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Original Article

Unilateral salpingo-oophorectomy as fertility-sparing surgery for borderline ovarian tumors

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Abstract

Background: To investigate recurrence rates and fertility outcomes of patients with borderline ovarian tumors (BOTs) treated with fertility-sparing surgery.
Methods: This was a retrospective study. All women with BOTs from 2000 to 2006 were evaluated. Clinical outcomes were compared among groups that underwent radical, unilateral salpingo-oophorectomy, or ovarian cystectomy. The effects of clinical characteristics on recurrence were analyzed by independent *t* test, chi-square test, and Cox proportional hazard model.
Results: After a mean follow-up period of 56.5 months, all 61 patients were alive. Seven (11.5%) had developed disease recurrence, and all were in the fertility-sparing group. Of these, five were in the cystectomy-only group and two in the unilateral salpingo-oophorectomy group. There was significant difference in tumor recurrence rates between the two groups (hazard ratio: 0.26, 95% confidence interval: 0.11–0.61). Nine pregnancies were achieved in six women, resulting in five deliveries
Conclusion: Fertility-sparing surgery is an acceptable and safe option for women with BOTs who wish to preserve fertility. Unilateral salpingo-oophorectomy must be considered as the first choice.

Keywords: Borderline ovarian tumors; Conservative treatment; Cystectomy; Recurrence

1. Introduction

Borderline ovarian tumors (BOTs) account for 10–15% of all ovarian tumors. They are characterized by a degree of cellular proliferation and nuclear atypia in the absence of stromal invasion.[1] Compared with invasive ovarian cancer, they are typically present in a younger age group, mostly diagnosed at an earlier stage, and result in excellent prognosis. The five-year overall survival rate for early-stage disease is approximately 98% and for more advanced diseases, varies between 86 and 92%.[2]

Because of BOT's benign behavior, surgical management has evolved towards a more conservative and minimally invasive approach, allowing women to maintain fertility and childbearing potentials. Recent reports on the use of fertility-sparing surgery in women with BOTs suggested that it is well tolerated and is the best option to preserve fertility capacity in young women.[3,4] After fertility-sparing surgery, pregnancy outcomes are promising and most pregnancies are achieved spontaneously. However, as important as the fertility issue is whether morbidity caused by radical surgery can be removed, or whether a more conservative approach is a safer alternative in terms of cancer prognosis.

Although several studies indicate the safety of fertility-sparing surgery, there remains a lot of debate regarding the extent of the surgical procedure. Conservative surgery consists of doing unilateral salpingo-oophorectomy or cystectomy for

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those with early stage BOTs.[5,6] Ovarian cystectomy may provide a better chance of preserving fertility, however, the risk of leaving malignant cells behind inadvertently may be increasing. Although the question of fertility-sparing surgery has been addressed in many studies, only limited published data are available on the safety and outcome of treatment by cystectomy only.

Our study evaluated the outcome of BOTs in patients treated by fertility-sparing surgery through the recurrence rate and pregnancy outcomes. We also compared the outcome of patients treated by cystectomy only with that of patients treated by unilateral salpingo-oophorectomy.

2. Methods

The study group was composed of 61 patients with BOTs treated in Taipei Veterans General Hospital from 2000 to 2006. Collected data included in patient and out patient records, surgical notes, pathology reports, and clinical outcomes, retrospectively. All the patients had undergone laparotomy, and they were grouped according to the different surgical approaches.

Fertility-sparing surgery was defined as any procedure that left the uterus and at least some ovarian tissue intact. Radical surgery was defined as optimal debulking surgery, including total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal pelvic lymph node dissection and radical dissection of tumors. The criterion of disease staging was according to the 1988 International Federation of Gynecology and Obstetrics criteria, based on surgical notes and pathology reports. Follow-up was performed by clinical assessment, CA 125 testing, and trans-vaginal sonography every three months for two years and every six months up to five years from diagnosis, and then annually.

Tumor recurrence rate, disease-free survival, site of recurrence, and histology type were evaluated. Survival curves and rates were calculated using the Kaplan–Meier method. Differences in survival were assessed using the log-rank test for categorical factors and Cox proportional hazards model for continuous factors. Multivariate analysis was performed using Cox proportional hazards model by forward selection to determine survival benefit, after adjusting for favorable prognostic variables (Fig. 1).

Frequency distributions were compared using Chi-squared and Fisher's exact tests, whereas the mean and median values among groups were compared using Student's *t*-test and the Mann–Whitney *U*-test. A p value < 0.05 in a two-sided test was considered statistically significant. All analysis used the SPSS software for Windows (version 17.0; SPSS Inc., Chicago, IL).

