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Recurrence-predicting prognostic factors for patients with early-stage epithelial ovarian cancer undergoing fertility-sparing surgery: a multi-institutional study

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ABSTRACT

Objectives: We reviewed the clinical outcomes of patients with early-stage epithelial ovarian cancer (EOC) who had undergone fertility-sparing surgery (FSS) to assess recurrence-free survival (RFS).
Study design: After central pathological review and scanning of the medical records of multiple institutions, a total of 94 patients with stage I EOC (IA: 43 and IC: 51) treated with FSS were analyzed. IC substages were defined as follows: intraoperative spillage (IC1), preoperative capsule rupture or surface invasion (IC2), and positive cytology results (IC3).
Results: The median age was 30.5 (13–40) years. The median follow-up time was 66.6 months. Fourteen patients (14.9%) showed carcinoma recurrence. Eleven (11.7%) patients died of the disease. The total 5-year RFS rate including all women who received FSS was 84.3%. There was no significant difference in RFS between patients with IC1 and those with stage IA ($P = 0.9411$). In contrast, the RFS rate of patients with IC2/3 was significantly poorer than in patients with stage IA (IA vs. IC2/3: $P = 0.0487$, IC1 vs. IC2/3: $P = 0.0471$). In further analyses according to each histological type and grade, the RFS rate of subjects with the mucinous type was the same as that of those with a clear-cell histology ($P = 0.3350$). There was a significant difference in RFS of patients with grade 1 (G1) and G2–3 ($P = 0.0004$). To eliminate selection bias from a number of clinicopathologic factors as thoroughly as possible, the age, FIGO stage, histological type, grade, and postoperative adjuvant chemotherapy were entered into multivariate RFS analyses. Cox multivariable analysis showed that the substage group and grade were independent prognostic factors for RFS.
Conclusions: Confined to young women with intraoperative rupture, FSS may be proposed, if without tumor-associated dense adhesion. However, those with preoperative rupture, surface invasion, and positive cytology showed a greater risk of recurrence, suggesting that they are not recommended candidates. Although patients with G2–3 tumors showed a poorer prognosis than those with G1, the number of these subjects was so small that the current results should be reconfirmed in the next study.

1. Introduction

According to Cancer Statistics in 2011, it was estimated that 225,900 women were diagnosed with epithelial ovarian carcinoma (EOC), and 140,200 died of the disease worldwide [1]. In general, EOC is frequently observed in women of postmenopausal age, but according to previous reports, 3–17% of patients with EOC were aged under or equal to 40 years [2–6]. In Japan, approximately 7000 cases of EOC are diagnosed every year, and an estimated 4467 women died of this disease in 2007 [7]: the incidence in the reproductive age group was reportedly more than 8% of EOC in our country [8]. The standard surgery for patients with EOC is based on hysterectomy, bilateral salpingo-oophorectomy, and omentectomy with comprehensive surgical staging [9]. Most EOC patients of reproductive age are concerned with preserving their fertility despite anxiety regarding the oncologic outcome. Therefore, fertility-sparing surgery (FSS) has been selected in those EOC patients based on several criteria, including the patients' strong desire, stage, histological type, and tumor differentiation. Nevertheless, the amount of evidence is not necessarily sufficient to

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resolve whether, in choosing FSS, the risk of recurrence or death may be increased because these clinicopathologic indicators overlap with one another and present an unexpectedly complicated picture. Essentially, the randomized controlled trial is a solution to this problem, but it is difficult to perform from an ethical perspective.

In this study, we reviewed the long-term clinical outcomes of those cases to identify recurrence-free survival, comparing with those with above-mentioned individual clinicopathologic factors.

2. Patients and methods

The Tokai Ovarian Tumor Study Group, consisting of Nagoya University Hospital and 13 affiliated institutions, has accumulated clinical data on malignant ovarian tumors under the central pathological review system as a regional population-based study. From this database, between 1986 and 2012, a total of 94 stage I patients who had undergone FSS were extracted. Six patients were excluded from this study because of insufficient clinical data or being lost to follow-up immediately after surgery. Borderline tumors were also excluded. Data were collected from the medical records and clinical follow-up visits. This study was approved by the ethics committee of Nagoya University. We defined FSS for EOC as at least conservation of the uterus, contralateral ovary, and fallopian tube. In the present study, eligible patients fulfilled the following: (1) had histologically confirmed stage I EOC, (2) were less than or equal to 40 years of age at the time of the initial diagnosis, (3) strongly desired to retain fertility, (4) in a preoperative counseling session, these women were informed of the possible risks and benefits of FSS, and signed a consent form, (5) conservation of the uterus and contralateral ovary and fallopian tube 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), and (6) systematic retroperitoneal lymphadenectomy, wedge resection of the remaining ovary and omentectomy were optional (omentectomy: 14 (14.9%), wedge resection: 19 (20.2%), and lymphadenectomy: 5 (5.3%)).

