Cancer in Females

ORIGINAL ARTICLE

Risk factors of recurrence and pregnancy in patients with borderline ovarian tumors: A retrospective study with 16-year follow-up

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ABSTRACT

Background: This study aimed to analyze the risk factors that affect recurrence in patients with borderline ovarian tumors (BOTs) after radical surgery and the risk factors that influence recurrence and pregnancy in patients after fertility-sparing surgery (FSS). **Methods:** This retrospective cohort study collected data from clinical records of patients in the Affiliated Beijing Chaoyang Hospital of Capital Medical University from January 2005 to November 2021. Clinicopathological and surgical variables were analyzed using univariate analyses and survival curves. **Results:** A number of 169 BOT patients were included in this study, with a median age of 45 years and a median follow-up time of 81 months. Among these patients, twenty-one had relapsed. Of the 60 patients who received FSS, sixteen attempted to conceive, and 13 successfully conceived spontaneously. In univariate analyses, the International Federation of Gynecology and Obstetrics (FIGO) stage and invasive implantation were risk factors for the recurrence of BOTs. After multivariate analysis, the FIGO stage was the only identified risk factor. The tumor site was a risk factor for the recurrence of BOTs receiving FSS. No risk factors for pregnancy in BOTs receiving FSS were found. **Conclusion:** After univariate analysis and multivariate analysis, we identified some risk factors for recurrence after radical surgery or FSS, but they did not affect the overall survival rate and pregnancy rate. Laparoscopy procedures are recommended, and chemotherapy is not recommended for patients receiving FSS. We suggest that patients who preserve fertility should try to conceive as soon as possible and follow up closely.

Key words: borderline ovarian tumor, recurrence, pregnancy, fertility-sparing surgery

INTRODUCTION

Borderline ovarian tumors (BOTs), first described by Taylor in 1929, account for 10%-20% of epithelial ovarian tumors. BOTs are characterized by atypical epithelial proliferation without stromal invasion. Their histopathology and biological behavior are between benign and malignant tumors.[1] BOTs of every surface epithelial cell type (serous, mucinous, endometrioid, clear cell, transitional cell and mixed epithelial cell) have now been reported. However, the serous and mucinous BOTs are the most common by far.[2] It is estimated that about 2.5 to 5.5 out of 100,000 women are diagnosed with BOTs every year. BOTs of all stages combined have favorable 5- and 10-year survival rates of 95% and 90%, respectively.[3] The recommended treatment for BOTs consists of peritoneal washing, hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and multiple peritoneal biopsies. Appendectomy is also recommended for women with mucinous BOTs.

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Compared with malignant tumors, BOTs are more frequently diagnosed in young women of childbearing age, and approximately one-third of them are diagnosed before the age of 40.[4] For the past ten years, with the implementation of the two-child policy in China and the delay in childbearing age, fertility-sparing surgery (FSS) has been widely accepted for the treatment of BOTs. So far, the main issue with BOTs is that there is still no consensus on the risk factors for recurrence and pregnancy. This study aims to identify factors affecting BOTs recurrence and assess the effectiveness of FSS on fertility outcomes.

METHODS

Consecutive patients diagnosed with BOTs in the Affiliated Beijing Chaoyang Hospital of Capital Medical University from January 2005 to November 2021 were screened for inclusion in the analysis. The inclusion criteria were as follows: (1) Patients who received initial treatment and surgery in the Affiliated Beijing Chaoyang Hospital of Capital Medical University. (2) Patients with BOTs that were confirmed by pathology. (3) patients who were diagnosed based on the World Health Organization's (WHO) pathological diagnosis standard of BOTs. (4) patients with complete clinical and follow-up data. The exclusion criteria were as follows: (1) Patients with gynecological malignancies. (2) Patients with a history of other malignant tumors. (3) Patients with severe heart, lung, liver, or kidney dysfunction. (4) patients without complete clinical and follow-up data. This study was a retrospective study, the ethics approval and consent to participate were waived by the Medical Ethics Committee of Beijing Chaoyang Hospital (2021-ke-506). All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

The clinical and pathological data collected included age, fertility history, menopause status, chief complaint, tumor size and location, pathology, micropapillary pattern, invasive implantation, surgical approach, fertility-preserving surgery, lymphadenectomy, omentectomy, the International Federation of Gynecology and Obstetrics (FIGO) stage (2014 FIGO classification system), preoperative *CA125* levels.