3. Results

Of the 61 BOT patients, 30 underwent radical surgery and 31 had fertility-sparing surgery to preserve the uterus and unilateral/bilateral ovaries (Table 1). Among them, 41 (67.2%) were stage Ia, 4 (6.6%) stage Ib, 12 (19.7%) stage Ic, 1 (1.6%) stage II, and 3 (4.9%) stage III. Patients' age was significantly younger in the fertility-sparing surgery group than in the radical surgery group ($p = 0.003$). Other characteristics, including disease stage, tumor size, tumor histology, and serum CA 125, did not differ significantly between the two surgery groups. However, within a mean period of 56.5 months (range, 12–103 months), seven (11.5%) of 61 women developed disease recurrence, and all were in the fertility-sparing group. The recurrence rate was significantly higher in the fertility-sparing group than in the radical group (22.6% *vs.* 0%, $p = 0.006$).

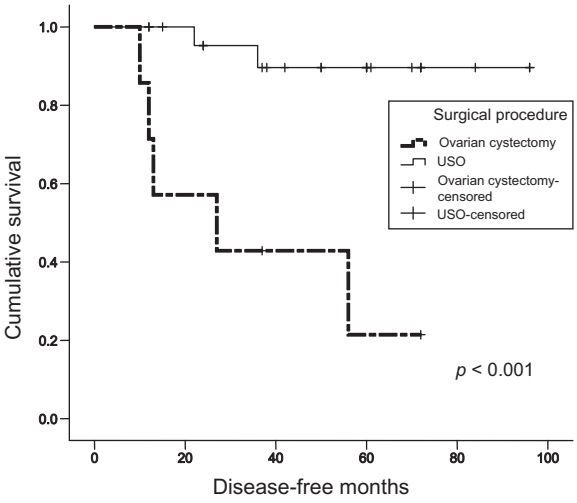

Fig. 1. Disease-free survival by surgical procedures. The statistical differences of univariate Kaplan–Meier curves were calculated using log-rank comparisons. USO = unilateral salpingo-oophorectomy.

Among 7 cases with disease recurrence, five were in the cystectomy-only group and two from the USO group. The median time for recurrence was 25.1 months (range, 10–56 months) (Table 2). Two cases developed invasive carcinomas, whereas the other five had recurrent borderline tumors. The most common site of recurrence was the remaining ovarian tissue: 3 in the ipsilateral ovary, 3 in the contralateral ovary, and 1 in the both ovaries. Three patients underwent second-round fertility-sparing surgery whereas the other four were successfully treated with complete staging surgery. All of the patients with recurrences were alive and disease-free at a mean follow-up of 36 months from diagnosis of recurrence.

Univariate analysis showed the disease-free survival in the fertility-sparing group was significantly influenced by surgical type ($p = 0.005$) and intra-operative tumor rupture ($p = 0.026$) (Table 3). Disease-free survival was not significantly influenced by age, parity, International federation of obstetrics and gynecology stage, lymphadenectomy, tumor size, and pre-operative serum CA 125 level. Prognostic factors in the multivariate analysis showed that only surgical type was an independent prognostic factor for disease-free survival [USO *vs.* cystectomy, hazard ratio (HR): 0.26 95% confidence interval (CI), 0.11–0.61] (Table 4).

After treatment of the borderline tumor in the fertility-sparing group, 18 (58%) patients had regular menstruation, 4

Table 1
Patients' characteristics ($n = 61$)

Characteristics		Radical surgery	Fertility-sparing surgery	p
Numbers of patients		30	31	
Age mean ± SD (yr)		53.5 ± 15.70	40.7 ± 16.50	0.003*
Parity, n (%)	$p = 0$	5 (16.7%)	17 (54.8%)	0.002*
	$p \geqq 1$	25 (83.3%)	14 (45.2%)	
Stage, n (%)	Ia	18 (60%)	23 (74.2%)	0.242
	Ib, Ic, II, III	12 (40%)	8 (25.8%)	
Lymphadnectomy, n (%)	Performed	29 (96.7%)	15 (48.4%)	<0.001*
	Not performed	1 (3.3%)	16 (51.6%)	
Tumor size (cm)	<10 cm	11 (36.7%)	14 (45.2%)	0.504
	≧10 cm	19 (63.3%)	17 (54.8%)	
Frozen pathology, n (%)	Do	27 (90%)	22 (71.0%)	0.064
	Not do	3 (10%)	9 (29.0%)	
Histology, n (%)	Serous	8 (26.7%)	6 (19.4%)	0.935
	Mucinous	21 (70%)	22 (70.9%)	
	Others	1 (3.3%)	3 (9.7%)	
CA 125 (U/mL)	≦35	17 (56.7%)	13 (41.9%)	0.223
	>35	13 (43.3%)	18 (58.1%)	
Recurrence, n (%)		0 (0%)	7 (22.6%)	0.006*

Data are mean ± standard deviation or case numbers. Numbers in parentheses refer to the percentage of the total number of patients in each group.
*A p value < 0.05 is statistically significant.
CA = cancer antigen; SD = standard deviation.

