

## Original Article

# A retrospective analysis of relapse-related factors for ovarian borderline tumors

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**Abstract:** Objectives: Since patients with borderline ovarian tumors (BOTs) are relatively young with good survival rates, conservative surgery is prioritized as a therapeutic intervention. However, the high recurrence rate of this tumor remains an issue that demands further attention. In addition, it is unclear whether the increment of recurrent risk is attributed to conservative surgery or staging surgery. This study was designed to analyze the relapse-related factors of BOTs. Methods: This retrospective cohort study was comprised of 74 patients with BOTs who underwent surgery at the Obstetrics and Gynecology Hospital of Fudan University from September 2014 to September 2017. The recurrence-free survival (RFS) rate was calculated using the Kaplan-Meier method, while the risk factors of RFS were evaluated using Cox-regression analysis. Results: The 3-year RFS was 2.7% with a median follow-up duration of 45 months (range: 28-62). Kaplan-Meier analysis indicated that low tumor node metastasis (TNM) stage ( $P = 0.005$ ), lymphadenectomy ( $P = 0.052$ ) and fertility-preservation surgery ( $P = 0.059$ ) were the factors that may lower recurrence. Meanwhile, Cox-regression showed that only low TNM stage was significantly associated with a better RFS ( $P = 0.005$ ). Conclusions: With the removal of visible lesions by standard surgery, patients at TNM stage I had a better RFS. Fertility-preservation surgery did not increase the recurrence risk. For bilateral ovarian cyst however, it was unclear whether bilateral cystectomy can increase the recurrence risk. Therefore, further study is required.

**Keywords:** Borderline ovarian tumors, fertility-preservation surgery, recurrent-free survival, stage

## Introduction

Borderline ovarian cancer, also known as low malignant potential ovarian cancer, has no obvious invasive lesion. Accounting for 10% to 20% of all ovarian tumors, borderline ovarian cancer is common in young women and when found at an earlier stage with it has relatively good prognosis [1, 2]. Serous borderline ovarian tumors (sBOTs) and mucinous borderline ovarian tumors (mBOTs) constitute 65-70% and 11% of BOTs, respectively. Meanwhile, sBOTs account for 15-20% of serous ovarian tumors. At the time of diagnosis, approximately 70% of BOTs at stage I result in a 5-year survival rate of 95-97% [2]. The annual morbidity of BOT ranges from 1.8 to 5.5 per 100,000 patients, and this number is gradually increasing every year [3].

The diagnosis of BOTs before operation is challenging, and there have been conflicting views

on the optimal surgical management approach [4]. Nevertheless, surgeries, such as conservative surgery and radical surgery, are used as the standard therapy for BOTs [5]. Conservative surgery based on fertility-preservation allows patients to keep at least one ovary and their uterus, while for bilateral BOTs, radical fertility-preservation surgery can keep both ovaries and the uterus [6, 7]. Conversely, radical surgery is based on the standard radical approach, such as a hysterectomy, bilateral salpingo-oophorectomy and appendix omentum resection. Staging is considered complete when all peritoneal surfaces have been carefully inspected and washed [8]. However, the surgical approaches for BOTs vary in different institutions. Some surgeons prefer comprehensive surgical staging, including lymph node biopsy and dissection, while others do not include lymph node biopsy in their surgical routine [9]. Despite many studies on staging surgery, the definition of staging surgery is diversified by geographical areas and

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different preferences of surgeons. Therefore, the optimal approach for treating BOTs remains debatable [10].

This study was designed to identify the relapse-related factors of BOTs by performing a retrospective review on a variety of clinical characteristics.

## Material and methods

### Patients

A total of 74 patients with BOTs who underwent surgery as the primary treatment at the Obstetrics and Gynecology Hospital of Fudan University from September 2014 to September 2017 were enrolled in this study. All of them were pathologically diagnosed with BOT according to the pathological classification criteria outlined by the World Health Organization (WHO) in 2015 [11].

The demographic, surgical and pathological data, and survival outcomes were prospectively recorded in a database and retrospectively analyzed. This study was approved by the Research Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University, with ethical approval number of KYY2014-13.

### Inclusion and exclusion criteria

Patients enrolled in this study met the following criteria: (1) patients admitted to the Obstetrics and Gynecology Hospital of Fudan University; (2) patients were pathologically diagnosed with borderline tumor, which excluded other gynecological tumors; (3) patients underwent surgery from September 2014 to September 2017.

Patients meeting the following conditions were excluded from this study: (1) patients diagnosed with ovarian carcinoma; (2) patients who underwent preoperative anti-cancer treatment, including chemotherapy and radiotherapy; (3) patients who were diagnosed with other cancer types; (4) patients with incomplete data.

