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ORIGINAL RESEARCH

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Exploring the impact of surgical interventions and identifying risk factors for recurrence in stage I of borderline ovarian tumors

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Abstract

This research aimed to evaluate surgical intervention's influence on borderline ovarian tumors (BOTs) outcomes and identify contributing recurrence risk factors. BOT patients at Korea University Anam Hospital (2006–2023) were classified based on recurrence. Surgical interventions were classified conservative, comprehensive or staging surgeries. Each group's characteristics, surgical interventions, disease-free survival (DFS), overall survival (OS), and recurrence risk factors were compared and analyzed. Statistical analyses included student's *t*-test, chi-square test, Fisher's exact test, Kaplan-Meier analysis, and Cox regression analyzing using SPSS. Of 177 patients, 170 were in the no recurrence group, and seven were in the recurrence group. Four relapsed patients had a borderline recurrence, and three had a malignant transformation. The median follow-up period for all participants was 47 months. There were no significant differences in DFS and OS on surgical interventions. Increased risk of BOT recurrence was observed with positive washing cytology (adjusted hazard ratio (HR), 36.02; 95% confidence interval (CI), 6.798, 641.204; $p = 0.003$) and intraoperative iatrogenic rupture (adjusted HR, 5.89; 95% CI, 1.003, 27.640; $p = 0.046$), but no significant OS risk factors were identified. In early stage BOT treatment, surgical intervention differences didn't affect outcomes, DFS or OS. Conservative, comprehensive and staging surgeries are options based on patient age and fertility preservation. To reduce BOT recurrence risk, avoiding rupture during surgery and closely monitoring postoperative patient with positive washing cytology is crucial.

Keywords

Borderline ovarian tumors; Conservative surgery; Comprehensive surgery; Staging surgery; Recurrence; Risk factors

1. Introduction

Borderline ovarian tumors (BOTs) are lesions caused by abnormal cell development and abnormal growth in the tissues that encapsulate the ovaries [1]. It is characterized by epithelial origin and low malignant potential. Since 1971, the International Federation of Gynecology and Obstetrics (FIGO) has classified it as an epithelial ovarian tumor [2]. The incidence of BOTs is low, with a rate of about 1.5 per 100,000 among American women and 4.8 per 100,000 among European women [3]. Statistics from the National Health Insurance Service of South Korea between 2014 and 2018 show that the incidence of BOTs in 2014 was approximately 0.12%, and BOTs in 2018 were approximately 0.11% [4].

BOTs are histologically characterized by complex papillary structures, multi-layered epithelium, mild nuclear atypia, mild increased mitotic activity, but no destructive stromal invasion, and they are histologically divided into serous type, mucinous type, endometrioid type and clear cell type. according to epithelial characteristics [5]. In addition, as a result of imaging tests such as Ultrasound Sonography and computed tomography (CT), BOTs can observe the following characteristics. On Ultrasound Doppler Sonography, BOTs tended to have decreased color Doppler flow compared to high grade malignant tumors. On CT imaging, BOTs have rare or small internal papillary projections compared to malignant tumors, and thin septations without definite contrast enhancement [6]. The survival rate of BOTs is excellent, with a 5-year survival rate of 95%–97% for stage I BOTs and a 5-year survival rate of 65%–87% for stage II–III BOTs [7]. However, several retrospective studies have reported that recurrence or malignant transformation of BOTs occurs at a rate of approximately 4%–20% with progression-free survival (PFS) of 14 months after the first treatment [8, 9]. In other words, even if histologically diagnosed as BOTs, the risk of recurrence cannot be excluded entirely, so close observation and awareness of risk factors affecting recurrence are necessary.

The National Comprehensive Cancer Network (NCCN) guidelines for treating BOTs suggest that depending on fertility desire, observation without surgical intervention or consideration of options such as fertility-sparing surgery, comprehensive surgery and staging surgery may be considered. However, the specific method of surgical interventions has not yet been established [10]. In general, the onset of BOTs is about 45 years, which is younger than the onset for epithelial ovarian cancer patients, which is 55 years [7]. Data from the Korean Health Insurance Review and Assessment Service also shows a relatively high prevalence of BOTs in women of reproductive age between 25 and 45 compared to other age groups [4]. When choosing between the surgical treatment of BOTs in women of childbearing age who need to preserve fertility and in older patients, there is a lack of clinical evidence on which surgical intervention is more appropriate. Therefore, the objective of this study was to explore whether differences in surgical interventions performed in the treatment of BOTs affect patient outcomes and to identify risk factors that influence the recurrence of BOTs.

2. Materials and methods

2.1 Patients selection and data collection

We retrospectively evaluated data from 177 women who underwent conservative, comprehensive or staging surgery for BOTs at the Korea University Anam Hospital from March 2006 to March 2023. To select 177 patients for this study, of the 219 patients diagnosed with BOT after surgical treatment, we excluded those with incomplete clinical data and those with post-operative follow-up loss. The flowchart of study participants selection is presented in Fig. 1. The presence of BOTs in the 177 patients in this study was detected preoperatively by imaging studies such as ultrasonography and computed tomography (CT). The average size of the largest BOTs in this study was 13.95 $\pm$ 8.33 cm, and in general, we performed laparotomy among the surgical approach methods for BOTs of larger than average size. In this study, the average size of the largest BOT in the laparotomy group was 18.00 $\pm$ 8.68 cm. In addition, the average size of the largest BOT in the laparoendoscopic single site (LESS), laparoscopy (LPS) and Robot groups was 12.46 $\pm$ 8.19 cm, 12.94 $\pm$ 7.25 cm and 9.09 $\pm$ 4.78 cm, respectively.

In this study, patients were divided into no recurrence and recurrence groups according to whether they had recurrence after surgical treatment of BOTs. Medical information was used to identify age, height, weight, body mass index (BMI), parity, menopausal state, comorbidity, previous abdominal surgery history, tumor marker (cancer antigen (CA) 125, CA 19-9 and carcinoembryonic antigen (CEA)), location of BOTs, largest BOTs size, stage, histology, surgical approach, surgical interventions, washing cytology results, intraoperative iatrogenic rupture, presence of endometriosis, microinvasion and ovarian surface involvement to compare the characteristics of each group.