The histological types and tumor grade were assigned according to the criteria of the World Health Organization (WHO). The stage was based on the International Federation of Gynecology and Obstetrics (FIGO), 1988. Histological slides were reviewed by one of the authors under a central pathological review system with no knowledge of the patients' clinical data. In this study, we classified patients with IC into three sub-groups: Sub-staging criteria used in stage reassignment were defined as follows: surgical spillage (IC1), capsule rupture before surgery or tumor on the surface (IC2), and positive cytology results (IC3).

2.1. 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, CA125 evaluation, magnetic resonance imaging (MRI), and periodic computed tomography (CT) scan. Radiologic recurrence was defined as tumor recurrence based on CT, MRI, or ultrasound, and clinical recurrence was defined as the development of ascites and/or a clinically palpable mass. When an elevated CA125 value was continuously detected, the presence or absence of a tumor was radiologically confirmed. Recurrence-free survival (RFS) was defined as the time interval between the date of surgery and that of recurrence or the last follow-up or death from any cause. Survival curves were based on the Kaplan–Meier method. Comparison between the curves was conducted employing the log-rank test. Multivariable analysis was performed with the Cox proportional hazards model to evaluate independent factors affecting survival. A P value < 0.05 was considered significant.

3. Results

The clinical and histological characteristics of the patients are illustrated in Table 1. The median age was 30.5 (SD: ±6.7) years, ranging from 13 to 40. The median follow-up time was 66.6 months. The stage distribution was as follows: IA in 43 and IC in 51 patients. Regarding the IC substage, 6 patients showed surface involvement or preoperative capsule rupture, 31 showed intraoperative capsule rupture/negative cytology/no surface involvement, and 14 showed positive ascites/washing cytology. The most frequent histological type was mucinous (N = 52, 55.3%), followed by endometrioid (N = 21, 22.3%) and clear-cell carcinoma (N = 17, 18.1%). The tumor grade was G1, G2, and G3 in 62.8% (N = 59), 14.9% (N = 14), and 4.3% (N = 4) of patients, respectively. Since the tumor grade of clear-cell carcinoma is not defined in the WHO classification, this tumor was categorized individually (N = 17, 18.1%). Sixty-one patients (64.9%) were treated postoperatively with 3 to 6 cycles of adjuvant chemotherapy; 26 patients (27.7%) received platinum-based chemotherapy, and 35 patients (37.2%) received platinum plus taxane chemotherapy. In 11 patients (11.7%) detailed information on chemotherapy was missing.

Fourteen patients (14.9%) showed carcinoma recurrence. Regarding the final oncologic outcome of the patients, 11 died of the disease. The 5-year RFS rate of all patients who received FSS was 84.3%. Subsequently, we analyzed RFS with stratification by sub-classification of the FIGO IC. As a result, we observed 5 recurrences in 43 patients with IA tumors (11.6%), 3 in 31 with IC1 (9.7%), and 6 in 20 with IC2/3 (30.0%). Regarding long-term survival, there was no significant difference in RFS between patients with stage IC1 and those with stage IA (P = 0.9411). In contrast, RFS of the patients with stage IC2/3 was significantly poorer than in patients with stage IA or IC1 (IA vs. IC2/3; P = 0.0487, and IC1 vs. IC2/3; P = 0.0471) (Fig. 1).

Next, we carried out further survival analysis according to each histological type. In general, mucinous carcinoma was the most frequent tumor in young patients with EOC, and clear-cell carcinoma is the most controversial pathologic type in a candidate

Table 1
Patients' characteristics.

Total	94	
Age		
Mean (SD)	30.5 ± 6.7	
≤30	47	50.0
≥31	47	50.0
FIGO stage		
IA	43	45.7
IC	51	54.3
IC1	31	33.0
IC2/3	20	21.3
Histological type		
Serous	3	3.2
Mucinous	52	55.3
Clear-cell	17	18.1
Endometrioid	21	22.3
Undifferentiated	1	1.1
Grade		
G1	59	62.8
G2	14	14.9
G3	4	4.3
Clear-cell	17	18.1
Chemotherapy		
Absent	22	23.4
Present	61	64.9
Unknown	11	11.7

IC substages were defined as follows: surgical spillage (IC1), capsule rupture before surgery or tumor on the surface (IC2), and positive cytology results (IC3).