Treatment

Surgery without fertility preserving consists of peritoneal washing, hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and multiple peritoneal biopsies. Appendectomy is performed for patients with mucinous BOTs. FSS is defined as the preservation of the uterus and at least part of one ovary. It includes the following surgical methods: unilateral cystectomy (UC), unilateral salpingo-oophorectomy (USO), bilateral cystectomy (BC), USO combined with contralateral ovarian cystectomy (USO + CC). There is no evidence supporting lymph node dissection in BOTs. Adjuvant treatment is not accepted as standard care for BOTs patients. The indications for chemotherapy or radiotherapy depend on the pathological results, including the characteristics of peritoneal implants (noninvasive versus invasive) and the persistence of residual tumors at the end of initial surgery.

Follow-up

Patient follow-up consisted of physical and gynecological examinations, *CA125*, and ultrasound scans every 3 months during the first 2 years and every 6 months afterward. Disease-free survival (DFS) was defined as the duration from primary surgery to the first recurrence or the last visit, while overall survival (OS) was defined as the duration from primary surgery to death or the last visit.

Data analysis

Data were statistically analyzed using SPSS 25.0 statistical software (IBM Corporation, Armonk, NY, USA). The comparison between groups was performed by t-test. The adoption rate of counting data was expressed by the *chi-square* test and Fisher exact probability method. The variables with statistically significant differences in univariate analysis were included in the COX regression model for multivariate analysis. DFS and OS were assessed using the Kaplan-Meier method, while the statistically significant difference was examined by log-rank test. The difference was statistically significant at $P < 0.05$.

RESULTS

A total of 169 BOTs patients were included in the study, from January 2005 to November 2021 in Beijing Chaoyang Hospital. The median age of the patients was 45 years (range, 14-88 years), and 49 patients (29%) had no history of fertility. The median follow-up time was 81 months (1-203 months). The characteristics of patients are shown in Table 1. The majority of patients (54.4%) were diagnosed through physical examination, followed by abdominal pain. The diameter of BOTs was larger than 10 cm in 55% of patients, and 81.7% of these tumors were unilateral. The most common pathology type was serous (48.5%), followed by mucinous (43.8%). 57.4% of patients underwent laparoscopic surgery, and 127 patients were diagnosed at an early stage.

A total of 21 patients experienced relapse, resulting in a recurrence rate of 12.4%. The shortest interval of recurrence was 2 months and the longest was 148 months, with a median recurrence interval of 62 months.

Table 1: Clinicopathological and biological data of BOTs patients

Characteristics	Number	Percentage (%)
History of fertility		
No	49	29.0
Yes	120	71.0
Menopause		
No	105	62.1
Yes	64	37.9
Chief complaint		
Abdominal pain	48	28.4
Touching mass	9	5.3
Physical examination	92	54.5
Others	20	11.8
Tumor size (cm)		
<10	76	45.0
⩾10	93	55.0
Tumor site		
Unilateral	138	81.7
Bilateral	31	18.3
CA125		
⩽35	89	52.7
>35	80	47.3
Frozen section diagnosis		
Benign	49	29.0
Borderline	104	61.5
None	16	9.5
Ovarian tumor rupture		
Spontaneous rupture	24	14.2
Intraoperative rupture	6	3.6
None	139	82.2
Pathology		
Serous	82	48.5
Mucinous	74	43.8
others	13	7.7
Micropapillary pattern		
No	76	45.0
Yes	93	55.0
Invasive implantation		
No	159	94.1
Yes	10	5.9
Surgical approach		
Laparotomy	97	57.4
Laparoscopy	72	42.6
Lymphadenectomy		
No	71	42.0
Yes	98	58.0
Omentectomy		
No	52	30.8
Yes	117	69.2
Fertility-sparing surgery		
No	109	64.5

(To be Continued)

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Yes	60	35.5
FIGO stage		
I	127	75.1
⩾II	42	24.9
Chemotherapy		
No	133	78.7
Yes	36	21.3
Complete staging surgery		
No	60	35.5
Yes	109	64.5

BOTs, borderline ovarian tumors; FIGO, International Federation of Gynecology and Obstetrics.

