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Is There Re-Staging Surgery Necessity for Women with Borderline Ovarian Tumors

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Abstract

Purpose: To assess the necessity of re-staging surgery in women with Borderline Ovarian Tumors (BOTs) and to evaluate the impact of complete surgical staging, lymphadenectomy or omentectomy on disease recurrence and survival.

Methods: We retrospectively reviewed the medical records of patients with BOTs. A total of 901 patients were eligible for the study. Some of the variables, clinical and surgical characteristics of the cases were evaluated. The effects of type of surgery procedures, surgical staging, complete or incomplete staging on prognosis were calculated. The disease-free survival, overall survival and recurrence rates were compared. COX regression analysis was employed to identify potential prognostic factors. Survival curves were constructed using Kaplan-Meier method.

Results: The overall recurrence rate was 13.9%. Recurrence rates were comparable within complete surgical staging group or incomplete groups (p>0.05). But performance complete staging surgery has not been shown to reduce long-term survival. Complete surgical staging, omentectomy and lymphadenectomy didn't cause any difference on survival. In multivariate analyses, only performance of radical surgery and adjuvant chemotherapy were risk factors for the recurrence of BOTs. Furthermore, we found that omentectomy lead to a relative lower recurrence rate in patients FIGO stage >I (p=0.022).

Conclusion: Our study suggests that complete staging surgery should be considered as a standard treatment for patients with advanced stage BOTs but not stage I. It might be safe to shrink the scope of the surgical procedures in early-stage BOT patients. There is no necessity to do restaging operations for BOT with macroscopically normal ex-ovarian appearance.

Keywords: Borderline ovarian tumor; Staging surgery; Management; Recurrence

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Abbreviations

BOT: Borderline ovarian tumor; OS: Overall Survival; DFS: Disease Free Survival; Lymn: Lymph node; FIGO: International Federation of Gynecology and Obstetrics

Introduction

Borderline Ovarian Tumors (BOTs) account for 10% to 20% of ovarian malignancies. BOTs have histologic features and biological behavior between benign and frankly malignant epithelial ovarian neoplasms [1,2]. The majority of women with BOTs have significantly better survival rates. Currently, the mainstay of the management for BOTs when fertility preservation is desired remains conservative surgery regardless of cancer stage [3]. Otherwise, complete staging surgery is recommended which defined as hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and resection of macroscopically visible peritoneal lesions, lymphadenectomy as well.

The preoperative diagnosis of Borderline Ovarian Tumors (BOT) is typically limited by unspecific clinical symptoms and lack of effective diagnostic means. Therefore, surgical decisions are established intraoperatively *via* the frozen section. Nevertheless, intraoperative frozen section evaluation is less sufficient and accurate for diagnosing BOTs because of its high false diagnosis rate [4-6]. So, the primary surgical procedures for BOT patients frequently results in unstaged surgery leading to a second surgical procedure to complete surgical staging. However, in spite of the high remission rate of BOT, more attention needs to be paid in lessening long-term effects associated with treatment. Comprehensive surgical staging has raised much controversy in recent years [7-9]. The most debate issue remains comprehensive surgical staging may result in lymphatic cyst,

transverse colon or stomach injury, hemorrhage from a gastrocolic ligament ligature, or possible splenic injury and so on, which adding risks of surgical mortality and benefits for staging information. Therefore, it is important to reduce the scope of surgery by aiming for high cure rate.

Little is known about the prognostic impact of each individual staging procedure in BOT. However, this information is importance when counseling BOT patients after incomplete surgical staging, especially for younger BOT patients who desire to preserve fertility [10]. Therefore, we performed a retrospective study exploring the impact of each individual staging procedure on prognosis of patients with BOT, and to evaluate how often microscopic disease is found in healthy-looking tissues in operations for BOT, in order to provide evidence for clinical clinicians determining treatment strategies for patients with BOT.

Patients and Methods

Patients

Patients with BOT were admitted in the Department of Obstetrics and Gynecology of Tongji Hospital from January 2003 to December 2018 and were taken into account for analysis. All the clinical records were carefully reviewed and the pathological diagnoses verified. Our study was confined to original BOTs, only cases with a finally confirmed diagnosis of BOT were included in the present analysis. So, we excluded some applicable patients such as primary gastrointestinal, and the patients combined with breast cancer or adenocarcinoma. The study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology.

Treatment and follow-up

Therapeutic strategies were documented according to patients' charts and surgery reports and aligned with pathology reports. Staging quality was considered adequate following NCCN guidelines, if the following procedures were performed: bilateral salpingo-oophorectomy for patients older than 50 years or for younger patients without attempted organ preservation, omentectomy or omentum biopsy, peritoneal biopsies, and peritoneal cytology. It was assumed that fertility-sparing surgery had been intended in patients who were younger than 40 years at diagnosis and had the uterus and at least parts of one ovary left after operation.

