorized as ‘stage I’. In 23 patients with CCC at stage IA, all excluding one (4.3%) were alive without recurrence. In addition, in 24 patients with CCC at stage IC, six patients (25.0%) experienced recurrence. In all 46 patients with CCC at stage I, seven cases of recurrence (13.2%) were identified. On the other hand, the recurrence rates of stage IA, IC and all stage I patients with non-CCC were 8.0, 11.4 and 10.9%, respectively. Therefore, the frequency of recurrence did not significantly alter between patients with and without CCC (P = 0.614). Furthermore, we examined whether the recurrence frequently occurred at a particular site in patients with and without CCC. The frequency of recurrence in the remaining ovary and/or uterus alone did not significantly alter in patients with CCC compared with those with non-CCC (P = 0.409).

### Discussion

According to previous reports, patients with CCC, even those at an early stage, have a greater risk of recurrence and poorer survival in comparison with those with other pathological types of ovarian cancer, despite platinum-based adjuvant chemotherapy (O’Brien et al., 1993; Sugiyama et al., 2000; Chan et al., 2008). Reflecting this background, the application of FSS in patients with CCC markedly varied from guideline to guideline. In the guidelines of the American College of Obstetrics and Gynecology, or those of the European Society for Medical Oncology, CCC is viewed as a contraindication for FSS as an unfavorable histological type (American College of Obstetricians and Gynecologists, 2007; Aebi and Castiglione, 2008). In contrast, in the 2010 guidelines of the National Comprehensive Cancer Network (NCCN Clinical Practice Guidelines in Oncology, 2010), a stage I patient with this tumor is an acceptable candidate for FSS. The reason for this controversy is the extreme rarity of reports in the literature. Nonetheless, for women with CCC, the possibility of being able to select FSS is of the greater importance.

We recently reported the clinical outcome of 10 patients with stage I CCC treated with FSS: four stage IA and six stage IC. While only one patient with stage IC CCC experienced recurrence in distant organs and died of disease, the other nine patients showed no evidence of disease (Kajiyama et al., 2008). However, these results were based on the recurrence rates alone, so it was not clarified whether the choice of FSS itself influenced the long-term outcome of patients with CCC. In the current study, we first compared the survival between patients with stage I CCC who had undergone FSS and those who received radical surgery. In addition, we subsequently examined whether there was a difference in survival between patients with or without CCC who were treated conservatively. In both investigations, we identified no significant inferiority in the findings of CCC/FSS patients compared with those in other groups, although we fully understand that the number of patients was very limited. Nevertheless, to our knowledge, there has been no report comparing survival between these groups. According to a recent sophisticated analysis by Satoh et al., the 5-year recurrent-free survival rate of 15 patients with stage IC CCC was 66.0%; in contrast, 15 patients with stage IA CCC showed no recurrence (Satoh et al., 2010). Furthermore, regarding the recurrence rates of patients with stage I CCC including those in the current study and the literature (Zanetta et al., 1997; Schilder et al., 2002; Morice et al., 2005; Satoh et al., 2010), 7 out of 53 at stage I (13.2%) experienced recurrence, which did not differ from the rate in non-CCC patients (10.9%) (Table II, P = 0.614). Considering the
results for both the recurrence rates and long-term survival, we think that FSS may be one of the options at least for patients with stage IA CCC when adequate staging and chemotherapy are conducted.

Our subsequent concern was the adhesive character of CCC tumors. The pre- and intraoperative capsule rupture of a CCC tumor is likely to be induced by the dissection of strong adhesion to the surrounding tissues, which may be associated with tumor invasion or endometriosis. Although rupture in itself appears to be related to a poorer prognosis compared with that in its absence, Takano et al. (2006) previously showed, through the analysis of 125 patients with stage I CCC, that those with intraoperative capsule rupture did not show a poorer DFS than those at stage IA. Although we unfortunately had no data regarding the association between the extent of adhesion and a poor prognosis, it is possible to expand the indication to cover patients with intraoperative capsule rupture or, even further, if they fully understand the absence of comprehensive evidence and possibly increased risk of recurrence. We can bear in mind that, with or without adhesion, the remaining ovary and/or uterus alone was not necessarily the more frequent recurrence site in patients with CCC compared with those with non-CCC, according to the very limited

Figure 1 (A and B) Kaplan–Meier estimated OS (A) and DFS (B) of patients with stage I CCC of the ovary stratified by the surgical procedure. Solid line: CCC/FSS group \( n = 16 \), dotted line: CCC/Radical group \( n = 205 \). P-values between two groups on univariate analysis are listed under the survival curves. (C and D) CCC/Radical group was further stratified to two subgroups: \( \leq 40 \) years of age \( n = 17 \) and over 40 years \( n = 188 \). The differences in OS (C) and DFS (D) among these three groups were also non-significant (OS: \( P = 0.684 \), DFS: \( P = 0.495 \)).

