

Clinicopathological aspects of patients with recurrence of borderline ovarian tumors

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Objective

Despite the good prognosis of borderline ovarian tumors (BOTs), a few BOT patients experience the relapse of disease, either borderline or malignant. However, the risk of recurrence of BOTs is somewhat controversial. We intended to find out the specific characteristics and prognosis of the recurrence of BOTs.

Methods

Between 1995 and 2012, 130 women were diagnosed with BOTs at a single institution. Eleven patients diagnosed and treated for the recurrence of BOTs including seven cancerous and four borderline relapses were included for the analysis in this retrospective study. Clinicopathological characteristics and surgical procedures as well as follow-up data with overall survival were assessed. Statistical analyses were performed using the χ^2 test, *t*-test and log-rank test with Cox regression.

Results

One hundred and thirty patients with mean follow-up of 65.8 months were evaluated, of whom half were below 40 years old at their first diagnosis of BOTs. Among 11 recurrent cases (8.5%), 7 cancerous transformations (5.4%) and 4 borderline recurrences (3.1%) were detected with median time of 6 and 71 months after the primary surgery, respectively. Nine out of 11 recurrences were happened at their equal or below 40-years-old age at the primary diagnosis ($P=0.027$). Also, all 7 cancerous relapses arose from premenopausal women of median age of 35 years old. Twenty (15%) patients had laparoscopic surgery and they were all treated conservatively. Among those 20, 5 were suffered from relapse of BOTs and laparoscopic approach was proved to be a significant risk factor for disease relapse in our study ($P=0.013$). Although laparoscopic surgery was revealed had meaningful influence on disease free survival ($P=0.024$), it was not significant on overall survival ($P=0.226$).

Conclusion

Laparoscopic conservative surgery for BOTs can be accepted under close follow-ups. And younger patients should be followed for long period to evaluate recurrence.

Keywords: Epithelial-mesenchymal transformation; Laparoscopy; Ovarian neoplasms; Recurrence

Introduction

Borderline ovarian tumors (BOTs) refer to the tumors of intermediate malignant potential which have low rate of growth and low potential to invade or metastasize. It is known that it has exceptionally good prognosis and high rate of survival. Trimble et al. [1] has reported 10-year relative survival of stage I BOTs was up to 99% and more than 80% of cases were diagnosed stage I, which means that BOTs tend to be confined to ovary for long period. By histological manifestation, BOTs have nuclear atypia, increased mitotic activity, stratification of epithelial lining and microscopic papillary projections, but do not show stromal invasion. BOTs are considered distinctive disease entity from benign epi-

thelial ovarian tumor or invasive epithelial ovarian cancer clinically and histologically both.

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BOTs are more prevalent in 30 to 50 years-old women of reproductive age who want to preserve their childbearing potential. Although a complete staging surgery with total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) is recommended as standard management of BOTs in the world, relatively young aged patients make clinicians to hesitate to follow the standard guidelines. As this, many clinicians have been tried applying minimally invasive conservative surgery for patients with BOTs and researching feasibility of those approaches in management of BOTs [2-4].

BOTs matter when it relapses and sometimes it transforms to ovarian malignancy. Invasive implant, microinvasion, elevated pre-operative CA-125 level, age, advanced stage and types of surgical approach are known as possible risk factors for relapse of BOTs [5,6]. However, the results vary between studies. We aimed to evaluate the characteristics and prognosis of relapse of BOTs through reviewing each case of recurrence of BOTs in our institution.

Materials and methods

Between 1995 and 2012, 130 women were diagnosed with BOTs at a single institution. We conducted a retrospective review of the demographic and clinical data of each patient. Variables including age, body mass index, parity, menopausal status, CA-125 and CA-19-9 level, tumor size and bilaterality, stage (International Federation of Gynecology and Obstetrics [FIGO], 2012), recurrence, malignant transformation, histologic type on primary diagnosis and on relapse, site of recurrence, washing cytology and intra-operative rupture of tumor on primary surgery, surgical modality of primary and secondary surgery (laparoscopy vs. laparotomy), surgical category of primary and secondary surgery (conservative vs. comprehensive operation), operative extent of primary surgery (cystectomy vs. oophorectomy) and patient's status on last follow-up were obtained for analysis.