Patient follow-up were evaluated every 3 months for the first years after surgery, every 6 months for 2 years and then yearly subsequently.

Statistical analysis

We used SPSS 22.0 for the statistical analysis. Descriptive data are presented as frequencies and percentages. Patient characteristics in the two groups were compared using X^2 test. Survival was calculated using the Kaplan-Meier method and compared using the log-rank test. Cox's proportional-hazards regression model was used to adjust for possible prognostic factors and $P<0.05$ was considered statistically significant.

Results

Patient characteristics

During the study period, a total of 901 patients met the inclusion criteria for further analysis. Patient selection schema is shown in Figure S1. The median age at diagnosis was 38.2 years (range: 11-87 years). The majority of patients were diagnosed in FIGO stage I (82.2%), stage II (6.4%), stage III (11.3%), respectively. About half of the tumors (452, 50.2%) were of mucinous histology. Microinvasion was reported in 80 (8.9%) of the BOTs. The demographic and clinicopathologic characteristics are presented in Table 1.

A clear correlation between different staging procedures and histologic subtype or FIGO stage was found in Table 2. 478 (53%) patients underwent complete staging surgery, especially for advanced stage BOTs. Independently of each other, omentectomy was performed in 567 patients (62.9%), and omental involvement was seen in 70 patients. Appendectomy was performed in 257 patients (28.5%) with appendiceal involvement in only 6 patients. Lymphadenectomy

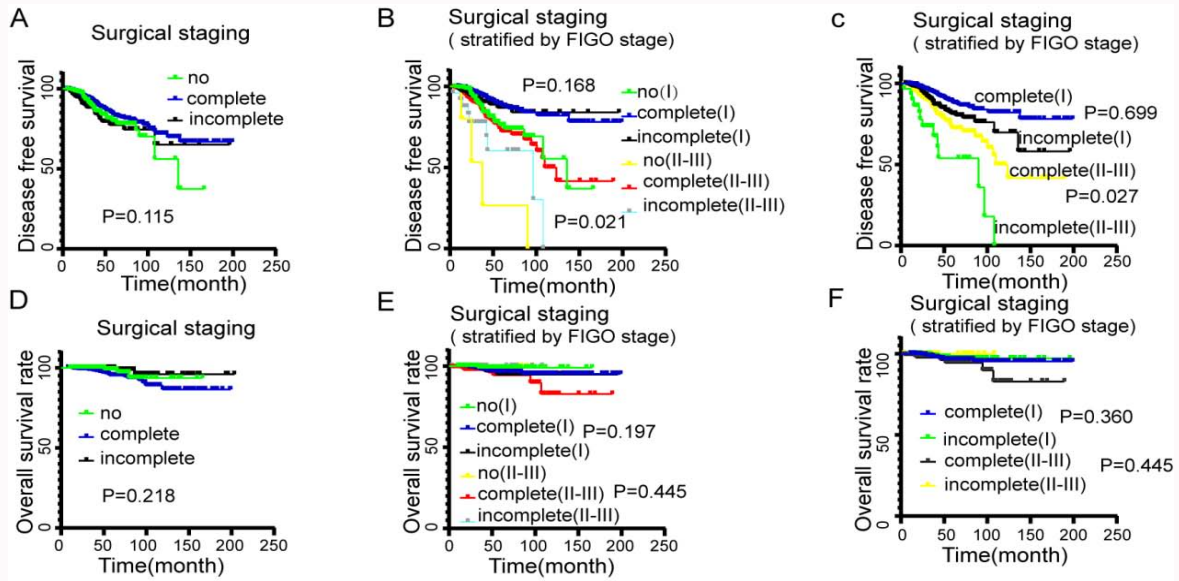

Figure 1: The DFS and OS of patients with BOTs treated different surgical staging.
a/d. Comparing DFS and OS rates among complete staging surgery, incomplete staging or no staging surgery; b/e. Comparing DFS and OS rates among different staging surgery stratified by FIGO stage; c/f. Comparing DFS and OS rates between complete staging surgery and incomplete staging surgery stratified by FIGO stage (patients divided into two groups according to whether do complete staging surgery, put the no staging surgery patients into incomplete staging surgery group).

Table 1: Demographic and clinical characteristics of 901 patients with BOTS.

