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Original Research

The outcomes of fertility sparing surgery in epithelial ovarian cancer

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Summary

Conservative surgery has long been discussed as a treatment option in women with ovarian cancer at reproductive age. However, current guidelines recommend conservative surgery only in selected patients. There is considerable interest on pregnancy and delivery rates after fertility-sparing surgery (FSS), with several ongoing studies on this subject. The aim of the present multi-center study was to evaluate survival and pregnancy outcomes in patients that underwent fertility-sparing surgery. This retrospective study included 19 patients who underwent fertility-sparing surgery due to invasive epithelial ovarian cancer between 2002 and 2014. The median duration of follow-up was 59.5 months (range 10-152 months). A total of 10 full-term pregnancies and 3 spontaneous abortions occurred in 7 patients (36.8%) following FSS. Ten patients (52.6%) underwent prophylactic surgery after a median period of 49 months (16-119 months), while 2 patients (10.5%) developed recurrent disease after prophylactic surgery. Accurate staging in patients with early stage epithelial ovarian cancer and regular follow-up has shown promising reproductive outcomes. In light of the current data, fertility-sparing surgery should be considered in selected patients with stage I epithelial ovarian cancer. There is still no consensus, however, on the selection criteria of eligible patients for fertility-sparing surgery.

Key words: Epithelial ovarian cancer; Fertility-sparing surgery; Surgical staging.

Introduction

Epithelial ovarian cancer (EOC) accounts for one fourth of all reproductive cancers in females and is the most common cause of death associated with gynecologic malignancy. The incidence of EOC increases with age and most commonly occurs in the seventh decade of life [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) guidelines, standard treatment of EOC involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, para-aortic and bilateral pelvic lymph node dissection, infracolic omentectomy, examination of peritoneal lavage fluid, and peritoneal biopsy followed by taxane-platinum-based adjuvant chemotherapy [2, 3].

Extensive surgery may cause irreversible loss of fertility in women of reproductive age, with preservation of fertility clearly very important for the quality of life in young patients. Fertility-sparing surgery (FSS) involving preservation of unilateral or bilateral adnexal structures and uterus is recommended in young patients with non-epithelial ovarian cancer, particularly germ-cell tumors. FSS is also recommended for patients with borderline EOC where the disease has been confirmed as confined to a single ovary. However, the role of FSS in young patients with EOC has not been fully elucidated [4-6]. According to recent reports, 20% of patients with EOC are diagnosed with Stage I disease, 3-17% of patients are aged < 40 years, while 7-8% of patients with Stage I cancer are aged < 35 years. The 5-year survival is as high as 76-93% in Stage I disease [7-12].

There has been a long-standing debate on the use of conservative surgery in women of reproductive age. However, current guidelines recommend this option only in selected cases. Some authors report that FIGO stage IA and grade 1 tumors are appropriate for a conservative approach, while others recommend a conservative approach in all patients with stage I disease [13-21]. Avoiding extensive surgery in patients with FSS and the subsequent inability to perform accurate surgical staging makes it difficult to ascertain the true extent of disease and therefore raises concerns about disease recurrence and negative impact on survival. Most studies to date have failed to provide a high level of evidence that a conservative approach to FSS does not negatively impact survival compared to radical surgery in stage IA, grade 1-2 tumors. The impact of a conservative approach on survival is debatable for stage $>$ 1A and grade 3 tumors [22]. There is considerable interest surrounding the pregnancy and delivery rates following FSS, with several ongoing studies on this subject. Hence, the aim of the present multi-center study was to evaluate survival and pregnancy outcomes in patients that had undergone FSS.