Surgical approach methods were categorized into LESS, conventional LPS, robotic and laparotomy. In this study, 66 patients underwent surgical approach by LESS, 43 by LPS, 15 by robot and 53 by laparotomy. The surgical concept of performing a unilateral salpingo-oophorectomy, preserving uterus and saving the contralateral ovary and fallopian tube is commonly referred to as fertility preservation surgery. However, fertility preservation strictly means saving or protecting eggs, sperms or reproductive tissue so that a woman can have children in the future. Therefore, in this paper, surgical intervention is subdivided into conservative surgery, comprehensive surgery and staging surgery based on the concept of saving the uterus, which corresponds to female reproductive tissue, and the function of the ovary to preserve eggs. The definition for each of the surgical interventions are as follows. Conservative surgery was defined as surgery that saved at least one ovary, with or without a hysterectomy, and comprehensive surgery was described as removing both ovaries through bilateral salpingo-oophorectomy (BSO) with or without hysterectomy. The procedures performed during the staging surgery adhered to the methods outlined in the principles of primary surgery in version 2 of the NCCN guidelines. Notably, since our study participants were early-stage patients with lesions limited to the pelvis, we executed the procedures specified for "ovarian cancer apparently confined to an ovary or to the pelvis". This includes guidelines on performing hysterectomy, BSO, omentectomy, pelvic lymph node dissection, and aortic lymph node dissection. Additionally, the guidelines under special circumstances recommend appendectomy for all stages of epithelial ovarian cancer or when a mucinous tumor is suspected. Consequently, the staging surgery procedures in this study encompassed hysterectomy, BSO, lymph node removal, omentectomy and appendectomy [10]. In this study, pre-operative radiological evaluation of all participants undergoing staging surgery showed no suspected metastatic lesions in the pelvic lymph nodes or finding suggestive of metastasis in the para-aortic lymph nodes. Therefore, we performed bilateral pelvic lymph node dissection for lymph node sampling purposes on every patient undergoing staging surgery. The decision to perform any of the aforementioned surgical interventions was based on the results of preoperative imaging studies and careful consultation with the patient. In general, for women of reproductive age under 45 who wish to preserve their fertility, conservative surgery was performed to preserve at least one ovary. In addition, staging surgery was performed in cases where the imaging examination such as CT showed BOT, but the possibility of invasive malignant ovarian tumor could not be excluded, such as irregular margins, tumor septations thicker than 3 mm, tumor texture containing solid materials and papillary projections. In cases except for the aforementioned criteria of conservative surgery and staging surgery, we performed comprehensive surgery.

BOTs patients were followed up every 3 months for the first year after primary surgical treatment with ultrasonography, abdomen enhanced computed tomography (ECT) imaging, and reassessment of tumor markers such as CA 125, CA 19-9 and CEA. For the next two years, patients were followed up every six months with imaging tests such as the CT, ultrasound scans and tumor marker tests mentioned above, and then once a year for follow-up, including imaging tests and tumor marker tests. For survival analysis, disease-free survival (DFS) was calculated as the time from the date of primary surgery to the

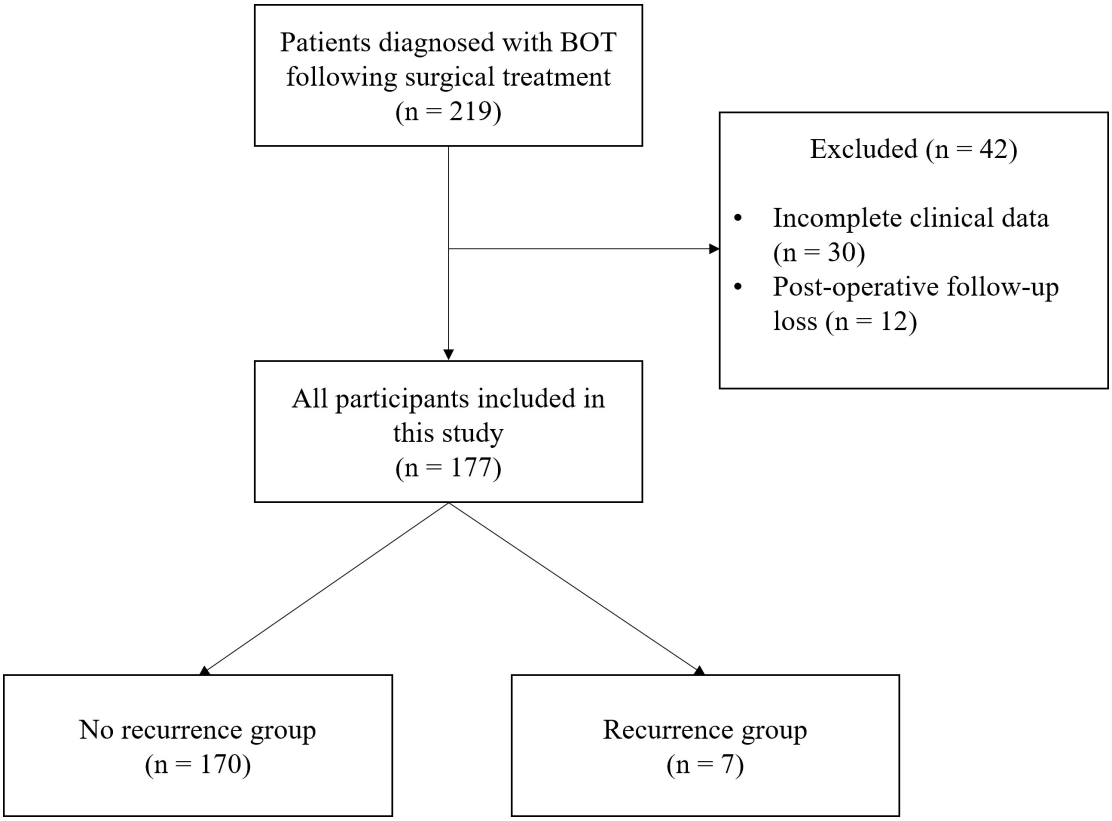

FIGURE 1. Flowchart of study participants selection. BOT: Borderline ovarian tumor.

date of recurrence confirmed by imaging, and overall survival (OS) was defined as the time from the date of primary surgery to the last follow-up period or death.

2.2 Statistical analysis

A student's *t*-test was conducted to compare and analyze continuous variables between the no-recurrence and recurrence groups, and categorical variables were analyzed a chi-square or Fisher's exact test. PFS and OS were analyzed using the Kaplan-Meier method, and the time-to-event outcome was compared with the log-rank test. Cox proportional hazards for univariate analyses were performed to identify risk factors associated with BOTs recurrence and OS. Statistical significance was defined as a p-value < 0.05. All analyses were performed using SPSS statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, USA).