Figure 2 Kaplan–Meier estimated OS (A) and DFS (B) of patients with stage I CCC or non-CCC who underwent FSS. Dotted line, non-CCC \( n = 64 \); solid line, CCC \( n = 16 \). P-values between two groups on univariate analysis are listed under the survival curves.
A recent report highlights the new possibility of using the grading system in CCC has not been established (Shimizu et al., 2005; Satoh et al., 2010). Nevertheless, it may be safer to avoid FSS when there is strong adhesion to the uterus or contralateral ovary, which seems to be associated with tumor invasion.

We did not investigate the tumor grade in the current study as the significance of the previous grading system in CCC has not been established (Shimizu et al., 1998; Silverberg, 2000; Ishioka et al., 2003). However, a recent report highlighted the new possibility of using the grade as a prognostic factor in patients with CCC (Ryu et al., 2009). The difference in the results among a variety of retrospective reports, including ours, may partly depend on the differences in the tumor grade of CCC. Therefore, we plan to perform a subsequent confirmatory analysis with tumor grade using this grading system in our next study.

In summary, although there is no established criterion for FSS in CCC patients, FSS may be an option for patients with early-stage CCC who are of reproductive age. However, our retrospective analysis did not have sufficient power to yield a definite conclusion [Power (OS) = 0.1406, CCC/FSS versus CCC/Radical, n = 221, comparison in 10-year survival]. Accordingly, our present study was preliminary and had several limitations, such as small number of cases, the possibility of type II error, variable follow-up length and different treatment protocols during the study period. On this occasion, we merely went FSS may not show a poorer prognosis than those receiving radical surgery. Therefore, FSS for patients with CCC should only be applied to women with a sufficient comprehension of the potential risks when we unavoidably adopt this surgical procedure. We should accumulate further experiences regarding this tumor to clarify the applicability of FSS.

Acknowledgements

We are indebted to Drs H. Mitsui (Nagoya University Hospital), R. Sekiya (Nagoya University Hospital) and K. Sakai (Daido Hospital) who were performed registration as collaborators. The authors sincerely thank Drs Y. Kinoshita (Ogaki Municipal Hospital), K. Sakakibara (Okazaki Municipal Hospital), A. Takeda (Gifu Prefectural Tajimi Hospital), O. Yamamuro (Japanese Red Cross Nagoya Second Hospital), K. Mizuno (Japanese Red Cross Nagoya first Hospital) and K. Matsuzawa (Anjo Kosei Hospital) to collaborate with data collection.

References


### Table II Series of patients with stage I CCC or without CCC who were treated conservatively in the current study or in studies in the literature.

<table>
<thead>
<tr>
<th></th>
<th>CCC</th>
<th>Recurrence</th>
<th>%</th>
<th>Non-CCC</th>
<th>Recurrence</th>
<th>%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>23</td>
<td>1</td>
<td>4.3</td>
<td>176</td>
<td>14</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>24</td>
<td>6</td>
<td>25.5</td>
<td>123</td>
<td>14</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary/uterus alone</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>78</td>
<td>14</td>
<td>17.9</td>
<td>0.409*</td>
</tr>
<tr>
<td>PC/distant/RPN</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>78</td>
<td>14</td>
<td>17.9</td>
<td>0.409*</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>7</td>
<td>13.2</td>
<td>377</td>
<td>41</td>
<td>10.9</td>
<td>0.614</td>
</tr>
</tbody>
</table>

*Fisher's exact test.

**Note:**
- PC, peritoneal cavity; RPN, retroperitoneal lymph node.
- *A substage was not documented in each original paper.
- Analysis based on the studies by Morice et al. (2005), Satoh et al. (2010), Schilder et al. (2002) and Zanetta et al. (1997), and the current study.

Authors’ roles

H.K., K.S., M.M. and F.K. designed the initial study. H.K. performed all the procedures. K.S., M.M. and M.K. coordinated, collected, analyzed and interpret the data. H.K., T.N. and S.H. participated in analyses and interpretation of the data. H.K., K.S. and M.M. drafted the paper. S.H., M.K., T.N. and F.K. revised the manuscript. All authors approved the final draft. F.K. will act as guarantor for the paper.