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Table 1. — *Clinical and histological characteristics of the patients.*

Patient	Age (year)	Parity*	Histology	Grade	Type of Surgery	Stage
1	29	0	Endometrioid	1	USO + Omm + BPPALND	1A
2	26	0	Serous	2	USO + Omm + BPPALND + APP	1C
3	27	0	Endometrioid	2	USO + Omm + BPPALND	1A
4	24	1	Serous	1	USO + Omm + BPPALND + APP	1A
5	21	1	Endometrioid	1	USO	1A
6	33	0	Endometrioid	2	USO + Omm + BPPALND	1C
7	24	0	Mucinous	2	USO + Omm + BPPALND + APP	1A
8	29	0	Endometrioid	1	USO + Omm + BPPALND	1A
9	24	0	Mucinous	1	USO + Omm + PL	1A
10	18	0	Serous	1	USO + Omm + BPPALND	1A
11	38	0	Endometrioid	1	USO + Omm + BPPALND + APP	1A
12	27	0	Serous	1	USO + Omm + BPPALND + APP	1A
13	19	0	Mucinous	1	USO + Omm + BPPALND	1C
14	33	0	Serous	1	USO + Omm+BPPALND + APP	1A
15	27	1	Mucinous	1	USO + Omm	1A
16	30	1	Mucinous	1	USO + Omm + BPPALND + APP	1C
17	23	0	Mucinous	1	USO + Omm	1A
18	22	0	Endometrioid	1	USO + Omm + BPPALND	1C
19	37	0	Serous	1	USO + Omm + PL	1A

*Before initial diagnosis, USO: unilateral salpingo-oophorectomy; Omm:omentectomy; BPPALND: bilateral pelvic-paraaortic lymph node dissection; PL: pelvic lymph node dissection; APP: appendectomy

Materials and Methods

The study included patients with invasive EOC who underwent FSS between 2002 and 2014. Medical charts of patients from the Ankara Private Medical Oncology Clinic were retrospectively reviewed. Approval was first obtained from the local ethics committee of Antalya Education and Research Hospital (number: 2016-022-72-8).

Study inclusion criteria: 1) histologically confirmed stage IA or IC, grade 1, 2, or 3 ovarian cancer, 2) age < 40 years at the time of diagnosis, 3) patients with a preserved uterus and ovary or the adnexa during primary surgery. Excluded from the study were patients with tumor stage higher than IC, patients with borderline epithelial ovarian tumors, germ-cell tumors or ovarian stromal tumors, patients with a history of abdominal or pelvic radiotherapy, and those with missing data or outdated contact details.

Surgical staging involved para-aortic and bilateral lymph node sampling, multiple peritoneal biopsies, multiple peritoneal lavage fluid sampling and subtotal omentectomy. Lymphadenectomy and biopsy from the contralateral ovary and appendectomy were optional. Tumor classification was conducted according to World Health Organization (WHO) criteria and tumor staging was conducted according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines.

After primary treatment, patients were asked to attend follow up visits every 3 months in the first 2 years, every 6 months in the following 3 years, and then annually. Patient follow-up involved physical examination, assessment of tumor markers and various imaging methods such as ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and/or PET/CT. Demographic data, clinical and pathological characteristics, surgical data and reproductive information given during the follow-up visits were retrieved from the medical records of 19 patients who were deemed eligible for the study. Phone contact was also established with the patients or their relatives in order to gather additional data. All patients/relatives accepted phone communication and all relevant information was obtained. Recurrence rate, overall survival (OS), disease-free survival (DFS), fertility outcomes and obstetric outcomes were all evaluated.

Statistical Analysis

Patient data were recorded and analyzed on the SPSS (Statistical package for social science) 17.0 software package. The distribution of data was tested using the Kolmogorov-Smirnov test. Data with a normal distribution was expressed as mean $\pm$ standard deviation, while data without normal distribution was expressed as median (min-max). Discrete variables were expressed as a percentage. The independent samples *t-test* was used to compare parametric variables, the Mann-Whitney U test was used for non-parametric variables, while the chi-square test was used to analyze discrete variables. A p value of < 0.05 was considered statistically significant.

