International Journal of Clinical Oncology (2019) 24:857–862
https://doi.org/10.1007/s10147-019-01416-y

ORIGINAL ARTICLE

Oncologic and reproductive outcomes of cystectomy as a fertility-sparing treatment for early-stage epithelial ovarian cancer

Hiroaki Kajiyama[1] · Shiro Suzuki[1] · Kaoru Niimi[1] · Satoshi Tamauchi[1] · Michiyasu Kawai[2] · Tetsuro Nagasaka[3] · Kiyosumi Shibata[4] · Fumitaka Kikkawa[1]

Received: 8 December 2018 / Accepted: 2 February 2019 / Published online: 15 February 2019

Abstract

Background Fertility-sparing surgery (FSS) has mainly been chosen for young women with ovarian-confined/well-differentiated epithelial ovarian cancer (EOC). In general, FSS consists of at least conservation of contralateral ovary and the uterus with a staging surgery. However, information on the clinical outcome in women who underwent cystectomy as a fertility-preserving option is lacking.

Methods After a central pathological review and search of the medical records from multiple institutions between 1987 and 2015, a total of eight early-stage EOC patients treated with cystectomy as FSS were retrospectively evaluated. Diagnosis and staging were based on International Federation of Gynecology and Obstetrics criteria (2014). Surgery consisted of uni- or bilateral cystectomy. The oncologic and reproductive outcomes were assessed.

Results The median age was 29 years (range 26–38 years). The median follow-up time was 103.6 months (range 42.2–218.3 months). The stage was IA in 3, IC1 in 4, and IC3 in one patient. Five patients received adjuvant chemotherapy. After cystectomy, two patients experienced recurrence in the pelvic cavity and bilateral ovaries, respectively. The former patient died of the disease 42 months after cystectomy, and conversely, the latter one was rescued by subsequent radical surgery. Four full-term childbirths were observed in three patients.

Conclusions Although oophorectomy is considered as an appropriate fertility-preserving operation, cystectomy may be an unavoidable option when it is the only surgical procedure available. It is desirable to verify the utility by accumulating larger numbers of patients through a future registry system.

Keywords Epithelial ovarian carcinoma · Fertility-sparing surgery · Cystectomy · Oncologic outcome · Reproductive outcome

Abbreviations

EOC	Epithelial ovarian carcinoma
FSS	Fertility-sparing surgery
FIGO	International federation of gynecology and obstetrics

Introduction

Epithelial ovarian carcinoma (EOC) is one of the leading causes of cancer-related mortality among women with gynecological malignancies [1]. Since EOC often remains silent in clinical practice, the majority of patients display aggressive peritoneal metastasis at the time of diagnosis [2]. In principle, the standard surgical treatment for patients with this tumor is based on radical surgery, including maximum cytoreductive surgery or hysterectomy/bilateral salpingo-oophorectomy/omentectomy plus staging surgery [3]. Although EOC is commonly diagnosed at a postmenopausal generation, prior studies have shown that this disease in reproductive-age women accounts for 3–17% of all patients [4–7]. According to previous studies, younger patients with EOC showed a more favorable clinical outcome than the elderly, although the age was not an independent prognostic

✉ Hiroaki Kajiyama
kajiyama@med.nagoya-u.ac.jp

[1] Department of Obstetrics and Gynecology, Graduate School of Medicine, Nagoya University, Truma-cho 65, Showa-ku, 466-8550 Nagoya, Japan

[2] Department of Obstetrics and Gynecology, Toyohashi Municipal Hospital, Toyohashi, Japan

[3] Division of Medical Laboratory Sciences, School of Health Science, Nagoya University, Nagoya, Japan

[4] Department of Obstetrics and Gynecology, Bantane Hospital, Fujita Health University, Nagoya, Japan

indicator because of a close relationship with increasing rates of an early stage and a lower tumor grade [5, 8]. Particularly, based on our earlier report, in younger patients aged ≤ 40 years, 67.3% had stage I disease and 36.7% had a mucinous type [8]. However, if we select such a radical surgical procedure for women at reproductive age, female-specific endocrine/reproductive functions will be lost. As well as the achievement of complete curability of the disease, conserving such a female function is also crucial for maintaining their quality of life.