3. Results

Of the 177 patients, 170 were in the no recurrence group, and seven were in the recurrence group. The patients' characteristics are shown in Table 1. The ages of the participants in this study range from a minimum of 17 to maximum of 84 years old. The mean age of all subjects was 46.45 ± 16.34 years, the mean age in the no recurrence group was 46.75 ± 16.29 years, and the mean age in the recurrence group was 39.00 ± 17.16 years. There was no significant statistical difference for age, height, weight, BMI, parity, menopausal state, comorbidity or previous abdominal surgery history in the no recurrence and recurrence group. There were no statistical differences in tumor markers such as CA 125, CA 19-9 and CEA, largest BOT size or histology results between the no recurrence and recurrence groups. Stage I BOTs were observed in both the no recurrence and recurrence groups. There were no statistical differences; however, the recurrence group was more likely to undergo a surgical approach with LESS (no recurrence, 37.1%; recurrence, 42.9%; $p = 0.574$) and LPS (no recurrence, 23.5%; recurrence, 42.9%; $p = 0.574$). In this study, 130 patients underwent conservative surgery, 26 patients underwent comprehensive surgery, and 21 patients underwent staging surgery. Furthermore, no pathological findings were observed in the pelvic lymph nodes removed during the staging surgery. Surgical interventions such as conservative surgery, comprehensive surgery and staging surgery showed no statistically significant difference between the no recurrence and recurrence groups, but the rate of conservative surgery was slightly higher in the recurrence group (no recurrence, 72.9%; recurrence, 85.7%; $p = 0.837$). In addition, when the washing cytology result was positive (no recurrence, 0.6%; recurrence, 14.3%; $p = 0.078$), when the BOTs became iatrogenic rupture during surgery (no recurrence, 28.8%; recurrence, 71.4%; $p = 0.067$) when accompanied by endometriosis (no recurrence, 10.0%; recurrence, 14.3%; $p = 0.534$), and the presence of microinvasion in the BOTs (no recurrence, 14.1%; recurrence, 42.9%) were more frequent in the recurrence group compare to the no recurrence group. In this study, the initial post-operative CT scan conducted for follow-up purposes after the primary surgery of all participants showed no residual lesions. The median follow-up period for all participants was 47 months, and there were no statistical differences in DFS and OS between the no recurrence and recurrence groups.

TABLE 1. Characteristics of the study participants by recurrence status of borderline ovarian tumors.

	Total (N = 177)	No recurrence (N = 170)	Recurrence (N = 7)	*p*-value
Age	46.45 ± 16.34	46.75 ± 16.29	39.00 ± 17.16	0.220
Height	158.21 ± 5.78	158.20 ± 5.69	158.60 ± 3.12	0.902
Weight	60.14 ± 9.62	60.01 ± 9.41	63.16 ± 14.37	0.399
BMI	24.07 ± 3.90	24.02 ± 3.79	25.23 ± 6.35	0.423
Parity				
Nulliparous	67	64 (37.6%)	3 (42.9%)	1.000
Multiparous	110	106 (62.4%)	4 (57.1%)	
Menopausal state				
Premenopausal	94	88 (51.8%)	6 (85.7%)	0.123
Postmenopausal	83	82 (48.2%)	1 (14.3%)	
Comorbidity				
None	133	128 (75.7%)	5 (71.4%)	0.605
Cardiovascular	23	22 (13.0%)	1 (14.3%)	
DM	5	5 (3.0%)	0 (0.0%)	
Others	10	9 (5.3%)	1 (14.3%)	
Previous abdominal surgery history				
No	104	102 (60.0%)	2 (28.6%)	0.126
Yes	73	68 (40.0%)	5 (71.4%)	
Tumor marker				
CA 125	76.83 ± 427.70	79.32 ± 436.78	19.76 ± 14.68	0.720
CA 19-9	1129.55 ± 10524.38	1175.26 ± 10752.60	91.34 ± 216.89	0.791
CEA	11.24 ± 85.62	11.47 ± 87.39	5.92 ± 12.15	0.877
Location				
Unilateral	164	158 (92.9%)	6 (85.7%)	0.419
Bilateral	13	12 (7.1%)	1 (14.3%)	
Largest borderline ovarian tumor size	13.95 ± 8.33	13.87 ± 8.28	16.07 ± 10.10	0.494
Stage				
I	177	170 (100.0%)	7 (100.0%)	
II	0	0 (0.0%)	0 (0.0%)	
III	0	0 (0.0%)	0 (0.0%)	
IV	0	0 (0.0%)	0 (0.0%)	
Histology				
Serous	13	42 (24.7%)	1 (14.3%)	0.212
Mucinous	115	110 (64.7%)	5 (71.4%)	
Endometrioid	3	2 (1.2%)	1 (14.3%)	
Seromucinous	15	15 (8.8%)	0 (0.0%)	
Clear cell	1	1 (0.6%)	0 (0.0%)	
Surgical approach				
LESS	66	63 (37.1%)	3 (42.9%)	0.574
LPS	43	40 (23.5%)	3 (42.9%)	
Robot	15	15 (8.8%)	0 (0.0%)	
Laparotomy	53	52 (30.6%)	1 (14.3%)	

TABLE 1. Continued.

	Total (N = 177)	No recurrence (N = 170)	Recurrence (N = 7)	*p*-value
Surgical intervention				
Conservative surgery	130	124 (72.9%)	6 (85.7%)	0.837
Comprehensive surgery	26	25 (14.7%)	1 (14.3%)	
Staging surgery	21	21 (12.4%)	0 (0.0%)	
Washing cytology				
Negative	175	169 (99.4%)	6 (85.7%)	0.078
Positive	2	1 (0.6%)	1 (14.3%)	
Intraoperative iatrogenic rupture				
No	122	120 (70.6%)	2 (28.6%)	0.067
Yes	54	49 (28.8%)	5 (71.4%)	
Endometriosis				
No	159	153 (90.0%)	6 (85.7%)	0.534
Yes	18	17 (10.0%)	1 (14.3%)	
Microinvasion				
No	150	146 (85.9%)	4 (57.1%)	0.073
Yes	27	24 (14.1%)	3 (42.9%)	
Ovarian surface involvement				
No	168	161 (94.7%)	7 (100.0%)	1.000
Yes	9	9 (5.3%)	0 (0.0%)	
DFS	45.59 ± 41.83	46.09 ± 42.32	33.43 ± 26.76	0.434
OS	46.83 ± 42.61	46.09 ± 42.32	64.86 ± 49.17	0.254

Note: Values are presented as mean ± standard deviation or N (%).
BMI, body mass index; DM, diabetes mellitus, LESS, laparoendoscopic single site; LPS, laparoscopy; DFS, disease-free survival; OS, overall survival; CA, cancer antigen; CEA, carcinoembryonic antigen.