Table 2. — *Operative and follow-up results of the patients.*

Patient	The number of pelvic lymph nodes removed	The number of paraaortic lymph nodes removed	The number of live birth after surgery	Prophylactic surgery at x months	Recurrence	Follow-up (months)
1	19	2	-	-	no	13
2	21	20	-	-	yes	29
3	18	12	2	47	no	63
4	31	20	1	49	no	52
5	-	-	-	-	no	28
6	12	4	1	29	no	137
7	21	-	-	-	no	43
8	30	5	-	-	no	28
9	9	-	2	62	no	120
10	10	5	-	-	no	45
11	24	12	-	37	no	59
12	19	9	1	-	no	48
13	14	10	2	119	no	125
14	56	12	-	70	no	87
15	-	-	-	-	no	25
16	25	2	1	16	yes	43
17	-	-	-	-	no	25
18	25	10	-	-	no	10
19	11	5	-	59	no	152

Results

Nineteen patients with stage IA-IC EOC that underwent FSS between 2002 and 2014 were included in the study. The median duration of follow-up was 59.5 months (range 10-152 months) and the mean patient age was 26.89 ± 5.57 years (range 18-38 years). Fifteen patients (78.9%) were nulliparous. The mean Ca125 level at the time of diagnosis was 193.4 ± 161.7 U/ml (range 25-550). Of the 19 study patients, 6 (31.6%) had serous ovarian tumor, 6 (31.6%) had mucinous tumor and 7 (36.8%) had endometrioid tumor. Fourteen patients had stage IA tumor (73.7%) and 5 (26.3%) had stage IC tumor. Clinical and histopathological characteristics of the patients are summarized in Table 1. During primary surgery, 7 patients (36.8%) underwent unilateral salpingo-oophorectomy (USO) + para-aortic bilateral pelvic lymphadenectomy (PABPLND) + omentectomy (Omm), 7 patients (36.8%) underwent USO + PABPLND + Omm + Appendectomy , 2 patients (10.5%) underwent USO + Omm + pelvic lymhpadenectomy, 2 patients (10.5%) underwent USO + Omm, and 1 patient (5.3%) underwent USO. The mean number of lymph nodes removed from the pelvis was 21.5 ± 11.4 and the mean number of para-aortic lymph nodes removed was 8.5 ± 6.1.

Five patients were treated with paclitaxel + platinum-based adjuvant chemotherapy (Ctx). Of these, 2 patients (40%) received 4 cycles of chemotherapy and 3 patients (60%) received 6 cycles. None of these patients underwent second look surgery. Following FSS, 10 full-term pregnancies and 3 spontaneous abortions occurred in 7 patients (36.8%). No congenital abnormality was reported in any of the babies. Nine patients (47.3%) underwent prophylactic surgery after a median duration of 49 months (range 16-119 months). Intra-operative and follow-up data for the patients are summarized in Table 2.

During a median follow-up period of 59.5 months (range 10-152), 2 patients (10.5%) developed recurrent disease after prophylactic surgery. Patient number 2 underwent repeat surgery 2 years after their primary surgery due to recurrent disease in the pelvic area. This surgery involved TAH + USO + PABPLND + Total Omm. The patient died 7 months after the second surgery. Patient number 16 had a live birth 24 months after primary surgery and complementary surgery was performed. She developed widespread recurrent disease 32 months after primary surgery, for which secondary cytoreductive surgery was performed. Unfortunately, this patient died 43 months after the primary surgery.

Discussion

Over the last two decades, less radical surgery has gained popularity for the treatment of early stage breast, cervical, vulvar and ovarian cancers. This conservative surgical approach aims to reduce operative morbidity and mortality, while also preserving fertility in the case of ovarian cancer.

The upward shift in the age of mothers at first birth has led to more cases of EOC during the reproductive period and hence to an increasing demand for FSS. Although many studies have been conducted on this subject, the safety of FSS in patients with stage I disease remains unclear. There

is no strong evidence to date for young patients wishing to retain their fertility. In most studies, a conservative approach has been observed to be a safe and feasible option in stage IA and grade 1-2 EOC. However, there is still debate over FSS in patients with stage IA and grade 3 EOC, and in patients with stage > IA EOC. There is also no consensus on the patient selection criteria to be used for studies that evaluate the conservative approach. In most studies to date, the patient numbers are small and the results have been mixed.