### Methods

The basic clinical information collected included patient age, diagnosis date, surgical history and methods, marital status and histology, etc. The post-operation recurrence time, site and treatment were followed in patients. The disease stage was evaluated according to the guidelines outlined by the 2017 AJCC (American

Joint Committee on Cancer) Cancer Staging [12].

In the event of incomplete surgical staging, the stage was assessed based on the availability of pathologic findings, whereas areas not assessed were considered to have no metastatic lesions.

### Statistical analysis

Statistical analysis was performed with SPSS 24 (IBM, Chicago, IL, USA). Measurement data were expressed by mean  $\pm$  standard deviation, where group comparisons were performed by independent sample t-test, and within-group comparisons by paired t-test. The Counting data were expressed by percentage (%). Survival curves were conducted using the Kaplan-Meier method, and the differences were analyzed using the log-rank test. Prognostic factors found to be significant on univariate analysis ( $P < 0.05$ ) were subjected to multivariate analysis using the Cox proportional hazards regression model. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or death. A  $p$ -value of 0.05 or less was considered statistically significant.

## Results

### Patient characteristics

Out of a total of 74 patients with BOT identified in this study, 7 (9.5%) patients did not complete the follow-up. The median follow-up duration was 45 months (range: 28-62 months).

Recurrence was observed in 18 (24.3%) patients, with the pelvis being the most common site of recurrence. The median recurrence time was 25 months, and the 3-year RFS was 2.7%.

The baseline characteristics, such as age, menopause, reproductive history, pathology types, tumor node metastasis classification (TNM) stage and tumor size were recorded, as shown in **Table 1**. The median age was 32.5 years old (range: 18-71 years old). There were 9 (12.2%) patients with menopause, and 66 (89.2%) who were married. In addition, 39 (52.7%) patients had given birth. In terms of pathology types, 34 (45.9%) patients were diagnosed with a serious type while the other 40 (54.1%) patients were diagnosed with the mucinous type. Moreover, 63 (85.1%), 4 (5.4%) and 7 (9.5%) patients were found to be at TNM stage I, II, and III, respectively. A total of 55

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**Table 1.** Clinical characteristics of patients with borderline ovarian tumors

Variables	Overall (n = 74)
Age (years)	
Median (range)	32.5 (18-71)
Mean ± SD	34.8 ± 11.8
Menopause	
Yes	9 (12.2)
No	65 (87.8)
Marital status	
Single	8 (10.8)
Married	66 (89.2)
Past reproductive history	
Yes	39 (52.7)
No	35 (47.3)
Pathology types	
Serous	34 (45.9)
Mucinous	40 (54.1)
AJCC TNM stage	
I	63 (85.1)
II	4 (5.4)
III	7 (9.5)
Cyst number	
Unilateral	60 (81.1%)
Bilateral	14 (18.9%)
Tumor size	
≤5 cm	19 (25.7)
>5 cm	55 (74.3)
Staging surgery	
Yes	13 (17.6)
No	61 (82.4)
Lymphadenectomy	
Yes	26 (35.1)
No	48 (64.9)
Fertility-preservation surgery	
Yes	57 (77)
No	17 (23)
Surgical method	
Laparoscope	55 (74.3)
Laparotomy	19 (25.7)
PPLND	
Yes	2 (2.7)
No	72 (97.3)
Omentectomy	
Yes	31 (41.9)
No	43 (58.1)
Cystic rupture	
Yes	45 (60.8)
No	29 (39.2)

Chemotherapy	
Yes	7 (9.5)
No	67 (90.5)
Recurrence	
Yes	18 (24.3)
No	56 (75.7)

Note: AJCC (American Joint Committee on Cancer), TNM (tumor node metastasis classification), PPLND (para-aortic lymph node dissection).

(74.3%) patients had a tumor size of >5 cm, while the other 19 patients (25.7%) had a tumor size of ≤5 cm.

### *Surgical details*

The surgical characteristics, including lymphadenectomy, omentectomy, fertility-reservation surgery and para-aortic lymph node dissection (PPLND), were summarized in **Table 1**. Amongst all 74 patients who underwent surgery, 13 (17.6%), 26 (35.1%) and 57 (77%) patients received staging surgery, lymphadenectomy and fertility-preservation surgery, respectively. There were 31 (41.9%) patients who underwent omentectomy, and 45 (60.8%) patients were reported to have cystic rupture. There were only 2 (2.7%) patients who underwent PPLND. Additionally, 7 (9.5%) patients underwent post-operation chemotherapy.