Fertility-sparing surgery (FSS) has been acceptably chosen for not only young patients with germ cell, stromal, and borderline tumors, but also those with ovarian-confined/capsulated/well-differentiated EOC. In prior studies, FSS was defined as at least conservation of the uterus, contralateral ovary, and fallopian tube [9, 10]. Usually, the standard procedure of FSS is considered as unilateral salpingo-oophorectomy, omentectomy, and staging surgery. However, we occasionally encounter a clinical situation whereby cystectomy is the only surgical choice if they strongly wish to preserve their reproductive function. Naturally, compared with unilateral salpingo-oophorectomy, to perform cystectomy is thought to be a big challenge for such patients because of a risk of remaining an occult tumor in the contralateral ovary with fear of impairing complete curability. Most gynecologists may hesitate to select cystectomy for FSS. Nevertheless, information on clinical outcomes in women who underwent cystectomy as a fertility-preserving option is extremely lacking.

To investigate the oncologic plus reproductive outcome of young women with early-stage EOC who underwent unilateral/bilateral cystectomy, we conducted a retrospective study, including eight patients who were accumulated from a total of four Japanese University/general hospitals and assessed, based on a central pathological review system.

Materials and methods

Patient enrollment

Patients with malignant ovarian neoplasms have been registered and accumulated by the Tokai Ovarian Tumor Study Group (TOTSG), consisting of 14 collaborating institutions. Between 1987 and 2015, 2,922 patients with EOC were identified in this registry system. Eligible patients included: (1) patients who underwent initial surgery and periodic follow-up at the aforementioned institutions; (2) patients for whom there was sufficient information on initial surgery, chemotherapy, the reproductive outcome, and details of recurrence or death; (3) borderline tumors were excluded; (4) each histological type of EOC was based on a central pathological review system using the criteria of the World Health Organization. Patients were excluded from this study due to insufficient clinical data, a history of other malignancies, or being lost to follow-up immediately after surgery. This study was approved by the ethics committee of Nagoya University. The stage was defined based on the classification of the International Federation of Gynecology and Obstetrics (FIGO, 2014) [11]. All histological slides were reviewed by two expert pathologists with no knowledge of the patients' clinical data under a central pathological review system. Data were collected from the medical records and clinical follow-up visits.

Treatment

Of all patients, eight were eligible after fulfilling the subsequent criteria: (1) were less than or equal to 40 years of age at the time of the initial diagnosis; (2) strongly desired to retain fertility; (3) in a preoperative counselling session, these women were informed of the possible risks and benefits of FSS, and signed a consent form; (4) had histologically confirmed stage I EOC; (5) the presence of healthy ovary and macroscopically definite borderline between tumor and normal ovarian tissue during intraoperative findings, (6) uni- or bilateral cystectomy was performed as an FSS procedure; (7) finally conservation of the contralateral ovary and uterus with at least full peritoneal staging (cytology of peritoneal washing or ascites, careful palpation and observation throughout the peritoneal cavity, and, multiple peritoneal biopsies if necessary); (8) in a postoperative counselling session, adequate consent to a risk of recurrence by very careful explanation.

Follow-up and analysis

After the initial treatment, all patients underwent periodical checkups, including a pelvic examination, CA125 evaluation, ultrasonography, and radiologic imaging. Radiologic recurrence was defined as tumor recurrence based on computed tomography (CT), magnetic resonance imaging (MRI), PET (positron emission tomography), and/or ultrasound, and clinical recurrence was defined as the development of ascites, elevated CA125, or a clinically palpable mass according to the Gynecologic Cancer InterGroup (GCIG) criteria in principle [12]. Recurrent tumors were classified into the two types: (i) recurrence as a borderline tumor and (ii) recurrence as an invasive EOC. Recurrence-free survival was defined as the time interval between the date of initial surgery and that of recurrence, death, or the last follow-up. Survival curves were based on the Kaplan–Meier method.