A conservative approach was found to be safe even for stage IC disease in a 56 EOC patient series reported by Zanetta *et al*. [20] and in a similar study by Schilder *et al*. [21] that evaluated 52 patients. Another study compared 754 patients that underwent radical surgery with 423 patients that underwent FSS for stage IA and IC EOC [23]. These authors concluded that FSS was a safe option for young patients with stage IA and IC EOC. There are, however, many studies that have reached the opposite conclusion. In a review conducted by a Japanese gynecology group and involving 30 different centers, the recurrence and mortality rates were compared between 108 patients with stage IA grade 1-2 disease and 103 patients with stage IA and grade 3 disease, all of whom underwent FSS [19]. These authors found that FSS was safe for stage IA grade 1-2 disease, but that its safety in the higher risk group was not guaranteed. Therefore, they recommended adjuvant therapy if FSS was performed in stage IA and grade 3 patients. An Italian study evaluated 240 EOC patients that underwent FSS and reported that only grade 3 tumors had a negative impact on prognosis and that these tumors showed an extra-ovarian pattern of relapse [14].

The present study evaluated 19 patients with stage IA-IC disease that underwent FSS due to EOC (14 patients with stage IA disease and 5 patients with stage IC disease). There were no grade 3 tumors amongst the study patients. All but two patients underwent staging surgery. Of these 17 patients, 2 developed recurrent disease and both had stage IC disease. No recurrences were observed in patients with stage IA disease. Although the number of patients in our study was relatively small, our results support the position that FSS is a safe option for patients with stage IA disease. There is still debate over the use of FSS for stage IC disease and the results remain controversial.

Previous studies have investigated whether radical surgery is a superior option in terms of survival for early stage EOC patients. FSS has been reported to show a similar recurrence rate to radical surgery. However, FSS was also associated with earlier relapse compared to radical surgery (10 months *vs.* 50 months) [14].

Eligibility for FSS depends on disease stage and thus accurate surgical staging is critically important. Current standard surgical staging involves TAH + BSO and additionally para-aortic bilateral pelvic lymph node dissection, infracolic omentectomy, peritoneal biopsy, and cytological examination of intra-abdominal lavage fluid. However, approximately 30% of patients assumed to have early stage cancer have been found to have a higher stage of disease following microscopic examination of lymph nodes, diaphragm, peritoneal fluid and omentum. Lymph node involvement has been found after lymph node dissection in 10-25% of patients and para-aortic lymph node involvement has been diagnosed in 6% of patients with stage I disease. In light of these findings, systematic lymph node dissection is strongly recommended for the accurate staging of EOC [24-27]. In the present study, none of the patients were upstaged by pathological examination following staging surgery.

Studies in the literature have reported comparable pregnancy rates and pregnancy outcomes in patients who underwent FSS (pregnancy rate was 38%). Zanetta *et al*. [21] reported pregnancies in 20 out of 56 EOC patients that underwent FSS, with delivery in 17 of these patients. Morice *et al*. [17] reported 9 pregnancies resulting in delivery in 7 out of 34 patients. Park *et al*. [18] reported pregnancies resulting in delivery in 22 out of 62 patients and Satoh *et al*. [19] reported pregnancies in 76 out of 211 patients, of which 53 patients delivered. The above results are similar to those of the present study, in which 13 pregnancies occurred in 7 patients (36.8%).

In conclusion, accurate staging in patients with early stage EOC and regular patient follow-up has revealed good reproductive outcomes. In light of current evidence, conservative surgery should be considered an option for selected patients with stage I EOC. There is still no consensus on the selection criteria for patient eligibility for FSS.

Author contributions

EK, BK and EMG designed the research study. CK, MFK analyzed the data. EK, CK and MMN wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol for the research project has been approved by the local Ethics Committee of Antalya Education and Research Hospital (number: 2016-022-72-8) within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004). The participants provided written informed consent.

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Conflicts of interest

The authors have no relation with the companies and products mentioned in this study and declare no conflict of interest.

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