Comprehensive staging surgery was defined by including BSO regardless of whether hysterectomy was done or not. If a patient had had hysterectomy before due to other causes (i.e., myoma) and had BSO this time because of BOTs, we considered that she had comprehensive operation. Those cases with remained at least one ovary were designated conservative surgery regardless of hysterectomy. We assumed it is acceptable idea because the most common site of recurrence of BOTs is the remaining ovary.

For survival analysis, overall survival (OS) was calculated as

the time of primary surgery to the time of death or last follow-up. Disease-free survival (DFS) was calculated as the duration of months from the date of primary surgery to either the date of secondary surgery for the treatment of recurrence or the date when the relapse detected on imaging. The clinicopathological parameters related with recurrence of BOTs and its malignant transformation were analyzed by independent sample *t*-test, chi-square test, and cox proportional hazard model. Survival curves were plotted with Kaplan-Meier method and tested using the log-rank test. A *P*-value of <0.05 was considered statistically significant. IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) was adopted for data analysis.

Results

Characteristics of 130 patients are shown in Table 1. Mean age of the patients at diagnosis was 42.4 years old and half were below 40 years-old at their first diagnosis of BOTs. Twenty (15%) cases were treated by laparoscopic approach, and 110 by laparotomy initially. All twenty laparoscopic operations were conservative ones. Seventy (53.8%) cases underwent conservative surgery of preservation of at least one ovary and sixty (46.2%) of 130 received comprehensive surgery of BSO with or without hysterectomy. Among 70 patients who received conservative surgery, 19 cases had cystectomy and the others undertook oophorectomy. Most of the patients (83%) demonstrated stage IA. One woman presented stage IIIB which involved bilateral salpinges, omentum and peritoneum with noninvasive implants. For the histopathologic type, mucinous type was the most common one (66.9%).

There were some debatable cases. A patient whose age was 38 years old at primary diagnosis of BOT and she had had unilateral salpingo-oophorectomy before due to the endometriosis of the other ovary and wanted to preserve her uterus when discussing about the management of her BOT with the doctor. Finally, she had BSO with remaining her uterus. We focused the comprehensive surgery as removal of both ovarian tissue and assigned her to comprehensive surgery group although she had remained uterus.

During the mean follow-up time of 65.8 months (range, 1 to 241 months), 11 patients has encountered recurrences (8.5%). Among them, 7 cases developed invasive carcinoma (5.4%) and other 4 revealed recurrent borderline tumors. Median time for cancerous and borderline recurrence was 6 months (range, 1 to 31 months) and 71 months (range, 39 to 79 months),

Table 1. Characteristics of patients

	Without recurrence	With recurrence	Total	P-value
Total no. of patients	119	11	130	
Mean age at primary diagnosis (yr)	43.3	32.5	42.4	0.010
Age at diagnosis				0.027
≤40	56	9	65	
>40	63	2	65	
Body mass index	24.2	23.3	24.1	0.479
Parity				0.899
Nulliparous	41	4	45	
Multiparous	78	7	85	
CA-125 (U/mL)	51.3	116.2	54.5	0.474
CA-19-9 (U/mL)	236.0	22.6	226.2	0.598
Tumor size (cm)	13.1	11.3	13.0	0.489
Stage				0.657
IA	100	8	108	
IB	7	2	9	
IC	11	1	12	
≥II	1	0	1	
Histology				0.239
Serous	27	6	33	
Mucinous	83	4	87	
Endometrioid	2	0	2	
Mixed	6	1	7	
Others	1	0	1	
Surgical approach				0.013
LS	15	5	20	
LT	104	6	110	
Operative Extent				0.189
Conservative	62	8	70	
Comprehensive	57	3	60	
Types of surgery				0.008
LS conservative	15	5	20	
LT conservative	47	3	50	
LT comprehensive	57	3	60	

LS, laparoscopic; LT, laparotomy.

respectively. Table 2 shows characteristics of patients with malignant transformation of disease and Table 3 does those of patients with borderline recurrence of disease. The most common site of recurrence of BOTs was the contralateral ovary and 8 cases of 11 showed this feature.

