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Fertility-sparing surgery in young women with mucinous adenocarcinoma of the ovary

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ABSTRACT

Objectives. The purpose of this study was to clarify the clinical outcome of patients with stage IA mucinous epithelial ovarian cancer (mEOC) treated with fertility-sparing surgery (FSS).

Methods. After a central pathological review and search of the medical records from multiple institutions, a total of 148 stage I mEOC patients were retrospectively evaluated in the current study. All mEOC patients were divided into three groups: group A (FSS; age, 40≥); groups B and C {radical surgery; age, 40≥ (B); 40< (C)}. Survival analysis was performed among these three groups using Kaplan–Meier methods.

Results. The median follow-up time of all mEOC patients was 71.6 (4.8–448.3) months. Among the 41 patients in group A, 27 patients (65.9%) had IA disease, and 14 (34.1%) had IC disease. Five-year overall survival (OS) and disease-free survival (DFS) rates of patients in the groups were as follows: group A, 97.3% (OS)/90.5% (DFS); group B, 94.4% (OS)/94.4% (DFS); group C; 97.3% (OS)/89.3% (DFS). Collectively, there was no significant difference in OS or DFS among these groups even though they were stratified to each substage (IA/IC) (OS, $P=0.180$; DFS, $P=0.445$, respectively). Furthermore, in multivariate analyses, the surgical procedure was not an independent prognostic factor for either OS or DFS (OS, HR: 0.340, 95% CI: 0.034–3.775, $P=0.352$; DFS, HR: 0.660, 95% CI: 0.142–3.070, $P=0.596$).

Conclusions. Patients with stage I mEOC treated with FSS did not necessarily show a poorer prognosis than those receiving radical surgery.

Introduction

Epithelial ovarian carcinoma (EOC) is the leading cause of death from gynecological malignancy [1]. The standard surgical treatment for patients with EOC is based on hysterectomy and bilateral salpingo-oophorectomy with peritoneal sampling (peritoneal washing, omentectomy, multiple peritoneal biopsies, and the removal of peritoneal implants) with or without lymph node sampling. According to previous reports, 3–17% of all EOCs occur in women under 40 years of age [2–7]. To preserve the reproductive and endocrine functions, fertility-sparing surgery (FSS) has been occasionally adopted in young patients with stage I /grade 1 invasive EOC as well as borderline and germ cell tumors. However, on selecting FSS, the amount of evidence has been too small to accurately estimate the risk of leaving a microscopic tumor.

Based on morphological criteria, there are four major histological types in EOC, and the biological behaviors, including the sensitivity to anti-neoplastic reagents, or the proliferative activity, differ among these types. These variations in the histological types and differentiations of tumors make it difficult to assess the influence of FSS on the long-term prognosis. Thus, it is desirable to investigate the validity of selecting FSS in uniform histological types individually. Mucinous epithelial ovarian cancer (mEOC) accounts for approximately 10% of EOC [8]. However, this tumor is the most common histological type in young patients who have undergone FSS because of its frequency in young patients with EOC [7,9–14]. In addition, despite the fact that advanced mEOC shows a poor response to platinum-based chemotherapy and an unfavorable clinical outcome [15,16], the prognosis of patients with early-stage mEOC has been reported to be comparatively favorable [17]. Moreover, according to an earlier report, the 5-year disease-free survival rate of 410 patients with mEOC was 90.8%, and this pathological type was not a significant prognostic factor on multivariate analysis [18,19]. However, confining

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analysis to the mucinous pathology, the safety of selecting FSS has not been well defined.

In the current study, we therefore assessed the long-term clinical outcome, such as tumor recurrence and patient survival, in patients with early-stage mEOC who underwent FSS in comparison with those who underwent radical surgery.

Materials and methods

One hundred and forty-eight patients with stage I (FIGO, 1985) mEOC were registered and treated by the Tokai Ovarian Tumor Study Group, consisting of Nagoya University Hospital and affiliated hospitals, between January 1986 and December 2007.

Data were collected from the medical records and clinical follow-up visits. Six patients were excluded from this study since 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). Histological slides were reviewed by one of the authors under a central pathological review system with no knowledge of the patients' clinical data. Additionally, patients with FIGO stage IC were classified into two subtypes according to the pathological characteristics: IC(b) for patients with intraoperative capsule rupture and a negative cytology; IC (non-b) for those with IC excluding IC(b), including a tumor on the ovarian surface/preoperative capsule rupture, or with positive malignant cells in the positive peritoneal washing/ascites.

All mEOC patients were divided into three groups: group A, patients who underwent FSS under the criteria described below; groups B (under 40 years old) and C (over 41 years old), patients who underwent conventional surgery, including hysterectomy and bilateral salpingo-oophorectomy with peritoneal staging (peritoneal washing, omentectomy, multiple peritoneal biopsies, and the removal of peritoneal implants) with retroperitoneal lymphadenectomy or sampling.