Table 1 Clinical characteristics of patients

Case	Age	FIGO stage	Surgery	Tumor size[# (mm)]	Cytology	Histology	Grade	Chemotherapy
1	27	IC1	Rt-cystec	50	Negative	Mucinous	1	None
2	25	IA	Lt-cystec + Rt-W	110	Negative	Mucinous	1	Platinum-based
3	38	IA	U-cystec	120	Negative	Mucinous	1	NA
4	30	IC1	Rt-cystec	39	Negative	Mucinous	1	Taxane + platinum
5	32	IA	Rt-cystec	NA	Negative	Endometrioid	1	Taxane + platinum
6	28	IC1	U-cystec	NA	Negative	Endometrioid	1	Platinum-based
7	26	IC1	Lt-cystec	NA	Negative	Mucinous	1	Taxane + platinum
8	32	IC3	Bil-cystec	60, 34	Positive	Mucinous	1	None

Rt-cystec right cystectomy, *Lt-cystec* left cystectomy, *U-cystec* unilateral cystectomy, *Bil-cystec* bilateral cystectomy, *Rt-W* right wedge resection, *#* larger diameter (mm), *NA* not applicable

Table 2 Oncologic and reproductive outcomes

Case	Recurrence	Recurrence site	Recurrence type	RFS	OS	Outcome	Pregnancy
1	No	(−)		88	88	NED	P2
2	No	(−)		119	119	NED	
3	No	(−)		135	135	NED	
4	No	(−)		45	45	NED	
5	Yes	Pelvis	IOC	21	42	DOD	
6	No	(−)		218	218	NED	
7	No	(−)		147	147	NED	P1
8	Yes	Bil ovary	BOT	30	61	NED	P1

IOC invasive ovarian carcinoma, *BOT* borderline ovarian tumor, *RFS* recurrence-free survival, *OS* overall survival, *NED* no evidence of disease, *DOD* died of disease

Results

Patients' characteristics

Table 1 shows the clinical characteristics of patients enrolled. The mean age was 29 years, ranging 26–38 years. The median follow-up time was 103.6 months, ranging 42.2–218.3 months. The FIGO stage was IA in three patients and IC in 5. The stage distribution was IA in 3, IC1 in 4, and IC3 in one patient. In the present study, there were no patients with IB or IC2. Five patients (62.5%) underwent postoperative chemotherapy: two received conventional cisplatin-based chemotherapy, and three underwent platinum plus taxane. Two patients rejected additional chemotehrapy. Table 2 shows subsequent oncologic and reproductive outcomes. After the cystectomy, two patients experienced recurrence. At the end of the follow-up, seven patients (87.5%) were alive without evidence of recurrence after the cystectomy {median survival: 119 (42–218) months}. Figure 1 shows the Kaplan–Meier estimated recurrence-free survival of all EOC patients who underwent cystectomy. One patient with a stage IA tumor (No.5) showed recurrence in the peritoneal cavity 21 months after the initial surgery, and consequently died of the disease at a follow-up time of 42 months. Another patient (No. 8) with stage IC3 was diagnosed as bilateral ovarian masses and underwent bilateral cystectomy (Fig. 2a). Preoperative tumor maker values of CA125 and CA199 were elevated as 51.9, and 1,259

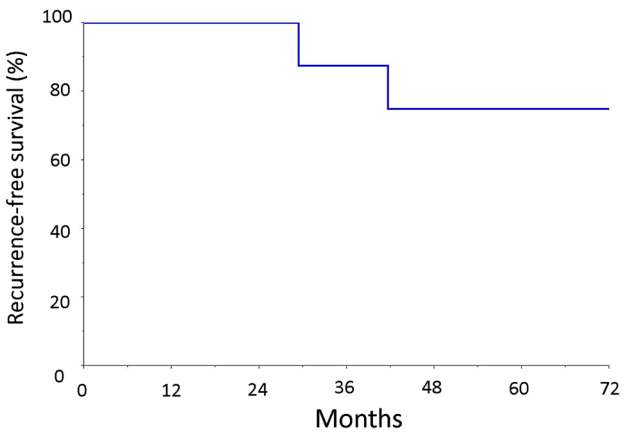

Fig. 1 Kaplan–Meier estimated recurrence-free survival of all EOC patients at stage I who underwent cystectomy