Characteristics of patients with recurrence of BOT or malignant tumors are presented in Table 2. Of the seven patients in the recurrence group, four recurred with BOTs, and three recurred and upstaged to malignant, corresponding to cases 2, 3 and 4 of the cases presented in Table 2. In case 2, LESS left ovarian cystectomy was performed with mucinous BOT as the primary surgery, and recurred as mucinous ovarian carcinoma IV after 33 months. Subsequently, the patient underwent adjuvant chemotherapy, initially with 6 cycles of taxol and carboplatin. However, due to the aggravation of the cancer, a second regimen of 21 cycles with gemcitabine, carboplatin and bevacizumab was administered. This was followed by a third chemotherapy of 8 cycles using docetaxel and carboplatin, a fourth regimen of 7 cycles with liposomal doxorubicin, and a fifth regimen of 6 cycles incorporating folinic acid, fluouracil, and irinotecan is being administered. Case 3 underwent LESS-right salpingo-oophorectomy (RSO) as primary surgery with Endometrioid BOT and was upstaged to Endometrioid ovarian carcinoma III after 12 months. The patient in case 3 underwent one cycle of first adjuvant chemotherapy using taxol and carboplatin. However, she died of septic shock after chemotherapy. Case 4 underwent laparotomy hysterectomy with BSO as primary surgery with Mucinous BOT and was malignantly upstaged to Mucinous ovarian carcinoma III after 18 months. The patient in case 4 underwent 8 cycles of first adjuvant chemotherapy using taxol and carboplatin and is currently under continuous outpatient follow-up. Six of the seven recurrent patients underwent surgical intervention with LESS or LPS, and one underwent a laparotomy surgical approach. Six patients underwent conservative surgery, such as ovarian cystectomy and unilateral salpingo-oophorectomy, and the remaining one patient underwent BSO as a comprehensive surgical method. When they recurred, four patients recurred with stage I BOTs, and three patients recurred with advanced stage malignant tumors of stage III or higher. The median follow-up of the seven patients with recurrence was 65 months. Six of the seven patients are still alive, except for one patient who died.

TABLE 2. Characteristics of patients with recurrence of borderline ovarian tumor or malignant tumor.

Case	Age (yr)	Primary surgical approach	Primary surgical interventions	Pathology on primary diagnosis	Primary BOT location	Largest BOT size (cm)	Pathology on recurrence	Site of recurrence	Stage of recurrence	Surgical approach at recurrence	Surgical intervention at recurrence	DFS (mon)	FU (mon)/last status
1	28	LESS	Ovarian cystectomy	Serous BOT	Lt. ovary	15	Mucinous BOT	Lt. ovary	I	LPS	Lt. salpingo-oophorectomy	20	21/alive
2	35	LESS	Ovarian cystectomy	Mucinous BOT	Lt. ovary	8.5	Mucinous carcinoma	Pelvis, peritoneum, omentum, diaphragm	IV	Robot	Staging surgery	33	69/alive
3	73	LESS	Salpingo-oophorectomy	Endometrioid BOT	Rt. ovary	7	Endometrioid carcinoma	Pelvis, peritoneum, omentum	III	Laparotomy	Staging surgery	12	14/dead
4	48	Laparotomy	Hysterectomy with BSO	Mucinous BOT	Both ovaries	35	Mucinous carcinoma	Pelvis, omentum	III	Laparotomy	Staging surgery	18	56/alive
5	37	LPS	Ovarian cystectomy	Serous BOT	Lt. ovary	7	Serous BOT	Rt. ovary	I	LPS	Ovarian cystectomy	71	137/alive
6	31	LPS	Ovarian cystectomy	Mucinous BOT	Lt. ovary	20	Mucinous BOT	Rt. ovary	I	LESS	Salpingo-oophorectomy	71	125/alive
7	21	LPS	Ovarian cystectomy	Mucinous BOT	Lt. ovary	20	Mucinous BOT	Lt. ovary	I	LPS	Salpingo-oophorectomy	9	32/alive

Note: DFS, disease-free survival; FU, follow-up; BOT, borderline ovarian tumor; LESS, laparoendoscopic single site; LPS, laparoscopy; BSO, bilateral salpingo-oophorectomy; Lt., left; Rt., right.

Kaplan-Meier curve analysis was performed to compare the outcomes of DFS and OS according to the differences in surgical interventions, presented in Fig. 2. The analysis showed that surgical interventions such as conservative, comprehensive and staging surgery did not cause statistically significant differences in DFS (p = 0.592, log-rank test) and OS (p = 0.807, log-rank test).

To explore the risk factors affecting recurrence of BOTs, we performed univariate analysis using Cox proportional hazards presented in Table 3. Risk factors associated with the recurrence of BOTs included positive washing cytology (HR, 30.02; 95% CI, 3.084, 292.210; p = 0.003) and intraoperative iatrogenic rupture (HR, 5.19; 95% CI, 1.006, 26.765; p = 0.049). In addition, univariate analysis utilizing the Cox proportional hazards model was undertaken to identify risk factors influencing OS of BOTs. However, no statistically significant risk factors correlating with OS of BOTs were observed. We further explored the risk factors associated with recurrence of BOTs by multivariate analysis using Cox proportional hazards adjusted in Table 3. The results showed that the risk factors associated with recurrence of BOTs included washing cytology (HR, 36.02; 95% CI, 6.798, 641.204; p = 0.003) and intraoperative iatrogenic rupture (HR, 5.89; 95% CI, 1.003, 27.640; p = 0.046), similar to the results of the univariate analysis using Cox proportional hazards.

As a result of Cox proportional hazard analysis, washing cytology positive and intraoperative iatrogenic rupture were identified as risk factors for the recurrence of BOTs, so we compared the degree of occurrence of washing cytology positive and intraoperative iatrogenic rupture according to the difference of surgical interventions and surgical approach methods. There was no statistically significant difference observed in the incidence of positive washing cytology or intraoperative iatrogenic rupture when comparing various surgical interventions, such as conservative surgery, comprehensive surgery and staging surgery, as well as different surgical approaches, including LESS, LPS, robot and laparotomy.