(13%) had irregular menses, and 4 (13%) had recurrent disease treated by complete staging surgery. Nine pregnancies were achieved in six women, resulting in five deliveries, including 2 in the cystectomy-only group and 3 in the USO group.

4. Discussion

BOTs are mostly present in a younger age group and therefore, fertility sparing is an important and inevitable issue. The generally benign behavior and favorable prognosis of BOTs allows for more conservative management. In our study, we demonstrated that unilateral salpingo-oophorectomy should be considered as the first choice of fertility-sparing treatment for younger women with BOTs who wish to preserve fertility. Although the higher risk of local relapses is found, it is not associated with decreased overall survival. Ovarian cystectomy should be reserved for patients with a previous history of unilateral adnexectectomy or bilateral ovarian tumors, and is advocated in incidental histologic discovery of BOTs.

Numerous studies have demonstrated the safety and possibility of conservative surgery.[4] In literature, relapse is generally increased if a fertility-sparing approach is chosen, with numbers that vary between 0 and 25% compared with ~5% in women with radical surgery.[7,8] Nonetheless, favorable prognosis and comparable survival rates are reported for women who undergo either fertility-sparing or radical surgery.[9] This is consistent with our results. In our study, the recurrence rate was 22.6% of women who had undergone fertility-sparing surgery, and all the patients with recurrences were alive and disease-free after treatment at a mean follow-up of 36 months from diagnosis of recurrence. Therefore, we suggest that fertility-sparing surgery is safe and possible to perform for women with BOTs.

Lately, although management has changed from radical surgery to a more conservative therapy for early stage BOTs,

Table 2
Characteristics of patients with recurrent disease

Case	Age	FIGO stage	Histology	Rupture during operation	LND	Surgical procedure	Site of recurrence	Histology at recurrence	Treatment at recurrence	PFS (M)	Pregnancy	Status
1	23	Ic	Mucinous	Yes	No	Cystectomy	Ipsilateral ovary	Borderline	Oophorectomy + LND	56	Yes	Alive
2	37	Ic	Serous	Yes	Yes	Cystectomy	Ipsilateral ovary	Borderline	Oophorectomy + LND	12	Regular mense	Alive
3	38	Ic	Clear	Yes	Yes	Cystectomy	Contralateral ovary	Borderline	Complete staging surgery	27	−	Alive
4	32	Ia	Mucinous	No	Yes	Cystectomy	Bilateral ovary	Endometrioid ovarian and endometrial cancer	Complete staging surgery	10	−	Alive
5	58	Ic	Mucinous	Yes	No	USO	Contralateral ovary	Mucionus ovarian cancer	Complete staging surgery	36	−	Alive
6	33	Ia	Mucinous	No	No	USO	Contralateral ovary	Borderline	Complete staging surgery	22	−	Alive
7	31	Ic	Mucinous	Yes	No	Cystectomy	Ipisilateral ovary	Borderline	Oophorecotmy + LND	13	Regular mense	Alive

FIGO = International federation of obstetrics and gynecology; LND = lymphadenectomy; PFS = progression-free survival; USO = unilateral salpingo-oophorectomy.

Table 3
Factors associated with disease-free survival after fertility-sparing surgery ($n = 31$)

Characteristics	n	Recurrence	Median Survival, months	HR	95% CI LL–UL	p
Surgery type						
Oophorectomy	24	2	89.1	1		
Cystectomy	7	5	36.3	10.73	2.07–55.60	0.005*
Age						
>35 yr	14	3	78.0	1		
≦35 yr	17	4	58.9	1.20	0.27–5.35	0.816
Parity						
=0	17	6	90.5	1		
≧1	14	1	59.1	0.16	0.02–1.35	0.093
FIGO stage						
Stage Ib, Ic, II, III	8	1	86.0	1		
Stage = Ia	23	6	73.9	2.46	0.30–20.47	0.405
Lymphadnectomy						
Not performed	16	4	75.8	1		
Performed	15	3	69.3	0.86	0.19–3.85	0.842
Tumor rupture						
No	21	2	88.0	1		
Yes	10	5	59.3	5.32	1.03–27.5	0.026*
Tumor size						
≦10 cm	14	5	66.3	1		
>10 cm	17	2	86.1	0.30	0.06–1.53	0.146
Serum CA 125 level						
>35 mg/dL	14	3	69.4	1		
≦35 mg/dL	17	4	75.3	2.05	0.40–10.60	0.391
Frozen pathology						
Performed	21	5	76.1	1		
Not performed	10	2	78.7	0.286	0.03–2.39	0.248

*A p value < 0.05 is statistically significant.
CA = cancer antigen; CI = confidence interval; FIGO = International federation of obstetrics and gynecology; HR = hazard ratio; LL = lower limit; OR = odds ratio; UL = upper limit.