Univariate analysis revealed that the FIGO stage and invasive implantation influenced BOTs recurrence significantly ($P < 0.05$). The recurrence rate for FIGO stage I was 8.7%, while FIGO stage II and III was 23.8%. The recurrence rate for patients with invasive implantation was 40%, compared to 10.7% for patients without invasive implantation. Univariate analyses of factors affecting recurrence are shown in Table 2. Multivariate analysis demonstrated that the FIGO stage was the only independent risk factor affecting the BOTs recurrence rate ($P = 0.039$).

Of the 169 patients, 60 underwent FSS with a median age of 28 years (range, 14-46 years). A total of 40 patients underwent USO, 10 underwent UC, 4 received BC, and 6 received USO + CC. The recurrence rates for these patients were 10%, 0, 25% and 33.3% respectively, indicating that the groups did not show any statistically significant differences. The recurrence rate for the laparoscopic group was 15%, and for the laparotomy group, it was 10%, but there was no statistically significant difference between them ($P = 0.570$). The recurrence rate for patients with unilateral tumors was 8%, while for those with bilateral tumors, it was 30% ($P = 0.048$). Univariate analyses of factors affecting recurrence in BOTs patients with FSS are shown in Table 3.

All the patients underwent fertility counseling. Due to various reasons, only 16 patients had a desire for fertility after the operation. Among them, 13 patients successfully conceived spontaneously, resulting in term live births. The pregnancy rate was 81.3%. Women who gave birth did not experience any significant obstetric or neonatal complications, and no tumor recurrence occurred during pregnancy. The pregnancy rates for patients who received USO, UC, BC or USO + CC were 88.9%, 66.7%, 50% and 100%, respectively ($P = 0.899$). The pregnancy rates for FIGO stage I and advanced FIGO stage were 81.1% and 80%, respectively ($P = 0.148$). The pregnancy rate for patients who underwent chemotherapy was 75%, which was lower than for patients who did not receive chemotherapy (83.3%). However, the difference was not statistically significant. The pregnancy rate in the laparoscopic group was 100%, while in the laparotomy group, it was 75% ($P = 0.825$). The pregnancy rates for patients who underwent lymphadenectomy and those who did not undergo lymphadenectomy were 80% and 81.8%, respectively. Univariate and multivariate analysis did not reveal any factor significantly correlated with the pregnancy rate (Table 4).

After a median follow-up time of 81 months, six patients in the radical surgery group died of their disease, while no patients in the FSS group died ($P = 0.135$). Among them, two patients in FIGO stage I and four patients in advanced FIGO stage died of their disease ($P = 0.086$). One patient with invasive implantation and five patients without invasive implantation died of their disease ($P = 0.852$). Five patients who received chemotherapy and one patient who did not receive chemotherapy died of their disease ($P = 0.887$).

DISCUSSION

Swanton *et al.* conducted a system review that included 923 BOTs patients from 19 studies. The recurrence rate reported in the system review was 16%.[5] In another literature, the recurrence rate of BOTs was reported to be 19%.[6] Alvarez *et al.* reported that the recurrence rate of BOTs ranged from 12% to 58%.[7] In this study, we found the recurrence rate of BOTs patients to be 12.4%, which is consistent with previous research.