4. Discussion

The results of this study confirmed that the surgical treatment of BOTs with conservative surgery, comprehensive surgery and staging surgery did not lead to statistically significant differences in disease outcomes such as DFS and OS. The mean age of the patients in this study was 46.45 ± 16.34 years, and the majority of patients were under the age of 45, which is the age of women of reproductive age, so conservative surgery should be considered for fertility preservation rather than comprehensive surgery or staging surgery when planning surgical treatment for BOTs. In the NCCN guidelines regarding the surgical management of BOTs, various surgical approaches are delineated, including observation, fertility-sparing, comprehensive and staging surgery [10]. However, the specific surgical intervention employed in each clinical scenario remains equivocal.

During our study's follow-up, 7 patients (3.9%) exhibited disease recurrence. This aligns with rates from Kim *et al.* [11] (3.7%) and Plett *et al.* [12] (5.1%). Kim *et al.* [11] found no post-operative residual disease for BOTs, mirroring our results. In Plett *et al.*'s [12] study, one patient who underwent USO for fertility preservation had a residual lesion but no recurrence over 3 years. Conversely, Trillsch *et al.* [13] observed a 7.8% recurrence rate after BOTs surgery. Of their 950 patients, 74 faced BOTs recurrence, with approximately two-thirds having post-operative residual ovarian lesions. The influence of such lesions on recurrence remains uncertain. Future studies should probe the impact of surgical methods and post-surgery residuals on recurrence.

We categorized surgical interventions into conservative surgery, comprehensive surgery and staging surgery. Comparing the recurrence rates after conservative surgery and staging surgery, we found that 6 out of 130 patients who underwent conservative surgery had recurrence (4.61%), and none of the 21 patients who underwent staging surgery had recurrence (0%). In other words, although there is no statistical difference, the results of this study show that the recurrence rate after conservative surgery is higher than the

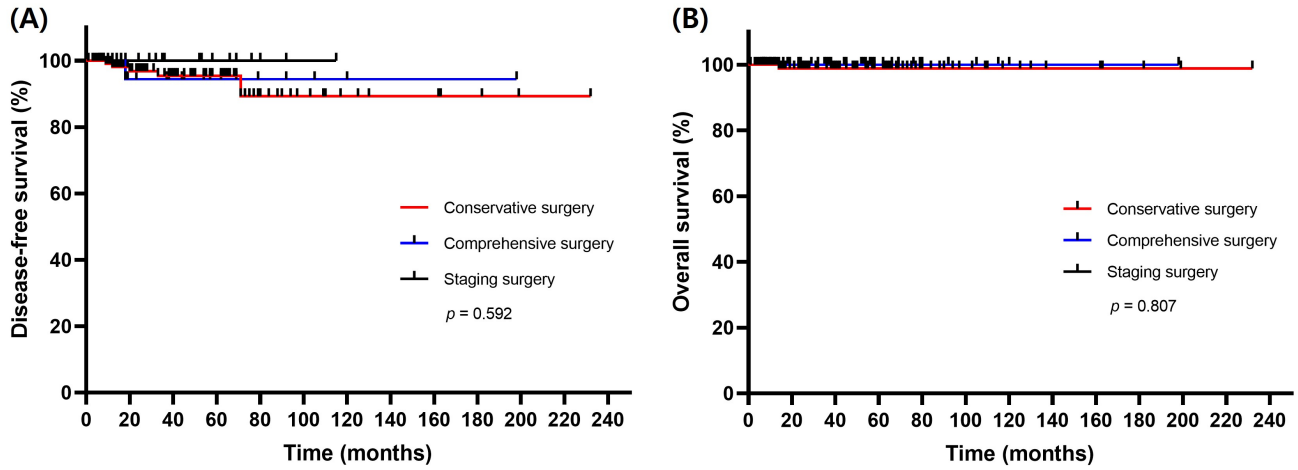

FIGURE 2. Survival plot by type of surgical interventions according to the Cox proportional hazard model. (A) Disease-free survival plot (B) Overall survival plot.

TABLE 3. Cox proportional hazards of disease-free survival in univariate analysis and multivariate analysis.

	Risk factors for DFS					
	HR	95% CI	*p*-value	HR*	95% CI	*p*-value
Age	0.98	(0.928, 1.033)	0.433	0.97	(0.916, 1.036)	0.407
Height	1.01	(0.885, 1.149)	0.900	0.98	(0.839, 1.137)	0.760
Weight	1.05	(0.969, 1.127)	0.250	1.05	(0.975, 1.130)	0.201
BMI	1.10	(0.917, 1.319)	0.303	1.13	(0.952, 1.329)	0.167
Parity						
Nulliparous	1.00	Reference		1.00	Reference	
Multiparous	0.89	(0.199, 3.977)	0.878	1.63	(0.209, 12.612)	0.642
Menopausal state						
Premenopausal	1.00	Reference		1.00	Reference	
Postmenopausal	0.29	(0.034, 2.427)	0.253	0.24	(0.015, 3.839)	0.314
Comorbidity						
None	1.00	Reference		1.00	Reference	
Cardiovascular	1.99	(0.224, 17.666)	0.536	4.22	(0.323, 54.954)	0.272
DM	0.00	(0.000, 0.000)	0.994	0.00	(0.000, 0.000)	0.994
Others	3.15	(0.366, 27.021)	0.296	4.72	(0.491, 45.366)	0.179
Previous abdominal surgery history						
No	1.00	Reference		1.00	Reference	
Yes	3.28	(0.635, 16.926)	0.156	5.19	(0.842, 32.019)	0.076
Tumor marker						
CA 125	0.99	(0.966, 1.017)	0.507	0.99	(0.963, 1.018)	0.499
CA 19-9	1.00	(0.998, 1.001)	0.723	1.00	(0.998, 1.001)	0.725
CEA	0.99	(0.984, 1.015)	0.901	1.00	(0.985, 1.014)	0.921
Location						
Unilateral	1.00	Reference		1.00	Reference	
Bilateral	2.49	(0.299, 20.764)	0.399	2.40	(0.280, 20.053)	0.418
Largest BOT size	1.02	(0.944, 1.108)	0.584	1.02	(0.938, 1.103)	0.681
Stage						
I	1.00	Reference		1.00	Reference	
II	0.00	(0.000, 0.000)		0.00	(0.000, 0.000)	
III	0.00	(0.000, 0.000)		0.00	(0.000, 0.000)	
IV	0.00	(0.000, 0.000)		0.00	(0.000, 0.000)	
Histology						
Serous	1.00	Reference		1.00	Reference	
Mucinous	20.28	(1.254, 327.726)	0.034	18.28	(1.123, 297.433)	0.041
Endometrioid	2.52	(0.292, 21.800)	0.400	2.45	(0.283, 21.270)	0.416
Seromucinous	0.00	(0.000, 0.000)	0.991	0.00	(0.000, 0.000)	0.991
Clear cell	0.00	(0.000, 0.000)	0.998	0.00	(0.000, 0.000)	0.998
Surgical approach						
LESS	1.00	Reference		1.00	Reference	
LPS	1.07	(0.209, 5.446)	0.939	1.10	(0.215, 5.576)	0.912
Robot	0.00	(0.000, 0.000)	0.987	0.00	(0.000, 0.000)	0.987
Laparotomy	0.30	(0.030, 2.885)	0.295	0.33	(0.033, 3.383)	0.353

TABLE 3. Continued.