### *Recurrence details*

As shown in **Table 2**, all 18 patients with recurrence had recurrence at the pelvic site. All patients received repeated surgery after recurrence, and 14 patients (77.8%) who underwent conservative surgery did not show any evidence of invasion. As shown in **Table 3**, there were 15 patients with unilateral ovarian cyst relapse, and there were 13 and 2 patients at stage I and III, respectively. In addition, 14 out of 15 patients underwent conservative primary surgery. Three patients with bilateral ovarian cysts developed recurrence. There was only 1 patient each at stage I, II and III, respectively. All the three patients underwent conservative primary surgery and conservative secondary surgery.

### *Survival analysis*

Recurrence was observed in 18 patients during follow-up. RFS is used as an indicator of prognosis. The Kaplan-Meier method was used to

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**Table 2.** Treatments for 18 patients after recurrence

	Stage I	Stage II	Stage III
Recurrence	14 (77.8%)	1 (5.6%)	3 (16.6%)
Chemotherapy after recurrence	0 (0)	0 (0)	2 (11.1%)
Recurrence site	pelvic	Pelvic	pelvic
First surgery (conservative)	14 (77.8%)	1 (5.6%)	3 (16.6%)
Second surgery (conservative)	8 (44.5%)	1 (5.5%)	3 (16.7%)
Second surgery (non-conservative)	6 (33.3%)	0 (0)	0 (0)

calculate RFS, and the results indicated that low TNM stage ( $P = 0.008$ , **Figure 1A**), lymphadenectomy ( $P = 0.741$ , **Figure 1B**), and fertility-preservation surgery ( $P = 0.423$ , **Figure 1C**) may play a role in lowering the recurrence. However, Cox regression analysis showed that only TNM stage was significantly associated with RFS ( $P = 0.005$ , **Table 4**). Patients at stage I had better RFS than patients at stage II or III.

### Discussion

In this study, we carried out a retrospective analysis in 74 patients with BOTs. Similar to previous study [2], most patients who participated in this study were premenopausal with a mean age of 34.8 years. Consistently, we found that a high proportion of patients received fertility preservation surgery, possibly because most of them were aged over 40 years old at first diagnosis.

BOT has a good prognosis, and the 5-year overall survival rate for patients at stage I is nearly 99% [13]. In this study, all 74 patients survived to the end of the follow-up, which was performed for 3-6 years. Recurrence was observed in 17 (22.97%) patients without invasive cancer. Similar to our results, a previous meta-analysis study showed that relapse occurred only in one third (or less) of the patients, and that few invasive lesions were observed after the relapse [14].

Although surgery is the standard therapy for BOTs, some previous studies found that surgical procedures such as staging surgery including lymphadenectomy or fertility-conservation surgery were not significantly associated with RFS. Consistently, a protocol review study by Darai [14] in collaboration with an expert librarian found the best available evidence that did not support staging the BOTs.

Similarly, our Kaplan-Meier analysis showed that patients may experience better RFS if they were diagnosed at an early stage or underwent lymphadenectomy or fertility-preservation surgery. In addition, our Cox regression analysis demonstrated that good RFS was related with only the disease stage.

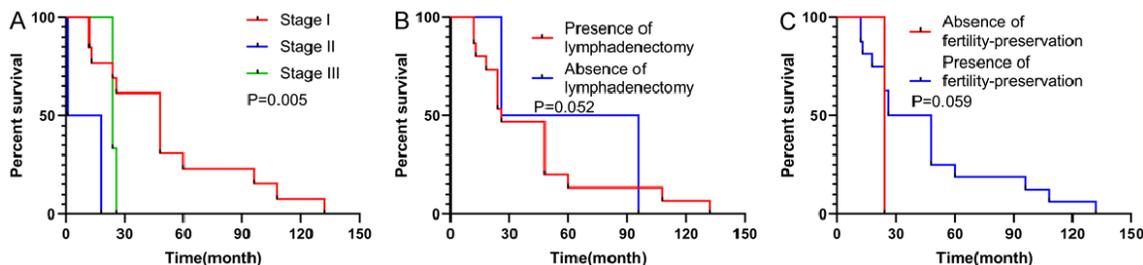
Stage I patients had distinctive lower recurrence risk or a longer time without recurrence. Accordingly, patients at later disease stages needed comprehensive surgery. In this study, nearly all patients at stage II and III had comprehensive surgery. Prior research showed that the recurrence rate of TAH-BSO, adnexectomy and cystectomy were 6%, 15% and 36%, respectively in patients at disease stages I-III [8]. Since the number of patients at stage II and III was relatively small in our study, the relevant recurrence rate could not be calculated. Lymph-node metastasis can obviously influence the disease stage progression, but upstaging during the second surgery is uncommon. There were 3 patients who chose to have the second surgery after the first incomprehensive surgery, but no one upstaged in our study. According to one study by Yahata et al. [15], upstaging of sBOTs is more common than mBOTs after a second complementary staging surgery. This showed that the disease stage can be a contributing factor for RFS, so lymphadenectomy should not be used as the standard therapy for BOTs patients.