Variable		NO
Age at first diagnosis	<40	527 (58.5%)
	≥ 40	374 (41.5%)
Tumor size	<10 cm	449 (49.8%)
	≥ 10 cm	452 (50.2%)
Histology	Serous	389 (43.2%)
	Mucinous	452 (50.1%)
	Others	60 (6.7%)
Pathological stage	Stage I	741 (82.2%)
	Stage II	58 (6.4%)
	Stage III	102 (11.4%)
Histologic characteristics	microinvasion	73 (8.1%%)
	No-Invasive implants	67 (7.4%)
	Invasive implants	107 (11.9%)
Surgical procedures	Laparoscopy	586 (65.0%)
	Laparotomy	315 (35.0%)
Surgical staging	Complete	478 (53.1%)
	Incomplete	209 (23.2%)
	No	214 (23.7%)
Up-staging re-staging surgery	Yes	33 (15.3%)
	No	182 (84.7%)
Surgery radicality	Fertility-sparing	464 (51.5%)
	Radical surgery	437 (48.5%)
Lesion lateral	Unilateral	677 (75.1%)
	Bilateral	224 (24.9%)
Omentectomy	Yes	567 (62.9%)
	No	334 (37.1%)
Lymphadenectomy	Yes	466 (51.7%)
	No	435 (48.3%)
Appendectomy	Yes	257 (28.5%)
	No	644 (71.5%)
Adjuvant chemotherapy	Yes	146 (16.2%)
	No	755 (83.8%)

was performed in 466 patients (51.7%), with positive lymph node in 39 patients. Patients undergoing complete staging surgery were diagnosed in higher FIGO stages and more serious histology. Omentum/peritoneal implants were found in women with serous tumors more than in other histologic subtype, there was statistic significant. There was no correlation between radical surgery and upstaging because of disease found in macroscopically normal-looking tissues (P=0.380).

Treatment outcomes

Total of 901 patients were included in our study and 687 (76.3%) patients underwent some degree of staging procedure. Complete staging procedures were performed in 478 patients (53%) either at primary surgery (n=263, 29.1%) or at a later staging operation (n=215, 23.9%) after BOT had been diagnosed. In other 214 (23.8%) patients no staging procedure was performed, only underwent ovarian cystectomy or unilateral salpingo-oophorectomy, because no macroscopic abnormalities in the omentum and pelvic peritoneal surface were seen. Meanwhile the patients desire to preserve fertility. Of the 901 post-patients, 146 (21.6%) underwent chemotherapy, especially in invasion implanted histological patients. The histologic and cytologic examinations led to upstaging in 33 cases (15.3%). Of these 33 patients, 20 had microinvasion omentum/peritoneal implants (10 with non-invasive histology, 5 with invasive histology, 10 patients with both positive lymph node and non-invasive/invasive omentum/peritoneal implants). Three cases had positive ascites cytology. The remaining 10 patients were up-staged because of positive lymph node involvement of the BOT. Upstaging occurred more frequency in women with serous BOT than no-serous BOT (28 *vs.* 5, P<0.001). In 29 of the 33 cases of upstaging, the woman received complete staging procedures.

The median follow-up period for the 901 patients was 62 months (range from 8 to 203 months; 95% CI, 15-89 months). The overall recurrence rate of the total cohort was 13.9%, 27 of 125 patients (21.6%) with recurrent disease experienced malignant transformation.

We next analyzed the patients by dividing them into two groups according to surgical staging. The recurrence rate in patients undergoing complete staging surgery had the similarities compared to incomplete staging surgery (14.0% *vs.* 13.7%, P=0.895). However, when stratified by FIGO stage to analyze, we found patients undergoing complete staging surgery had a relative lower recurrence rate compared with patients without complete staging surgery in patients FIGO stage >I (26.0% *vs.* 44.8%, P=0.027), showed in Figure 1.

Patients undergoing omentectomy were diagnosed in higher FIGO stages compared with patients without omentectomy (FIGO stage >I 26.1% *vs.* 3.6%, P<0.001, Table 3) and presented with higher rates of peritoneal/omentum implants. The recurrence rate in patients undergoing omentectomy/without omentectomy were 85.5% and 87.1%, respectively. However, when stratified by FIGO stage to analyze, we found patients undergoing omentectomy had a relative lower recurrence rate compared with patients without omentectomy in patients FIGO stage >I (27.0% *vs.* 58.3%, P=0.022), showed in Table 3 and Figure 2. However, there is no significance in FIGO stage I, the recurrence rate were 9.8% and 11.5%, respectively. Patients undergoing omentectomy were slightly younger (48 *vs.* 53 years, P=0.029), but a fertility-preserving approach was performed significantly less frequently in these patients. For 83.2% of patients with omentectomy, the surgical staging was assessed to be adequate after primary and restaging surgery.