Risk factors for DFS						
	HR	95% CI	*p*-value	HR*	95% CI	*p*-value
Surgical interventions						
Conservative surgery	1.00	Reference		1.00	Reference	
Comprehensive surgery	0.84	(0.101, 7.013)	0.874	1.17	(0.117, 11.708)	0.895
Staging surgery	0.00	(0.000, 0.000)	0.986	0.00	(0.000, 0.000)	0.986
Washing cytology						
Negative	1.00	Reference		1.00	Reference	
Positive	30.02	(3.084, 292.210)	0.003	36.02	(6.798, 641.204)	0.003
Intraoperative iatrogenic rupture						
No	1.00	Reference		1.00	Reference	
Yes	5.19	(1.006, 26.765)	0.049	5.89	(1.006, 26.640)	0.046
Endometriosis						
No	1.00	Reference		1.00	Reference	
Yes	1.23	(0.146, 10.392)	0.847	1.10	(1.128, 9.393)	0.932
Microinvasion						
No	1.00	Reference		1.00	Reference	
Yes	3.54	(0.789, 15.846)	0.099	3.53	(0.787, 15.807)	0.100
Ovarian surface involvement						
No	1.00	Reference		1.00	Reference	
Yes	0.05	(0.000, 1.924)	0.692	0.05	(0.000, 1.925)	0.692

Note: HR, hazard ratio; HR, hazard ratio adjusted for age variable; CI, confidence interval; DFS, disease-free survival; BMI, body mass index; DM, diabetes mellitus; LESS, laparoendoscopic single site; LPS, laparoscopy; CA, cancer antigen; CEA, carcinoembryonic antigen; BOT, borderline ovarian tumor.*

recurrence rate after staging surgery. Similar to this study, Plett *et al.* [12] found that the recurrence rate of BOT after fertility preservation surgery, which is the concept of saving at least one ovary, was 13/95% (13.7%), and the recurrence rate after radical surgery was 5/257 (1.9%), indicating that the recurrence rate of fertility preservation surgery was relatively higher than that of staging surgery. In general, the incidence on these rates, our results show a relatively low recurrence rate after conservative surgery and staging surgery. These results may differ from other studies in that the patients in this study were in the early stage, and the surgical skill of the surgeons may also be reflected, resulting in a trend toward lower recurrence rates compared to other studies. In the study by delle Marcchette *et al.* [14], recurrence rates of BOT after performing ovarian cystectomy and salpingo-oophorectomy were found to be 39.8% (105/264) and 32.1% (87/271), respectively. Notably, the recurrence rate was relatively higher following ovarian cystectomy compared to salpingo-oophorectomy. However, if one follows the definition as in our study and in the research by Plett *et al.* [12], where conserving at least one ovary is categorized as conservative surgery or fertility preservation surgery, then the patients who underwent unilateral salpingo-oophorectomy in the delle Marchette *et al.* [14] study would be included under conservative or fertility preservation surgery. This means the criteria for comparison change. Given such variations in defining comparison groups across studies, it is unsurprising that the findings of delle Marcchette *et al.* [14] differ from the results of our study.

Similar to our study, several studies have compared the outcomes of BOTs with surgical interventions. However, the results are not consistent. Notably, several studies have reported that conservative fertility surgery as a surgical treatment for BOTs is feasible and relatively safe [11, 15–17]. A retrospective study by Oh *et al.* [15] categorized surgical interventions as conservative surgery, comprehensive surgery and staging surgery for the surgical treatment of BOTs, similar to our study, and identified factors involved in the recurrence of BOTs. They reported that differences in surgical interventions did not affect the recurrence of BOTs, consistent with our results. Kim *et al.* [11] subdivided conservative surgery for BOTs patients into ovarian cystectomy and oophorectomy and compared the surgical outcomes of each group. As a result, they showed no deaths after BOTs treatment and that surgical methods such as cystectomy and oophorectomy did not cause significant differences in DFS. Therefore, they argue that cystectomy and oophorectomy can be a safe and effective surgical treatment options in young women with BOTs [11]. Tsai *et al.* [16] compared the recurrence rates, postoperative menstrual cycle recovery, and pregnancy success between groups that

underwent fertility preservation surgery and staging surgery to treat BOTs. Among 61 participants, recurrence of BOTs was observed in seven patients who received fertility preservation surgery, five of which had undergone ovarian cystectomy, and two had undergone unilateral salpingo-oophorectomy. However, the restoration of regular menstrual cycles in the group that underwent fertility preservation surgery was confirmed, and nine of the 31 patients with preserved fertility had positive pregnancy outcomes, suggesting that fertility preservation may be an acceptable surgical option for younger patients with BOTs who wish to preserve their fertility [16]. A review article by Cadron *et al.* [17] compared recurrence rates after adnexectomy, ovarian cystectomy and staging surgery as surgical treatments for BOTs. In contrast to our results, Cadron *et al.* [17] found that recurrence rates were lower in the staging surgery group than in the adnexectomy and ovarian cystectomy group (adnexectomy group, 0%–20%; ovarian cystectomy group, 12%–58%; staging surgery group, 2.5%–5.7%). However, it was noted that the recurrence of BOTs occurred approximately 39 years after the primary surgical treatment. Therefore, it was recommended that fertility preservation surgeries such as adnexectomy and ovarian cystectomy are feasible for patients with stage 1 BOTs. Staging surgery should be considered for patients with more advanced stages of BOTs as long as careful surveillance with imaging studies such as ultrasound is performed to prevent recurrence during the long DFS period [17].