For the 7 cases of cancerous recurrence, their median age was

35 years-old and all of them were premenopausal women. Four died of recurrent disease (patient no. 1, 2, 5 and 6 on Table 2) and the other 3 are alive on their complete remission status. Patient no. 2 (Table 2) who undertook comprehensive operation (total abdominal hysterectomy, BSO, and omentectomy) before has been proved to have malignant transformation on the peri-

Table 2. Characteristics of patients with malignant transformation of disease

Patient no.	Age (yr)	BMI	Primay surgical approach	Pathology on primary diagnosis	Pathology on recurrence	Bilaterality	Site of recurrence	Interval (mo)	Stage	WC /intra-operative rupture	Treatment for relapse	FU/last status
1	40	22.74	LT (TAH, LO, PLND)	M	M Adenoca	No	C-ov	54	IA	(-) / (-)	LT (RSO, SCOM, Appe)	7 yr/ dead
2	43	23.88	LT (TAH, BSO, OM)	S	Adenoca	Yes	Peritoneum and pleural effusion	24	IB	(-) / (-)	CTx	5 yr/ dead
3	37	27.92	LT (LSO)	S	S Adenoca	No	C-ov	6	IA	(-) / (-)	LT (TAH, RSO, PLND, ICOM, Appe)	1 yr/ alive
4	32	22.85	LS (BOC)	S	S Adenoca	Yes	C-ov	31	IB	(+) / (-)	LS (RSO, LOWR)	3 yr/ alive
5	28	29.90	LT (LOC)	M	Undifferentiated carcinoma	No	Both ov	2	IA	(-) / (+)	LT (TAH, BSO, PLND, PALNS, OM, Appe)	1 yr/ dead
6	30	18.79	LS (RSO)	M	M Adenoca	No	C-ov	9	IA	(-) / (-)	LS (LOC, PLNS, P-OM)	2 yr/ dead
7	28	18.36	LS (RSO)	S	S Adenoca	No	C-ov	1	IC	(+) / (-)	LT (TAH, BSO, PLND, PALNS, OM, PT, Appe)	6 mo/ alive

BMI, body mass index; WC, washing cytology; FU, follow-up; LT, laparotomy; TAH, total abdominal hysterectomy; LO, left oophorectomy; PLND, pelvic lymph node dissection; M, mucinous; Adenoca, adenocarcinoma; C, contralateral; ov, ovary; RSO, right salpingo-oophorectomy; SCOM, supracolic omentectomy; Appe, appendectomy; BSO, bilateral salpingo-oophorectomy; S, serous; CTx, chemotherapy; LSO, left salpingo-oophorectomy; ICOM, infracolic omentectomy; LS, laparoscopy; BOC, bilateral ovarian cystectomy; LOWR, left ovary wedge resection; LOC, left ovary cystectomy; PALNS, para-aortic lymph node sampling; PLNS, pelvic lymph node sampling; P-OM, partial omentectomy; PT, peritonectomy.

Table 3. Characteristics of patients with borderline recurrent of disease

Patient no.	Age (yr)	BMI	Primay surgical approach	Pathology on primary diagnosis	Pathology on recurrence	Bilaterality	Site of recurrence	Interval (mo)	Stage	WC/ intra-operative rupture	Treatment for relapse	FU/last status
8	23	ND	LS (LO)	S	Mixed (M&S)	No	C-ov	79	IA	ND / ND	LS (ROC)	13 yr/ alive
9	27	22.8	LS (BOC)	S	M	No	Ipsi-ov	63	IA	ND / (+)	LS (BOC)	10 yr/ alive
10	45	ND	LT (TAH, RSO)	M	M	No	C-ov	79	IA	ND / ND	LT (LSO, Appe)	15 yr 2 mo/alive
11	25	23.2	LT (LSO)	Mixed mullerian	Mixed mullerian	No	C-ov	39	IA	(-) / (-)	LT (ROC)	6 yr 2 mo/alive