Our retrospective analysis identified the FIGO stage and invasive implantation as risk factors for the recurrence of BOTs. Many studies have demonstrated that higher FIGO stages are associated with a worse prognosis. While only 5% of patients initially diagnosed with FIGO stage I experience relapse, patients with advanced disease face recurrence in up to 25% of cases.[8,9] In the

Table 2: Univariate analysis of factors affecting recurrence in patients with BOTs

Characteristics	No recurrence (*N* = 148)	Recurrence (*N* = 21)	*P* value
History of fertility			0.964
No	43 (87.8)	6 (12.2)	
Yes	105 (87.5)	15 (12.5)	
Menopause			0.982
No	92 (87.6)	13 (12.4)	
Yes	56 (87.5)	8 (12.5)	
Tumor size (cm)			0.794
<10	66 (86.8)	10 (13.2)	
⩾10	82 (88.2)	11 (11.8)	
Tumor site			0.196
Unilateral	123 (89.1)	15 (10.9)	
Bilateral	25 (80.6)	6 (19.4)	
CA125			0.691
⩽35	77 (86.5)	12 (13.5)	
>35	71 (88.7)	9 (11.3)	
Frozen section diagnosis			0.559
Benign	44 (89.8)	5 (10.4)	
Borderline	89 (85.6)	15 (14.4)	
None	15 (93.8)	1 (6.2)	
Ovarian tumor rupture			0.438
No	123 (88.5)	16 (11.5)	
Yes	25 (83.3)	5 (16.7)	
Pathology			0.225
Serous	73 (89.0)	9 (11.0)	
Mucinous	62 (83.8)	12 (16.2)	
others	13 (100)	0	
Micropapillary pattern			0.466
No	65 (85.5)	11 (14.5)	
Yes	83 (89.2)	10 (10.8)	
Invasive implantation			0.006
No	142 (89.3)	17 (10.7)	
Yes	6 (60.0)	4 (40.0)	
Surgical approach			0.359
Laparotomy	83 (85.6)	14 (14.4)	
Laparoscopy	65 (90.3)	7 (9.7)	
Lymphadenectomy			0.133
No	59 (83.1)	12 (16.9)	
Yes	89 (90.8)	9 (9.2)	
Omentectomy			0.460
No	47 (90.4)	5 (9.6)	
Yes	101 (86.3)	16 (13.7)	
Fertility-sparing surgery			0.824
No	95 (87.2)	14 (12.8)	
Yes	53 (88.3)	7 (11.7)	
FIGO stage			0.035
I	116 (91.3)	11 (8.7)	
⩾II	32 (76.2)	10 (23.8)	
Complete Staging surgery			0.824
No	53 (88.3)	7 (11.7)	
Yes	95 (87.2)	14 (12.8)	

Data were presented as *N* (%). BOTs, borderline ovarian tumors; FIGO, International Federation of Gynecology and Obstetrics.

Table 3: Univariate analysis of factors affecting recurrence in BOTs patients with FSS

History of fertility			0.704
No	34 (87.2)	5 (12.8)	
Yes	19 (90.5)	2 (9.5)	
Tumor size (cm)			0.335
<10	25 (86.2)	4 (13.8)	
⩾10	28 (90.3)	3 (9.7)	
Tumor site			0.048
Unilateral	46 (92.0)	4 (8.0)	
Bilateral	7 (70.0)	3 (30.0)	
CA125			0.336
⩽35	23 (85.2)	4 (14.8)	
>35	30 (91.0)	3 (9.0)	
Frozen section diagnosis			0.564
Benign	17 (85)	3 (15)	
Borderline	29 (87.9)	4 (12.1)	
None	7 (100)	0	
Ovarian tumor rupture			0.512
Spontaneous rupture	9 (90)	1 (10)	
Intraoperative rupture	4 (100)	0	
None	40 (87)	6 (13.0)	
Pathology			0.737
Serous	23 (88.5)	3 (11.5)	
Mucinous	26 (86.7)	4 (13.3)	
others	4 (100)	0	
Micropapillary pattern			0.795
No	26 (89.3)	3 (10.7)	
Yes	27 (87.1)	4 (12.9)	
Invasive implantation			0.151
No	51 (87.9)	7 (12.1)	
Yes	2 (100)	0	
Surgical approach			0.570
Laparotomy	36 (90)	4 (10)	
Laparoscopy	17 (85)	3 (15)	
Lymphadenectomy			0.055
No	25 (80.6)	6 (19.4)	
Yes	28 (96.6)	1 (3.4)	
Omentectomy			0.903
No	24 (88.9)	3 (11.1)	
Yes	29 (87.9)	4 (12.1)	
Fertility-sparing surgery			
USO	36 (90)	4 (10)	0.297
UC	10 (100)	0	
BC	3 (75)	1 (25)	0.778
USO + CC	4 (66.7)	2 (33.3)	
FIGO stage			0.232
Ⅰ	44 (91.7)	4 (8.3)	
⩾Ⅱ	9 (75)	3 (25)	
Chemotherapy			0.657
No	42 (89.4)	5 (10.6)	
Yes	11 (84.6)	2 (15.4)	