Gokcu et al. [2] found that lymph node removal in surgical staging failed to improve survival. Consistently, several systematic literature reviews found that staging surgery, including hysterectomy and lymphadenectomy for borderline ovarian tumors had no association with survival [16-19]. Previous study by Kanat-Pektas suggested that lymph node removal should not be part of the surgical staging protocol for BOTs. Kanat-Pektas [20] found that the overall and disease-free survival rates were statistically similar in patients with or without lymph node dissection. Camatte [21] reported that routine lymphadenectomy should only be performed in patients with enlarged lymph nodes, but not in patients at an early stage of the disease.

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**Table 3.** Treatments for recurrent bilateral and unilateral ovarian cyst

Site	Stage I	Stage II	Stage III	First surgery (conservative)	Second surgery (conservative)	Second surgery (non-conservative)
Unilateral	13/15 (86.7%)	0/15 (0)	2/15 (13.3%)	14/15 (93.3%)	9/15 (60%)	6/15 (40%)
Bilateral	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	3/3 (100%)	3/3 (100%)	0/3 (0)



**Figure 1.** The relationship between survival and clinical data of patients. A. Kaplan-Meier curves for recurrence-free survival according to the TNM stage,  $P = 0.005$ . B. Kaplan-Meier curves for recurrence-free survival according to the presence or absence of lymphadenectomy,  $P = 0.052$ . C. Kaplan-Meier curves for recurrence-free survival according to the presence or absence of fertility-preservation,  $P = 0.059$ .

**Table 4.** Multivariate (stepwise variable selection) Cox regression analysis for RFS

Characteristic	Recurrence-free survival		
	HR (95% CI)	Exp (B)	P-value
Stage	1.342-4.986	2.587	0.005

In our study, 15 out of 60 patients (25%) with unilateral ovarian cyst had relapse, and 3 out of 14 patients (21.4%) with bilateral ovarian cyst had relapse. There was no statistical significance of recurrence between unilateral and bilateral cyst. Because most of the patients who relapsed were treated conservatively for the first time, there was no data on non-conservative surgery, so we were unable to analyze whether conservative surgery can reduce the recurrence rate.

In a study [22] that divided 32 patients with bilateral ovarian cyst BOTs into two groups (those with bilateral cystectomy, and those with unilateral ovariectomy and contralateral ovarian cystectomy), the bilateral cystectomy group had recurrence after 16 months, while the other group had recurrence only after 48 months, but there was not statistical significant difference between the two groups. Therefore, it remains unknown whether ultra-conservative surgery causes a higher recurrence risk. Since there has been a shift over the past decade in women's attitude towards child-bearing

and the incidence of malignant tumors is increasing gradually, the birth-rate has been declining. Therefore, preserving fertility is important in the context of tumor prognosis. Conservative surgeries are clearly unable to increase the recurrent risk for BOT patients, only stage does, since upstaging is uncommon after the first surgery. Therefore, for patients with the desire to preserve their fertility, the probability of recurrence is unlikely to increase after the removal of visible lesions.

This study had several limitations. Firstly, the sample size of this study was relatively small, and more patients need to be enrolled to better consolidate the findings. Secondly, the follow-up period was limited so the long-term survival was unable to be analyzed. Thirdly, since most of the patients included in the study underwent conservative surgery at the first time, it is impossible to compare the influence of conservative surgery and non-conservative surgery with recurrence rate. Meanwhile, the number of patients with bilateral ovarian borderline tumors is small, so the recurrence rate between unilateral and bilateral ovarian cysts cannot be compared. Lastly, this is a retrospective study with its inherent defects. Still, we hope this study can provide a direction for future prospective research, and we are looking forward to a more thorough and comprehensive study on ovarian borderline tumors.

## Conclusions

It can be seen from this study that tumor stage is a factor affecting recurrence, and the higher the stage is, the higher the recurrence rate will be. As for the relationship between recurrence rate and fertility preservation surgery and lymph node dissection, it is necessary to expand the sample size in further study. In addition, whether bilateral cystectomy for bilateral BOTs can shorten RFS demands further evaluation.

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## Disclosure of conflict of interest

None.

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