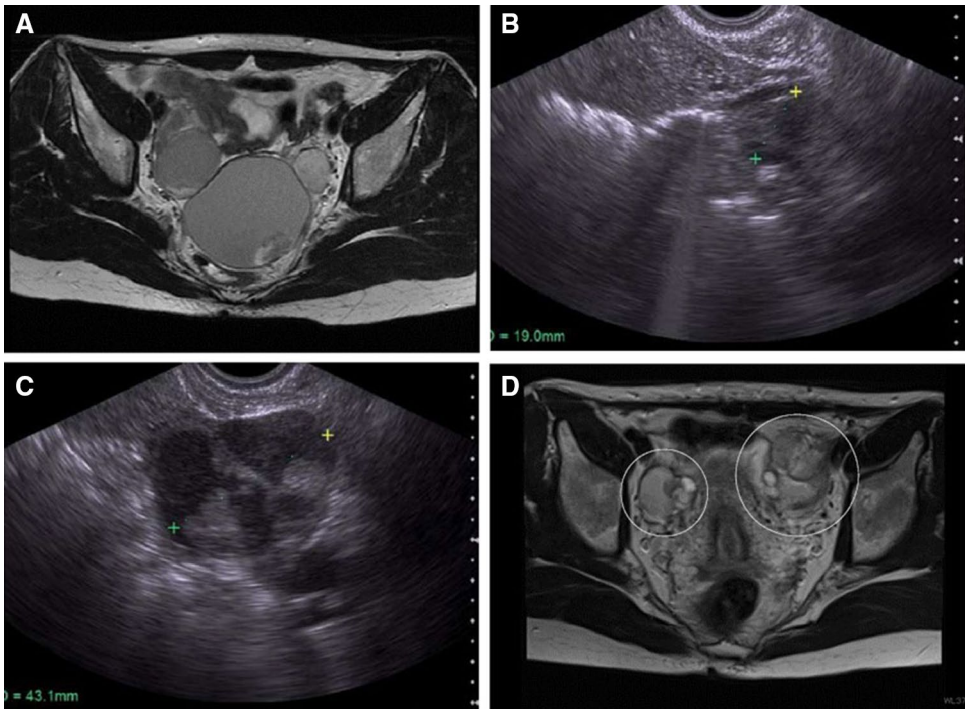

Fig. 2 Ultrasound and MRI images of the ipsilateral ovary in patient no. 8. **a** Bilateral ovarian mass at initial diagnosis, **b** 3 months before recurrence detection, **c** ultrasound image at recurrence detection, and **d** MRI image at recurrence detection

U/mL, respectively. According to intraoperative frozen section, the histological type of bilateral ovarian masses was presumed as mucinous borderline tumor. However, the final pathological diagnosis was bilateral mucinous carcinoma with positive washing. Although we accordingly recommend the additional chemotherapy followed by secondary aggressive surgery, she strictly refused them and hoped for close observation at outpatient clinic. Then she experienced recurrence in both ovaries 30 months after the cystectomy. Intrapelvic ultrasound and MRI images were obtained at 3 months before recurrence detection (Fig. 2b), and at the time of recurrence detection (Fig. 2c, d). At this time, tumor maker values of CA125 and CA199 were 27.1, and 583 U/mL, respectively. As a consequence, she was rescued by subsequent radical surgery, including hysterectomy, bilateral salpingo-oophorectomy, and pelvic and paraaortic lymphadenectomy. Recurrent tumors were identified in both ovaries. The histological type of the recurrent tumors (both ovaries) was mucinous borderline tumor. No additional chemotherapy following the initial and secondary salvage surgeries were carried out to this patient based on her wishes. She was without evidence of disease 31 months after recurrence.

Overall, excluding patient no. 5, all patients were alive without evidence of disease. Following treatment, four full-term childbirths were observed in three patients (37.5%). There were no congenital anomalies reported in any of the babies.