Data were presented as *N* (%). BOTs, borderline ovarian tumors; FSS, fertility-sparing surgery; UC, unilateral cystectomy; USO, unilateral salpingo-oophorectomy; BC, bilateral cystectomy; USO + CC, USO combined with contralateral ovarian cystectomy; FIGO, International Federation of Gynecology and Obstetrics.

Table 4: Univariate analysis of pregnancy factors in BOTs patients with FSS

Characteristics	Non-pregnancy (*N* = 47)	Patients achieving/attempting pregnancy (*N* = 13/16)	*P* value
History of fertility			0.094
No	28	11/13 (84.6)	
Yes	19	2/3 (66.7)	
Tumor size (cm)			0.282
<10	21	8/10 (80.0)	
⩾10	26	5/6 (83.3)	
Pathology			0.640
Serous	19	7/10 (70.0)	
Mucinous	25	5/5 (100.0)	
Others	3	1/1 (100.0)	
Micropapillary pattern			0.601
No	22	7/9 (77.8)	
Yes	25	6/7 (85.7)	
Invasive implantation			0.592
No	45	13/15 (86.7)	
Yes	2	0/1 (0)	
Surgical approach			0.825
Laparotomy	31	9/12 (75.0)	
Laparoscopy	16	4/4 (100.0)	
Lymphadenectomy			0.152
No	22	9/11 (81.8)	
Yes	25	4/5 (80.0)	
Omentectomy			0.469
No	20	7/10 (70.0)	
Yes	27	6/6 (100.0)	
Fertility-sparing surgery			0.899
USO	32	8/9 (88.9)	
UC	8	2/3 (66.7)	
BC	3	1/2 (50.0)	
USO + CC	4	2/2 (100.0)	
FIGO stage			0.148
I	39	9/11 (81.8)	
⩾ II	8	4/5 (80.0)	
Chemotherapy			0.889
No	37	10/12 (83.3)	
Yes	10	3/4 (75.0)	

BOTs, borderline ovarian tumors; FSS, fertility-sparing surgery; UC, unilateral cystectomy; USO, unilateral salpingo-oophorectomy; BC, bilateral cystectomy; USO + CC, USO combined with contralateral ovarian cystectomy; FIGO, International Federation of Gynecology and Obstetrics.

series by Seong *et al.*[10] the 5-year survival for FIGO stage I BOTs patients was approximately 95% to 97%, while stage II-III BOTs patients had only 65% to 87% survival rates. In our analysis, the recurrence rate of FIGO stage I was 8.7% and FIGO stage II-III was 24.4% ($P = 0.035$). The difference in DFS between the FIGO stage I group and the FIGO stage II–III group was significant ($P = 0.021$). However, the 5-year survival between the FIGO stage I (95.2%) and FIGO stage II-III (93.8%) groups did not differ significantly.