In contrast to our findings, other studies have reported significant differences in recurrence rates of BOTs based on surgical interventions [18, 19]. A retrospective study by Helpman *et al.* [18] compared the outcomes of patients with BOTs who underwent fertility preservation surgery with those who did not. Higher stages were associated with a significantly higher risk of recurrence of BOTs (HR, 4.15; 95% CI, 2.3–7.6; $p < 0.001$), with 133 of 213 patients in stage IA to stage IB, and 73 of 213 patients in stage IC to stage III. The risk of recurrence was significantly higher in the group that underwent fertility preservation surgery than in the group that did not (HR, 2.57; 95% CI, 1.1–6.0; $p = 0.029$) [18]. In our study, all BOT patients were stage 1 at the time of primary surgery, whereas the patient population in the Helpman *et al.* [18] study included stage 1 BOT patients and stage 2 and 3 patients. We cannot exclude the possibility that these differences in patient demographics may have led to different outcomes after surgical treatment compared with our study. Ifthikar *et al.* [19] defined and categorized surgical interventions for BOTs as follows (conservative surgery, saving at least one ovary; fertility-sparing surgery, saving at least one ovary with preservation of the uterus; staging surgery, BSO ± hysterectomy with omentectomy, peritoneal washing cytology, peritoneal biopsy, appendectomy) and evaluated whether the type of surgical intervention affected recurrence of BOTs. Ifthikar *et al.* [19] found that conservative surgery resulted in a DFS of 71 months, fertility-sparing surgery resulted in a DFS of 97 months, and staging surgery resulted in a DFS of 103 months, a significant difference ($p < 0.05$) [19]. The classification of surgical interventions in Ifthikar *et al.* [19] differs from the definition and classification of surgical interventions in our study. The difference was not statistically significant; however, recurrence occurred in 7 of 44 surgeries (15.9%) performed by non-oncologic surgeons and 8 of 59 surgeries (13.6%) performed by oncologic surgeons in the Ifthikar *et al.*'s [19] study ($p = 0.783$). It cannot be excluded that differences in the definition and classification of these surgical interventions and in surgeons' surgical skills may affect the outcomes related to BOT recurrence. In du Bois *et al.*'s [5] retrospective-prospective study, they assessed how fertility preservation and staging surgeries impacted BOT recurrence. Their results showed a higher recurrence risk with fertility preservation surgery (HR, 3.483; 95% CI, 2.228, 5.444; $p < 0.0001$) and incomplete staging surgery (HR, 2.174, 95% CI, 1.314, 3.596; $p = 0.0025$) [5]. In the study by du Bois *et al.* [5] staging surgery was defined as omentectomy, peritoneal biopsy, cytology and in the case of mucinous BOT additionally appendectomy. If all of these criteria were met, it was considered complete staging surgery, and if any of them were not met, it was considered incomplete staging surgery [5]. In this study, staging surgery was defined as hysterectomy, BSO, lymph node dissection, omentectomy and appendectomy. In addition, all patients in this study were stage I, whereas 82.3% of patients in the retrospective-prospective study were stage I, 7.6% were stage II, and 10.1% were stage III. It is possible that the different distribution of BOT stages in the study population, as well as differences in the procedures defined as staging surgery, may have contributed to the differences in the results of the impact of surgical interventions on BOT recurrence in our study.

We found no association between the surgical approach (laparoscopy, robotic surgery, laparotomy) and the outcome of BOTs. Although minimally invasive surgery (MIS) has the disadvantage of a relatively high incidence of complications such as bowel injury, bladder injury and subcutaneous emphysema compared to laparotomy surgery, it has recently gained attention for its advantages of minimal incision, less pain and shorter hospital stay [20]. However, there is a debate about the appropriateness of a laparotomy approach to surgically treating BOTs versus a surgical approach using MIS such as laparoscopy or robotic surgery. In several studies comparing the outcomes of surgical approaches for BOTs, such as laparotomy surgery versus MIS techniques, findings were consistent with our study, demonstrating no statistically significant differences [11, 19, 21]. These reports suggest that MIS approaches are feasible options for the surgical management of BOTs. Kim *et al.* [11] found no significant difference in the HR for the recurrence of BOTs between MIS and laparotomy methods (HR, 0.614; 95% CI, 0.112–3.353; $p = 0.573$) [11]. Another retrospective study has confirmed that the difference between MIS and laparotomy surgical approaches did not affect the recurrence rate of BOTs (MIS, 6/26 (23.1%); open, 9/77 (11.7%)) [15, 19]. A retrospective study by Seracchioli *et al.* [21] compared differences in surgical approaches and recurrence rates of BOTs in patients with early stage BOTs. They found no significant association between laparoscopic surgery versus laparotomy surgery and recurrence and reported a favorable outcome with 10 patients, 53% of the total, achieving pregnancy after surgical treatment [21]. However, the number of patients in the retrospective study by Seracchioli *et al.* [21] was insufficient to establish statistical significance,

given that the total number of patients in the study was 19.

Contrary to the findings mentioned earlier, some studies have reported that patients who underwent laparoscopic surgery to treat BOTs faced a higher risk of recurrence than those who received laparotomy surgery [15, 22]. In Oh *et al.*'s [15] retrospective study, they discovered that the recurrence rate after laparoscopic treatment for BOTs was statistically significantly higher compared to instances in which laparotomy surgery was carried out ($p = 0.013$) [15]. A multicenter Italian study reported a higher recurrence rate with the laparoscopic approach to BOTs than with the laparotomy approach (laparoscopy, 7/52 (13%); laparotomy, 6/61 (10%); p = no significance (NS)), as well as a higher degree of intraoperative BOT rupture and spilling of cyst contents (laparoscopy, 4/61 (7%); laparotomy, 18/52 (34%); $p < 0.0001$) [22].