BMI, body mass index; WC, washing cytology; FU, follow-up; ND, no data; LS, laparoscopy; LO, left oophorectomy; S, serous; M, mucinous; C, contralateral; ov, ovary; ROC, right ovarian cystectomy; BOC, bilateral ovarian cystectomy; Ipsi, ipsilateral; LT, laparotomy; TAH, total abdominal hysterectomy; RSO, right salpingo-oophorectomy; LSO, left salpingo-oophorectomy; Appe, appendectomy.

toneum and pleural effusion by the cytology confirmation and she received chemotherapy only for the recurrent disease. All of the other cases received operation for the management of relapse of BOTs.

In univariate analysis, age and surgical approach presented statistical significance between the women with or without relapses ($P=0.027$ and $P=0.013$). Laparoscopic approach was related to higher recurrence rate ($P=0.013$). Within 70 patients

of conservative surgery group, laparoscopic approach included more relapses compared to laparotomic approach and it was statistically significant ($P=0.038$). Eight recurrences (11.4%) of 70 conservative surgery group and 3 (5.0%) recurrent cases of 60 comprehensive surgery group were observed. However, it did not show significant difference ($P=0.189$). Our result points out laparoscopic surgery could be a significant risk factor of BOT relapse.

Laparoscopic surgery cases were all included in conservative ones and there were no cases of laparoscopic comprehensive operation ($n=0$) (Fig. 1). We thought it was more effective in retrieving significant result that grouping our cohort as laparoscopic conservative, laparotomic conservative and laparotomic comprehensive than grouping it as laparoscopic vs. laparotomy or conservative vs. comprehensive. Then we analyzed if there existed any tendency between disease recurrence and less invasive operative extent. By the linear by linear association analysis, laparoscopic conservative group showed higher tendency of relapse ($P=0.008$). Of 11 relapses, 5 cases happened in 20 laparoscopic conservative surgery group and 3 were cancerous and 2 were borderline recurrence. We analyzed DFS and OS according to the types of surgical approach (Table 4). In our center, 5-year and 10-year DFS for general BOTs were 92.8% and 86.3%. And OS was 94.3% and 91.8%, respectively.

Age was another risk factor of disease recurrence. Mean age of disease-recurrence group was 32.5 years old whereas the one of non-recurrent group was 43.4 years old ($P=0.001$) (Table 1), which means younger patients might have higher risk of relapse of disease. When we divided the age into two groups of equal or below 40 years old and above 40 years old, younger

group also showed significant recurrence rate ($P=0.027$). Nine out of 11 recurrent cases were below 40 years old at their primary diagnosis.

In multivariate analysis of Cox proportional hazard model, laparoscopic approach was the single independent risk factor which has significant impact on DFS ($P=0.024$). There was no items which had significant influence on OS (Fig. 2).

Discussion

Although most patients with BOT have an excellent prognosis, a minority will encounter a relapse of disease, either borderline or malignant. The recurrence rate of BOTs has been reported to range from 5% to 33% [3,7-12]. In general, 5 to 8% of women diagnosed with BOT will relapse, and 2% will relapse as invasive cell type and die of their disease [7]. In this study, total recurrence rate of BOTs were 8.5% and cancerous transformation rates 5.4%. Among 11 relapse cases, 4 were borderline and 7 were malignant recurrence. This result presumably reflects the population bias of the study population from the tertiary referral center.

In the current study, age and type of surgery are the important prognostic factors. Nine of 11 recurrence patients were under the age of 40 years-old at the primary diagnosis and mean age of disease-recurrence group was significantly younger ($P=0.001$) (Table 1). In our cohort, median time to borderline recurrence was 71 months and the one to malignant recurrence 6 months. Through this, we can assume the follow-ups after intervention for BOTs should be done closely for the first two years and it should be continued for 10 years or more. Similarly, Silva et al. [13] suggested that patients who were treated by BOTs should be followed for a minimum of 10 years to evaluate for recurrence and for 20 years to evaluate for survival because the recurrence and the OS rates of ovarian serous borderline