It has been postulated that the presence of invasive implants represents the most important risk factor besides the initial FIGO stage.[11] Morice *et al.* demonstrated that the main predictive factor of survival was the presence of implants, particularly invasive implants.[12] In the Bendifallah study, the overall recurrence rate was 34.4% (64/186), with noninvasive and invasive forms in 29% (54/186) and 5.4% (10/186) of cases, respectively.[13] Alvarez *et al.* showed the recurrence rate is higher in patients with invasive implantation.[7] Shih *et al.* also demonstrated that the

presence of invasive implantation was an independent risk factor for the recurrence of BOTs.[14] In our study, the recurrence rate of patients with invasive implantation was 40% and without invasive implantation was 10.7% ($P = 0.006$). Through Kapan-Meier analysis, the DFS and OS showed no significant difference between the two groups. Therefore, these patients have to be followed very closely. Invasive implants share many features with cancer and they may already mark the transformation to invasive carcinoma.

Many articles have reported that the micropapillary pattern is always accompanied by a higher recurrence rate. Shih *et al.* showed that of the 196 patients with borderline tumors of serous histology, those with a micropapillary pattern had a 3-year progression-free survival (PFS) of 75.9% compared with 94.3% for patients without a micropapillary pattern ($P < 0.001$).[10] In Silva's study, the micropapillary pattern was the only feature associated with a higher recurrence rate (26% *vs.* 4%, $P = 0.008$).[15] However, Uzan *et al.* demonstrated that the recurrence rate was 71% in patients without a micropapillary pattern and 51% in patients with a micropapillary pattern ($P = 0.1$).[16] In this study, we found that the recurrence rate was 14.9% in patients without a micropapillary pattern and 10.8% in patients with a micropapillary pattern. There was no significant difference in the recurrence rate between patients with or without a micropapillary pattern.

BOTs are typically present in women of reproductive age and are often diagnosed at an early stage, with a favorable prognosis. The median age at diagnosis is 45 years, with 34% of patients being under 40.[17–19] BOTs are more frequently limited to the ovaries compared to invasive carcinoma, with 78.9% of patients diagnosed at FIGO stage I.[20] Therefore, FSS is preferred for young patients who wish to preserve their fertility. In this study, the recurrence rate of FSS was 11.7%. Other studies have come to similar conclusions. Seong *et al.* reported a recurrence rate of 10% to 20% for BOTs patients who underwent FSS.[10] Qi *et al.* also reported a recurrence rate of 10.2% for BOTs patients who underwent FSS.[21] Park *et al.* reported that among 164 patients who received FSS with a median follow-up of 70 months, 9 recurrences were observed, of which only 1 was invasive (involving the lung and pericardium) and proved fatal 82 months after initial treatment.[22] In the study by Johansen *et al.*, a 5-year OS rate of 99% was observed for the total cohort, with a comparison of 5-year OS rates after FSS and radical surgery at 98% and 100%, respectively.[23] In this study, 7 patients experienced recurrence after conservative surgery, with a median recurrence time of 44 months, the shortest being 13 months and the longest being 117 months. In all cases, ovarian recurrences were detected in both ovaries and the contralateral ovary. However, there was no progression to invasive ovarian carcinoma or death observed. While conservative surgery may increase the rate of recurrence compared to radical treatment, it does not impact OS, as these recurrences are easily cured by exclusive surgery and do not have any impact on OS.[24] Therefore, FSS is a feasible and safe option for patients who want to preserve their fertility.

Through univariate analysis, we found that bilateral tumor was a risk factor for recurrence. In this study, the recurrence rate of bilateral BOTs was 30%, while unilateral BOTs had a recurrence rate of 8%. The difference was statistically significant ($P = 0.048$). Some researchers have reported that the 5-year recurrence-free survival (RFS) was 74% and 48% in patients with unilateral and bilateral tumors, respectively.[25] Fang *et al.* also showed that patients with bilateral tumors had a higher recurrence rate after FSS (27.9% *vs.* 63.6%, $P = 0.038$).[26] Qi *et al.* reported a recurrence rate of 7.4% in the unilateral group and 24.2% in the bilateral group ($P = 0.009$).[21] Chen *et al.* reported that patients with bilateral tumors had a higher recurrence rate (4.7% *vs.* 18.7%, $P = 0.07$) and a shorter recurrence interval (33.2 months *vs.* 23 months, $P = 0.00$) after conservative treatment.[27] In our population, FSS includes the following surgical approach: UC and USO for unilateral BOTs. BC and USO + CC for bilateral BOTs.