In principle, group A patients were eligible if they: (1) had histologically confirmed stage I mEOC, (2) were less than 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) underwent salpingo-oophorectomy on the side of the ovarian tumor with at least a peritoneal staging (cytology of peritoneal washing or ascites, careful palpation and inspection throughout the peritoneal cavity, and multiple peritoneal biopsies), and (6) systemic retroperitoneal lymphadenectomy or sampling, wedge resection of the remaining ovary, and omentectomy, were optional. In case systemic retroperitoneal lymphadenectomy or sampling was omitted, the absence of swelling lymph nodes of more than 1 cm in diameter was confirmed by a preoperative CT scan. Eighty-one patients (54.7%) were treated postoperatively with three to six cycles of adjuvant chemotherapy; 50 patients received conventional platinum-based chemotherapy, and 31 patients received platinum plus taxane chemotherapy.

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, and periodic CT scan. The overall survival (OS) was defined as the time between the date of surgery and the last date of follow-up or death due to mEOC. Disease-free survival (DFS) was defined as the time interval between that of surgery and the date of recurrence or the last follow-up. The distributions of clinicopathologic events were evaluated using Chi-square tests. The univariate survival analysis was based on the Kaplan–Meier method. Comparison between the survival curves was analyzed using the Log-rank test. Multivariate analysis was analyzed employing Cox's proportional hazard model. A P-value of <0.05 was considered significant.

Results

A total of 148 patients with stage I mEOC were entered into this study. The characteristics of patients in groups A, B, and C are summarized in Table 1. The median follow-up time of all patients was 71.6 (4.8–448.3) months. Among the 41 patients in group A, 27 (65.9%) had IA disease, and 14 (34.1%) had IC disease. Among the 107 patients in groups B–C, 53 (49.9%) had IA-B disease, and 54 (50.1%) had IC disease. The clinical characteristics excluding patients' age were similar among the three groups, including the stage distribution, rates of positive peritoneal cytology, and the presence of adjuvant chemotherapy.

With regard to the patients' long-term prognosis, 5-year OS rates in the individual groups were as follows: group A, 97.3%; group B, 94.4%; and group C, 92.2%. There was no significant difference in OS among these groups (Fig. 1A, $P=0.180$). In addition, the 5-year DFS rate of all group A patients was 90.5%, compared with 94.4% in group B, and 89.3% in group C. On Kaplan–Meier analysis, the difference in DFS among these groups was also non-significant (Fig. 1B, $P=0.445$). Subsequently, we performed further survival analysis according to the stage I substage (IA and IC). Fig. 2 shows the OS or DFS curves stratified by the FIGO IA (OS: *A*, DFS: *C*) and FIGO IC (OS: *B*, DFS: *D*). This analysis showed that the survival of patients in groups A was not poorer than that of patients who underwent radical surgery (including groups B and C).

Regarding further investigation of the prognostic factors, the FIGO stage (IA vs. IB-C), surgical procedure (conservative: group A vs. radical: group B/C), cytology of the ascites (negative vs. positive), and postoperative chemotherapy (absent vs. present) were entered into the uni- and multivariate OS/DFS analyses (Table 2). In the univariate analysis, a significantly poorer prognosis or clinical tendency was noted in the patients with stage IB-C, positive cytology of ascites, and the presence of chemotherapy than those with the other category (OS/DFS). However, these clinicopathologic factors did not retain significance as an independent prognostic indicator. Furthermore, multivariate analyses of stage I mEOC generated results similar to those of other clinicopathologic factors; the surgical procedure did not significantly influence survival (Table 2: OS, HR: 0.340, 95% CI: 0.034–3.775, $P=0.352$; DFS, HR: 0.660, 95% CI: 0.142–3.070, $P=0.596$).

Of all the 236 mEOC patients treated with conservative surgery listed in Table 3, including the previous representative literature [7,10,12,13] and our current cases, 17 showed relapse (17/236; 7.2%), four of which were rescued by subsequent salvage therapy without evidence of disease, and seven of these died of the disease (7/236;

Table 1
Patients' characteristics.

	FSS	Radical surgery		
	Group A	Group B	Group C	*P*-value
Total	41	18	89	
Age				
40≥	41	18	0	
40<	0	0	89	
FIGO stage				0.292
IA	27	7	45	
IB	0	0	1	
IC	14	11	43	
IC(b)[a]	8	6	25	
IC(non-b)[b]	6	5	18	
Cytology				0.490
Negative	35	13	71	
Positive	6	5	18	
Chemotherapy				0.201
Absent	23	6	38	
Present	18	12	51	
Conventional platinum-based	11	7	32	
Taxane plus platinum	7	5	19	

[a] Intraoperative capsule rupture.
[b] Washing/ascites positive or preoperative capsule rupture.