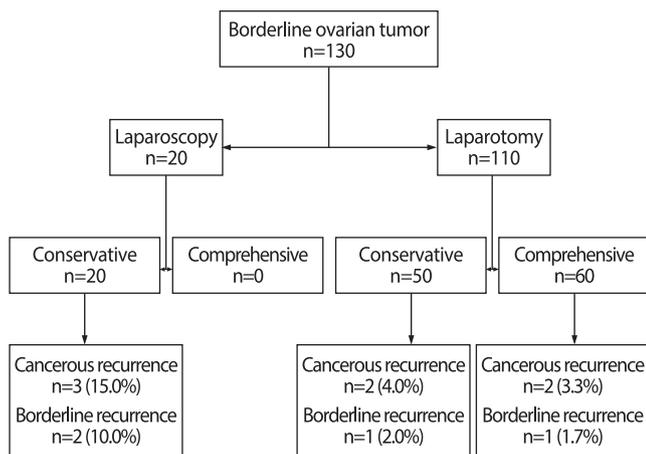


Fig. 1. Diagram of the borderline ovarian tumor patients in terms of the surgical approach.

Table 4. Five- and ten-year DFS and OS by types of surgical approach according to log rank test

Types of surgical approach	DFS ($P=0.014$)		OS ($P=0.383$)	
	5YSR	10YSR	5YSR	10YSR
LS conservative	84.0	54.0	87.5	87.5
LT conservative	92.7	92.7	97.8	97.8
LT comprehensive	96.1	91.0	94.1	89.2

Values are presented as percent. DFS, disease free survival; OS, overall survival; YSR, year survival rate; LS, laparoscopic; LT, laparotomic.

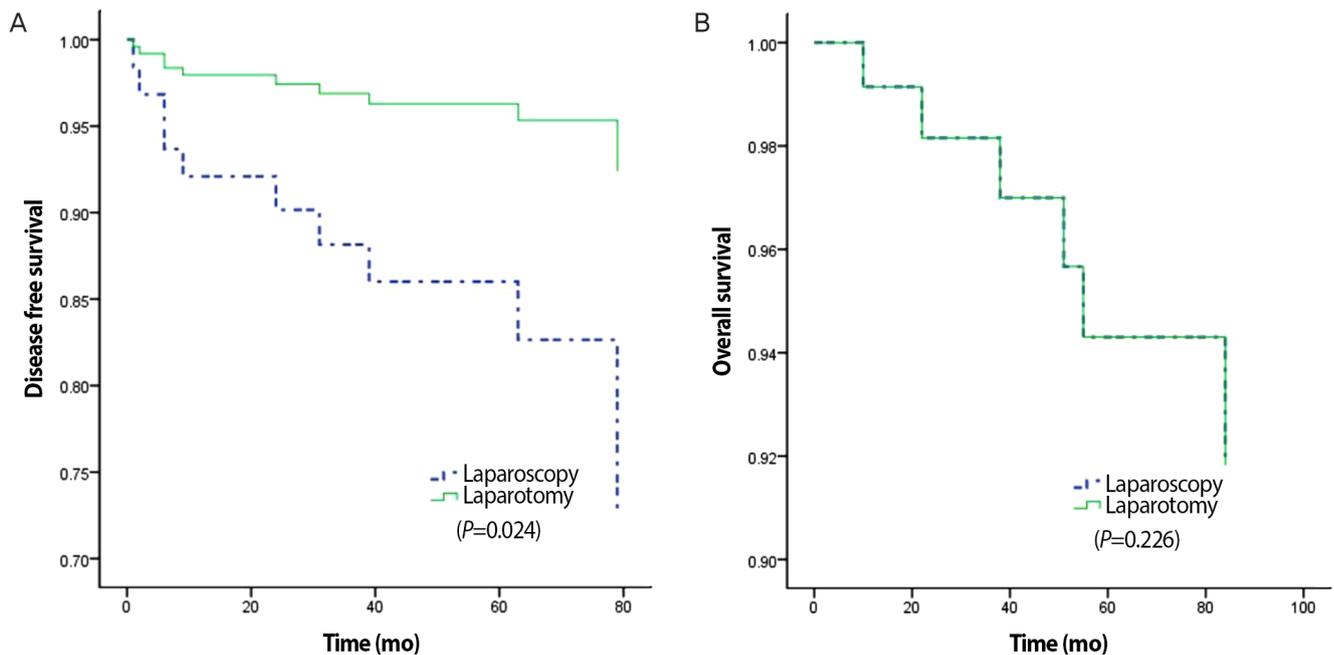


Fig. 2. Survival plot by type of surgery according to Cox proportional hazard model. (A) Disease free survival plot and (B) overall survival plot.

neoplasm with noninvasive implants is time dependent.