In this study, there was no significant difference in the recurrence rate between the UC and USO groups. A meta-analysis conducted in 2015 included 817 patients who underwent UC and 1686 who underwent USO, and the recurrence rates were 25.3% and 12.5%, respectively ($P < 0.001$).[28] A study of 106 patients with unilateral BOTs found that more patients relapsed in a shorter time in the UC group, although this difference was not statistically significant (6.8% *vs.* 2.1%, $P = 0.38$).[27] In the Marchette *et al.* study, 535 patients were included, 271 underwent USO, and 264 underwent UC, with a median follow-up of 13.5 years. The ten-year recurrence rate was 23% for the USO and 31% for the UC group ($P= 0.1$) in patients with unilateral tumors.[29] Fang *et al.* demonstrated that compared to the USO group, the UC group had a higher recurrence rate and a short recurrence interval (60% versus 24%, $P = 0.123$/36 months versus 55 months, $P = 0.133$).[26] Although it seems logical to speculate that women undergoing UC would have higher pregnancy rates than patients undergoing USO due to the higher loss of ovarian reserve in the latter, the pregnancy rate for women undergoing USO and UC was not significantly different (45.4% and 40.3%) in Vasconxelos' study.[28] Similar findings were also reported by Fang *et al.*, with pregnancy rates in the UC and USO groups being 50% and 69%, respectively ($P = 1.000$). Through analysis in this study, the surgical approach did not influence fertility. Ten cases became pregnant after UC, with a

pregnancy rate of 66.7%, which was higher than that of 56.2% after USO, but there were no significant differences between the two groups ($P = 0.498$). Biopsy of the contralateral ovary is ill-advised because clinically occult bilateral ovarian involvement has been noted in only 2.5% of women undergoing staging for ovarian malignancy and ovarian surgery may impair future fertility, culminating in mechanical infertility in up to 14% of women.[30] Therefore, we suggest the USO approach for patients with unilateral BOTs. It had a lower recurrence rate and a satisfactory pregnancy rate.

For patients with bilateral BOTs, our study has shown that there is no difference in recurrence rate and pregnancy rate between those treated with BC and those treated with USO + CC. In a prospective study conducted by Palomba *et al.* [31] in 2010, 15 patients were treated with BC while 17 patients received USO + CC. After 128 months of follow-up time, the difference in recurrence rate was not significant. Similarly, a meta-analysis conducted in 2015 reported that out of 89 patients who underwent BC and 118 who underwent USO + CC, the recurrence rates were 25.6% and 26.1%, respectively, and the difference was not significant.[28] However, Fang *et al.* reported that the recurrence rate in the USO + CC group was 67%, which was higher than the 50% observed in the BC group ($P = 1.000$). Additionally, the recurrence interval in the USO + CC group was shorter than that in the BC group (21 months versus 41 months, $P = 0.482$).[26] In a 2020 study conducted by Jia *et al.*, 79 bilateral BOTs patients underwent FSS, and during a median follow-up time of 64months (range, 4-243 months), the 5-year DFS rate of patients who underwent BC was 14%, compared with 35% in patients with USO + CC, but the difference was not significant.[32] In terms of fertility outcomes, a study conducted in 2019 reported that the 15-year pregnancy incidence was 88% in the USO + CC group and 85.9% in the BC group.[29] Jia *et al.* also showed that the difference in pregnancy rate between the BC and USO + CC groups was not significant.[32] Furthermore, when compared with USO + CC, the recurrence rate and pregnancy rate of BC were lower (18.7% *vs.* 29.4% and 40% versus 50%, respectively), but there were no significant differences between the two groups.[21] Overall, these findings suggest that the oncologic and fertility outcomes of BC and USO + CC are promising for patients with bilateral BOTs.