Discussion

It is very important to preserve the female reproductive function in young patients with gynecologic malignancies. With a widely confirmed consensus, FSS has been an acceptable surgical option for young women with early-stage EOC. Certainly, we understand that it is likely to be safer for patients with a well-differentiated/ovary-confined EOC undergo ipsilateral oophorectomy. However, how should we consider the possibility of FSS in young women with a bilateral ovarian tumor? Or, should FSS be carried out in EOC patients who underwent unilateral oophorectomy? If they strongly wish to preserve their reproductive function, an ovarian cystectomy/tumorectomy would be the only surgical choice. Actually, although cystectomy may provide a better opportunity for preserving fertility than oophorectomy, this surgical procedure is associated with the risk of an occult tumor remaining in the cystectomized ovary. Indeed, there has been much evidence reported on oncologic outcomes of patients with FSS. Nevertheless, only limited published data are available on using cystectomies as a fertility-preserving modality.

There were two major large-scale retrospective studies regarding FSS for early-stage EOC. According to a sophisticated European study, including 240 women who underwent FSS, cystectomy was carried out in 62 patients. On the other hand, based on a Japanese multi-institutional

study, examining 211 patients, there were six women who underwent cystectomy [9]. Cystectomy as an FSS option was performed more frequency in Europe than in Japan. Detailed clinical oncologic outcomes were described in the former European report. Indeed, recurrences were significantly observed in 11 of these 62 patients (17%) and in 17 of 178 (9%) patients who underwent oophorectomy. However, the cystectomy-group patients more frequently showed ovarian relapse and were successfully rescued by secondary radical surgery. Thus, a higher recurrence rate did not necessarily result in a higher mortality rate [13]. These results prompted us to hypothesize that a remaining tumor in the cystectomized ovary, even if present, could be successfully identified by elaborate image follow-up and resected by subsequent radical surgery. To verify this hypothesis, a future large-scale study is expected.

In the present study, mucinous carcinoma was the most frequent histological type. Needless to say, EOC is a heterogeneous tumor with a diverse histological type. More frequently, younger EOC patients have a mucinous histological type, and less frequently display a serous type, compared with elderly patients [8]. In spite of the fact that advanced-stage mucinous EOC is associated with an extremely poor clinical outcome, reflecting chemoresistance to platinum-based compounds [14]. Patients with an early-stage mucinous tumor were reported to show a favorable prognosis and be appropriate candidates for FSS [15]. This is because this type of EOC shares a lineage between benign cystic neoplasms and the corresponding carcinomas, often through an intermediate /borderline step, supporting the morphological continuum of tumor progression in these neoplasms [16]. In our series, a patient (No.8) with stage IC3 experienced recurrence in both ovaries as mucinous borderline tumors but she was rescued by subsequent radical surgery. In contrast, clear-cell and endometrioid carcinomas are frequently associated with marked adhesion to the surrounding tissues due to endometriosis, easily leading to the occurrence of capsule rupture. Thus, although further additional confirmatory research is required, mucinous carcinoma may be a possible candidate for cystectomy. At least, when a surgeon must perform cystectomy for early-stage EOC patients, the histological type may need to be considered.

It is clear that the cystectomized ovary would be a potent recurrence site reflecting the possible existence of an occult tumor. This prompted us to question whether the remaining invisible tumor can be eliminated by additional chemotherapy. In the present study, postoperative chemotherapies were carried out in 5 patients (62.5%). An earlier European randomized controlled trial demonstrated that women with early-stage EOC showed a more favorable oncologic outcome in the presence of adjuvant platinum-based chemotherapy than in the absence of chemotherapy [17]. Recurrence subsequently arises from "seeds" of an invisible tumor that was not removed by various treatments or the body's immune system. In this regard, we recommend adding postoperative chemotherapy for all EOC patients undergoing cystectomy for FSS as it can prevent such occult tumors.