For the type of surgery, laparoscopic approach was related to the higher recurrence rate and lower DFS in this study. This is probably due to the higher risk of intraoperative tumor rupture or incomplete staging of laparoscopy. However, it did not have significant influence on OS. Laparoscopic and laparotomic approaches have been compared in some reports in terms of BOT relapse. They similarly weighed the operative extent of conservative and comprehensive ones more than laparoscopic and laparotomic approaches [8,14-17]. However, current study gives us a glance that laparoscopic approach itself can be a risk factor of BOT relapse and the patients who undertook laparoscopic conservative operation should be considered high risk group of disease recurrence. Although laparotomic comprehensive surgery can reduce the recurrence, most reports agree that it has no favorable effect on OS. Thus, minimally invasive conservative surgery can be tried under close follow-ups for the patients with BOTs of young age who need to preserve their childbearing potential [4,18].

Some reports have mentioned initial CA-125 level is a meaningful predictor of recurrence of BOTs [5,6,11]. In contrast to these, our data could not approve initial tumor markers level (CA-125 and CA-19-9) and tumor size as significant predictors of relapse of BOTs (Table 1).

We were also interested in the malignant transformation of BOTs and tried to get it clear the clinicopathological aspect of

cancerous recurrence of BOTs through our data. We separated the recurrence group by borderline and malignant recurrence. However, there were no specific indicators for malignant recurrence rather than borderline relapse. In 130 patients of BOTs, 7 malignant transformation were detected, 4 died of disease progression and 3 are alive with complete remission after secondary surgery and chemotherapy. Median survival time for the dead were 22 months (range, 8 to 78 months) and calculated 5 year survival rate was 30%, which looks poorer than the formally known 60.4% of 5 year relative survival rate of ovarian cancer in Korean according to the Annual report of cancer statistics in 2010. Survival rate can be expected to be poor if malignant transformation of BOTs once occurs. But the small number of cases of cancerous recurrence is definite limitation of our study and the references from the other centers were also hard to rely on due to the rarity of the case number.

In this study, mucinous histologic type was the most common one (66.9%). It is different from the reports in Western countries, in which serous BOTs are known to be the most common one. In Korea and Japan, mucinous BOTs have been reported as the most common histologic type for the ages and our result was consistent to those reports [4,19,20].

One of limitations of this study is relatively small sample size and especially small number of relapse cases. The other limitation is that there were none who had laparoscopic comprehensive operation. This may be associated with the study

period (1995 to 2012). Although laparoscopy skills have been improved continually and complete staging under laparoscopy is possible these days, laparoscopic staging cases were still rare during the study period. This might have made some unrecognized bias on analysis. However, we could identify the tendency between disease recurrence and operative extent as mentioned before. In addition, either conservative or comprehensive operation did not effect on relapse rate significantly. Through this, in this study, laparoscopic surgery itself deserves significant risk factor of BOT relapse independently of conservative or comprehensive operation under laparoscopy. Further investigations should be encouraged in order to clarify the precise roles of surgical types and other predictive factors for BOT relapse.

In summary, although laparoscopic surgery seems to increase the recurrence rate of BOTs, it has no harmful effect on long-term survival. Additionally, it is unclear that comprehensive surgery has beneficial effect on OS and no superior modality was found in regard to OS. Therefore, minimally invasive operation can be accepted under close follow-ups especially for the younger patients who want to preserve their fertility. And if minimally invasive conservative surgery for the younger patients is taken once, they should be followed for a minimum of 10 years to evaluate recurrence.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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