The median time from the end of treatment to pregnancy was 10 months, with the shortest time interval being 3 months and the longest time interval being 17 months. Currently, there is no conclusive recommendation regarding the ideal timing for pregnancy after BOTs surgery. However, taking into account the patient's age and the possibility of tumor recurrence, it may be best to wait 6-12 months after BOTs surgery before attempting to conceive.[33] Previous studies have indicated that most BOTs recurrences occur within the first two years after surgery, which underscores the importance of close monitoring during this period. Although there is no consensus, scheduling a systematic 6-month follow-up visit during this initial period would seem to be a logical approach.[34,35]

Uzan *et al.* reported that the surgery approach (laparoscopic or laparotomy) was not associated with recurrence in patients who underwent FSS.[16,25] Chen *et al.* analyzed that, compared to laparotomy, laparoscopy had no disadvantage in terms of recurrence rate and pregnancy rate.[27] In this study, the surgical procedure was also not associated with the recurrence rate and pregnancy rate for patients who underwent FSS. Qi *et al.* showed that the recurrence rate of laparotomy in FSS patients is higher than that in laparoscopic surgery (14.3% *vs.* 4.3%, $P = 0.029$). The pregnancy rate between laparotomy and laparoscopic has no significant difference (60.6% *vs.* 50%, $P = 0.397$).[21] Therefore, laparoscopy seems to be the most attractive surgical approach to BOTs due to well-proven benefits such as faster recovery, lower perioperative complication rates, and reduced pelvic adhesion that could impair fertility.

In our study, 13 patients received chemotherapy after FSS. The recurrence rate was 15.4%, and the pregnancy rate was 75%. When compared to patients who did not receive chemotherapy, the difference was not statistically significant. Fang *et al.* studied 12 patients who underwent chemotherapy and concluded that there was no significant difference in recurrence rate and pregnancy rate.[26] All the evidence suggests that patients do not benefit from chemotherapy, especially those who underwent FSS. Chemotherapeutic agents that reach the ovaries can damage primordial follicles. The detrimental effect of cytotoxic agents on the ovary is thought to be caused by damage to peri-oocyte granulosa cells in the ovaries. Damage to ovarian tissue due to cytotoxic agents is irreversible. Histological samples of ovarian tissue after chemotherapy have shown a range of damage, from a reduction in follicle count to complete failure.[36] Therefore, chemotherapy is not recommended for patients, even those with advanced BOTs, especially for patients who have a desire for fertility.

There are some limitations to this study. It is a retrospective study, and its nature may be a source of bias. The number of included patients was limited, and the relatively small number of patients attempting to conceive might limit the statistical power of our findings.

CONCLUSION

BOTs are tumors with a favorable prognosis. After

univariate and multivariate analysis, we identified some risk factors for recurrence after radical surgery, but they do not affect the overall survival rate. FSS is a feasible approach for young patients. Although the tumor site is the only risk factor for recurrence, it does not affect long-term survival and pregnancy rates. Laparoscopic procedures are recommended, and chemotherapy is not recommended for patients receiving FSS. We suggest that patients who wish to preserve fertility should get pregnant as soon as possible and follow up closely.

DECLARATIONS

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Author contributions
Qi Lu and Chongdong Liu conceived of the study and participated in its design and implementation. Qi Lu and Yupeng Deng participated in the drafting of the manuscript; Yupeng Deng and Zhiqiang Zhang collected and analyzed the data; Hong Qu revised the manuscript critically.

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Not applicable. Because this study was a retrospective study, the ethics approval and consent to participate were waived by the Medical Ethics Committee of Beijing Chaoyang Hospital (2021-ke-506). All procedures performed in this study involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

Informed consent
Not applicable. No details on individual patients have been reported in this study.

Conflict of interest
All the authors declare that they have no conflict of interests.

Data availability statement
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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