Accordingly, the current study was preliminary with several limitations, including the small number of cases, different follow-up length, and various treatment protocols during the study period. In particular, the main limitation was the fact that only eight patients who underwent cystectomy were available despite the enrollment of over 2,900 patients with EOC. This limited patient number reflects the actual clinical practice whereby the selection of cystectomy is extremely rare. Therefore, the current results are merely hypothesis-generating. When we unavoidably adopt cystectomy, it should be applied only to women with a sufficient understanding of the potential risks. On the other hand, the strength of our study includes the central pathologic review, leading to reduced intraobserver variability on regarding the histological type.

In summary, although there is no established criterion for cystectomy as a fertility-maintaining treatment at present, it may be an unrecommendable option for young patients with early-stage EOC, if fulfilling the following clinicopathologic conditions: (1) encapsulated/well-differentiated tumor, (2) no sign of extra-ovarian spread, including negative cytology, (3) no sign of dense adhesion to the surrounding tissues, (4) existence of sufficient normal ovarian tissue, (5) the presence of a definite macroscopic border between the tumor and remaining ovary, (6) negative biopsy in the remaining ovarian tissue by multiple frozen sections, and (7) with sufficient follow-up. We should accumulate more experiences regarding this tumor to clarify the applicability of cystectomy for FSS. Further studies should be performed with a larger scale clinical trial in the future.

Acknowledgements We sincerely thank TOTSG members for collaborating in data collection.

Author contributions Conceptualization: HK; methodology: HK; validation: FK; formal analysis and investigation: HK; writing—original draft preparation: HK; writing—review and editing: HK, KS; resources: MK, KN, SS, ST, TN; supervision: FK.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A, Cancer Statistics (2017) CA Cancer J Clin 67:7–30
2. Kikkawa F, Nawa A, Ino K et al (2006) Nomura S Advances in treatment of epithelial ovarian cancer. Nagoya J Med Sci 68:19–26

3. NCCN Guidelines for Patients: Ovarian Cancer www.nccn.org/patients 2017; National Comprehensive Cancer Network
4. Bozas G, Dimopoulos MA, Kastritis E et al (2006) Bamias A Young age is associated with favorable characteristics but is not an independent prognostic factor in patients with epithelial ovarian cancer: a single institution experience. Oncology 70:265–272
5. Duska LR, Chang YC, Flynn CE et al (1999) Nikrui N Epithelial ovarian carcinoma in the reproductive age group. Cancer 85:2623–2629
6. Rodriguez M, Nguyen HN, Averette HE et al (1994) Sevin BU National survey of ovarian carcinoma XII. Epithelial ovarian malignancies in women less than or equal to 25 years of age. Cancer 73:1245–1250
7. Smedley H, Sikora K (1985) Age as a prognostic factor in epithelial ovarian carcinoma. Br J Obstet Gynaecol 92:839–842
8. Yoshikawa N, Kajiyama H, Mizuno M et al (2014) Clinicopathologic features of epithelial ovarian carcinoma in younger vs. older patients: analysis in Japanese women. J Gynecol Oncol 25:118–123
9. Satoh T, Hatae M, Watanabe Y et al (2010) Outcomes of fertility-sparing surgery for stage I epithelial ovarian cancer: a proposal for patient selection. J Clin Oncol 28:1727–1732
10. Kajiyama H, Shibata K, Mizuno M et al (2011) Long-term survival of young women receiving fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery. Br J Cancer 105:1288–1294
11. Prat J (2014) Oncology FCoG Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 124:1–5
12. Rustin GJ, Vergote I, Eisenhauer E et al (2011) Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 21:419–423
13. Fruscio R, Corso S, Ceppi L et al (2013) Colombo N Conservative management of early-stage epithelial ovarian cancer: results of a large retrospective series. Ann Oncol 24:138–144
14. Hess V, A'Hern R, Nasiri N et al (2004) Gore ME Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol 22:1040–1044
15. Kajiyama H, Shibata K, Mizuno M et al (2011) Kikkawa F Fertility-sparing surgery in young women with mucinous adenocarcinoma of the ovary. Gynecol Oncol 122:334–338
16. Kurman RJ, Shih Ie M (2010) The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 34:433–443
17. Trimbos JB, Parmar M, Vergote I et al (2003) International collaborative ovarian neoplasm trial 1 and adjuvant chemotherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. J Natl Cancer Inst 95:105–112