there remains a lot of debate regarding the extent of the surgical procedure. Ovarian cystectomy provides more chances of preserving fertility compared with unilateral salpingo-oophorectomy because of the removal of less ovarian tissue. However, ovarian cystectomy also elevates the risk of inadvertently leaving behind some malignant cells, as well as cyst rupture and intra-abdominal spillage. Yinon et al., in a single-center retrospective study of 62 patients treated conservatively with cystectomy ($n = 22$) and USO ($n = 40$) revealed no significant difference between the two groups in mean recurrence rate (22.7% and 27.5%, respectively, $p = 0.8$).[10] This did not change when analyzed according to tumor histology type. In contrast, the study by Morice et al. showed higher recurrence rates in cystectomy than USO (36.3% *vs.* 15.1%, $p < 0.01$).[11] However, such management indeed offers even patients with advanced disease the chance to have spontaneous pregnancy. In our study, there was also a significantly higher relapse rate (5/7, 71.4%) in the cystectomy group compared with the USO group (HR 10.725, 95% CI 2.07–55.60, $p = 0.005$). Recurrence was relatively related to local residual tumor after cystectomy rather than tumor localization in the other ovary. Furthermore, cystectomy resulted in cyst rupture and intra-abdominal spillage in 70% of the study patients, which is associated with a significant increase in local recurrence (HR: 5.32, 95% CI 1.03–27.5, $p = 0.026$). De Iaco et al. reported compatible results of the incidence of intra-operative rupture.[12] In a large French retrospective study published by Poncelet et al. on women diagnosed with early stage BOTs, patients who underwent cystectomy had higher rates of intra-operative cyst rupture and more recurrences compared with women who had unilateral or bilateral oophorecotmy.[13] A study by Vergote et al. clearly demonstrated that rupture of an ovarian cyst is one of the most important prognostic factors of disease-free survival in Stage I invasive ovarian cancer.[14] Although there are no prospective studies in BOT patients that address this issue, spilling should be avoided until otherwise confirmed. This suggests that ovarian cystectomy should be considered only for women with one ovary or with bilateral tumors who wish to preserve their childbearing potential. It is recommended that unilateral salpingo-oophorectomy may provide a safe therapeutic alternative for BOT in women wishing to preserve fertility.

Table 4
Cox multivariate regression analysis

Model covariate	HR	95% CI LL	95% CI UL	p (Cox model)
Surgery type	0.26	0.11	0.61	0.002*
FIGO stage	3.92	0.42	36.73	0.232
Lymphadnectomy	1.23	0.23	6.59	0.808

*A p value < 0.05 is statistically significant.
CI = confidence interval; FIGO = International federation of obstetrics and gynecology; HR = hazard ratio; LL = lower limit; UL = upper limit.

In this study, there were nine pregnancies in six women, resulting in five deliveries, including two in the cystectomy-only group and three in the USO group. After treatment of the borderline tumor in the fertility-sparing group, 18 (58%) patients had regular menstruation. The reported spontaneous fertility rates after conservative treatment of BOT vary between 32 and 65%.[7,15,16] The disease does not affect the gestation or the follow-up period after the pregnancy. Therefore, it is worthy for women with BOTs to receive fertility-sparing surgery to maintain their fertility and achieve their childbearing dreams. However, a recent concept concerning about the clinical behavior of borderline ovarian tumor is that it may be a precursor lesion of low-grade ovarian cancer. Therefore, accurate diagnosis and complete staging procedures seem to be important especially for patients who desire to preserve their fertility function.[17,18]

Long-term follow-up of these patients is required because recurrences can develop years after the primary treatment. For women treated conservatively, special attention should be given to the remaining ovary. Zanetta et al. evaluated the physical examination, pelvic ultrasonography, and CA 125 levels to determine the best modality for following patients after conservative treatment of BOTs.[19] It is advisable to observe these patients every three months during the first two years, every six months on the third to fifth year, and annually thereafter.

A limitation of this study is that surgical staging was not considered beforehand in all cases. The data might therefore be biased in this respect. Furthermore, our study was retrospective study with small sample sizes. Further studies using a prospective design with emphasis on surgical staging are required.

Fertility-sparing surgery is an acceptable and appropriate option for women with BOTs who wish to preserve fertility. The higher risk of local relapses is not associated with decreased overall survival. The results here show that unilateral salpingo-oophorectomy must be considered as the first choice of conservative treatment. Ovarian cystectomy should be reserved for patients with a previous history of unilateral adnexectectomy or bilateral ovarian tumors, and is advocated in incidental histologic discovery of BOTs. Whenever possible, the treatment options for each possible operative finding should be discussed thoroughly with the patient and her family. Close follow-up is required.

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