There is no consensus on whether intraoperative iatrogenic rupture of BOTs, resulting in spillage of BOT contents into the pelvic or abdominal cavity, affects the recurrence of BOTs in the future. According to the research findings by Casari *et al.* [23], for huge BOTs larger than 10cm, the incidence of intraoperative spillage was higher when laparoscopic surgery was performed compared to laparotomy surgery (laparoscopy, 167/285 (58.6%); laparotomy, 7/45 (15.6%); $p < 0.001$). Furthermore, a multicenter study reported a significantly increased occurrence of BOTs rupture during laparoscopic surgery compared with laparotomy surgery (laparoscopy, 33.9%; laparotomy, 12.4%; $p < 0.001$). However, in these studies, the presence of such ruptures did not have a significant impact on recurrence rates [23, 24]. In case of intraoperative iatrogenic rupture during surgery of ovarian tumor lesions, sufficient suction and irrigation of the pelvic and abdominal cavities are recommended to alleviate problems such as recurrence, as well as the use of an endo bag to minimize and prevent contents spillage during the evacuation of ovarian tumor lesions [21, 25]. However, the occurrence of intraoperative iatrogenic rupture or a positive washing cytology result, as seen in the study, can significantly impact the risk of recurrence of BOTs. For this reason, the ovarian tumor staging FIGO stage IC also subdivides and de-fines the classification as follows; IC1: surgical spill or the occurrence of a tumor rupture during surgery, IC2: capsule ruptured before surgery or tumor on the ovarian or fallopian tube surface, IC3: malignant cells in the ascites or peritoneal washings [26]. Intra-operative washing cytology is frequently utilized in ovarian tumor surgeries for several key advantages; it allows for easy specimen collection using affordable equipment, results in minimal tissue damage, and offers the potential to identify variable elements within large tissue fragments [27]. In a study by Naz *et al.* [28] assessing the correlation between positive washing cytology, ovarian tumor type and tumor invasion, it was found that 76.9% of serous carcinoma cases exhibited positive washing cytology, a rate higher than that of endometrioid carcinoma (44%) and mucinous carcinoma (25%). Moreover, a statistically significant association was observed between positive washing cytology, capsule invasion and omental metastasis ($p < 0.001$) [28]. Therefore, regardless of whether the surgical treatment is performed using a MIS approach or a laparotomy method, it is crucial to reduce the occurrence of iatrogenic rupture and content spillage in the surgical field.

Although we did not observe age as a statistically significant risk factor for recurrence of BOTs in this study, age is generally recognized as a risk factor for invasive tumor transformation. Three of the seven patients with BOT recurrence or malignant transformation in this study had malignant transformation. One in three died after malignant transformation. The results of existing published studies on age and transition to invasive tumor are not all consistent, but report the following trends. Song *et al.* [29] analyzed the risk factors for recurrence and disease-related death of BOT using HR. The results showed that the risk of recurrence of BOTs as well as the risk of disease-related death was increased in patients aged 65 and older [29]. This is similar to the 73-year-old woman of case 3 in this paper, who was one of the seven cases with recurrence BOTs who had a malignant transformation and was subsequently confirmed dead. Several studies have indicated that individuals over 40 have an elevated risk of malignant transformation in BOTs [13], and that the recurrence of BOTs also heightens the risk factors leading to mortality [30]. This is similar to case 4, who was 48-year-old among the seven patients with BOT recurrence and malignant transformation in this study. In BOTS or low-grade serous carcinomas, mutations in Kristen rat sarcoma viral oncogene homolog (*KRAS*), v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) and v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (*ERBB2*) are commonly observed. The frequency of these oncogenic mutations tends to increase with age [13]. This characteristics of BOTs supports findings suggesting a higher risk of recurrence and malignant transformation in individuals over 40. While our study generally aligns with this observed trend, it suggests the necessity for further evaluation involving a larger cohort of BOTs patients to more comprehensive assess the relationship between age and the risk of BOTs recurrence or malignant transformation. Further prospective studies can be planned on the aforementioned topics with the selection criteria of patients with BOT diagnosed by pathological examination after surgical treatment and no loss of follow-up during the 5-year follow-up period.

This study has several limitations. First, as a retrospective study, selection bias might have been induced during the selection process. Second, because it was designed as a retrospective study, there are limitations in performing longitudinal follow-ups for each patient. Third, conservative surgery, comprehensive surgery and staging surgery, presented as the suggested surgical interventions for BOTs in this study, were performed by several surgeons in the Department of Obstetrics and Gynecology at Korea University Anam Hospital, which may reflect heterogeneity in surgical outcomes. Fourth, this study was conducted at a single institution, and the number of study participants is smaller than the number of subjects in multicenter studies. For this reason, the statistical results of this study are limited in their generalizability to surgical interventions and risk factors affecting the outcome of BOTs. However, this study is significant in that it is a retrospective, observational-based study that showed trends in surgical interventions affecting the outcome of BOTs and the risk factors affecting recurrence of BOTs.

Nevertheless, the strength of this study is that it evaluated the

impact of surgical interventions categorized as conservative surgery, comprehensive surgery and staging surgery on the outcomes of BOTs and explored risk factors associated with the recurrence of BOTs. Although surgical treatment options for BOTs are mentioned in the NCCN guidelines, indications for specific surgical interventions are not established. In addition, clinical evidence on which surgical interventions are appropriate is lacking, and the results are not consistent. Therefore, it is important to report the results that various surgical interventions did not affect the DFS and OS of BOT patients, suggesting that surgical methods such as conservative surgery and comprehensive surgery can be considered and feasible even if not staging surgery, depending on the age and fertility of the patient.

5. Conclusions

The study found that differences in surgical interventions such as conservative surgery, comprehensive, and staging surgery, for treating of early stage BOTs did not affect BOTs' recurrence and outcomes. In addition, intraoperative iatrogenic rupture and positive washing cytology results were identified as risk factors for the recurrence of BOTs. Therefore, according to the patient's age with BOTs and the need for fertility preservation, surgical treatment such as conservative and comprehensive surgery may be feasible options in addition to staging surgery. Also, to reduce the risk of recurrence of BOTs, intraoperative iatrogenic rupture of the lesion should be avoided, and more careful postoperative follow-up is required for patients with positive washing cytology results or intraoperative iatrogenic rupture of BOTs.

ABBREVIATIONS

BOT, Borderline ovarian tumor; DFS, Disease-free survival; OS, Overall survival; HR, Hazard ratio; CI, Confidence interval; FIGO, International Federation of Gynecology and Obstetrics; NCCN, National comprehensive cancer network; CT, Computed tomography; LESS, Laparoendoscopic single site; LPS, Laparoscopy; BMI, Body mass index; CA, Cancer antigen; CEA, Carcinoembryonic antigen; RSO, right salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; ECT, Enhanced computed tomography; IRB, Institutional Review Board; FU, Follow-up; DM, Diabetes mellitus; MIS, Minimally invasive surgery; NS, No significance.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding authors.

AUTHOR CONTRIBUTIONS

SML and SL—conceptualization, writing-review and editing; SML, AS and KJM—data curation; SML, SL and JYS—formal analysis; SML, AS and HWC—writing-original draft preparation; SML and SL—writing review and editing; SML, JHH, JKL, KJM and NWL—visualization; SL—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in according to the guidelines of the Declaration of Helsinki (IRB number: 2023AN0090 and date of approval: 07 June 2023). This study is a retrospective study using anonymized data that does not include patient personal information, and informed consent was withdrawn from the participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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