Among the 466 patients who underwent lymphadenectomy, lymph node involvement was present in only 39 (8.4%) of them. The recurrence rate in patients undergoing lymphadenectomy/ without lymphadenectomy were 86.7% and 85.5%, respectively. It exhibited that surgical staging with lymphadenectomy does not improve survival. Meanwhile, we found the disease-free survival of patients with positive lymph node was the same as that of patients with negative lymph node (87.2% *vs.* 87.0%). The effect of lymphadenectomy and lymph node involvement is not a prognostic factor for BOTs (Table S1 and Figure S2).

The results of the univariate and multivariate analyses for recurrence are shown in Table S2. In the univariate analysis, performance of surgical staging or not, omentectomy and lymphadenectomy were not independent prognostic factors for recurrence. Only performance of radical surgery, FIGO stage, lesion lateral, presence of implants and adjuvant chemotherapy were risk

Table 2: Results of different staging procedures according to the FIGO stage and histology type.

		FIGO staging			Histology		
		I	II	III	Serous	Mucinous	others
		n=741	n=58	n=102	n=389	n=452	n=60
Complete staging	478 (53.1%)	347 (46.8%)	41 (70.7%)	90 (88.2%)	259 (66.6%)	183 (40.5%)	36 (60.0%)
Omentectomy							
performed	567 (62.9%)	419 (56.5%)	47 (81.0%)	101 (99.0%)	290 (74.6%)	237 (52.4%)	40 (66.7%)
positive	70 (12.3%)	0 (0/425)	0 (0/47)	70 (69.3%)	53 (18.3%)	13 (5.4%)	4 (10.0%)
Appendectomy							
performed	257 (28.5%)	201 (27.1%)	22 (37.9%)	34 (33.3%)	82 (21.1%)	163 (36.1%)	12 (20.0%)
positive	6 (2.3%)	0 (0/201)	0 (0/22)	6 (17.6%)	2 (2.4%)	4 (2.5%)	0 (0/12)
Lymphadenectomy							
performed	466 (51.7%)	338 (45.6%)	41 (70.7%)	87 (85.3%)	255 (65.6%)	176 (38.9%)	35 (58.3%)
positive	39 (8.4%)	0 (0/338)	0 (0/41)	39 (44.8%)	35 (13.7%)	3 (1.7%)	1 (2.9%)
Hysterectomy							
performed	437 (48.5%)	330 (44.5%)	39 (67.2%)	68 (66.7%)	194 (49.9%)	204 (45.1%)	39 (65.0%)
positive	31 (7.1%)	0 (0/330)	7 (17.9%)	24 (35.3%)	26 (13.4%)	4 (2.0%)	1 (2.6%)

Table 3: Clinical characteristics of patients with or without omentectomy.

Variable		Omentectomy	No-omentectomy	P-value
Age at first diagnosis	<40	316 (55.7%)	211 (63.2%)	0.029
	≥ 40	251 (44.3%)	123 (36.8%)	
Tumor size	<10 cm	285 (50.3%)	164 (49.1%)	0.736
	≥ 10 cm	282 (49.7%)	170 (50.9%)	
Histology	Serous	290 (51.1%)	99 (29.6%)	0
	Mucinous	237 (41.8%)	215 (64.4%)	
	Others	40 (7.1%)	20 (6.0%)	
Pathological stage	Stage I	419 (73.9%)	322 (96.4%)	0
	Stage II	47 (8.3%)	11 (3.3%)	
	Stage III	101 (17.8%)	1 (0.3%)	
Histologic characteristics	microinvasion	59 (10.4%)	14 (4.2%)	0
	No-Invasive implants	60 (10.6%)	7 (2.1%)	
	Invasive implants	99 (17.5%)	8 (2.4%)	
Surgical procedures	Laparoscopy	342 (60.3%)	244 (73.1%)	0
	Laparotomy	225 (39.7%)	90 (26.9%)	
Surgical staging	Complete	472 (83.2%)	6 (1.8%)	0
	Incomplete	95 (16.8%)	114 (34.1%)	
	No	0 (0.0%)	214 (64.1%)	
Up-staging re-staging surgery	Yes	31 (16.1%)	2 (8.7%)	0.349
	No	161 (83.9%)	21 (91.3%)	
Surgery radicality	Fertility-sparing	234 (41.3%)	230 (68.9%)	0
	Radical surgery	333 (58.7%)	104 (31.1%)	
Lesion lateral	Unilateral	397 (70.0%)	280 (83.8%)	0
	Bilateral	170 (30.0%)	54 (16.2%)	
Lymphadenectomy	Yes	453 (79.9%)	17 (3.9%)	0
	No	114 (20.1%)	317 (96.1%)	
Appendectomy	Yes	231 (40.7%)	26 (7.8%)	0
	No	336 (59.3%)	308 (92.2%)	
Adjuvant chemotherapy	Yes	131 (23.1%)	15 (4.5%)	0
	No	436 (76.9%)	319 (95.5%)	

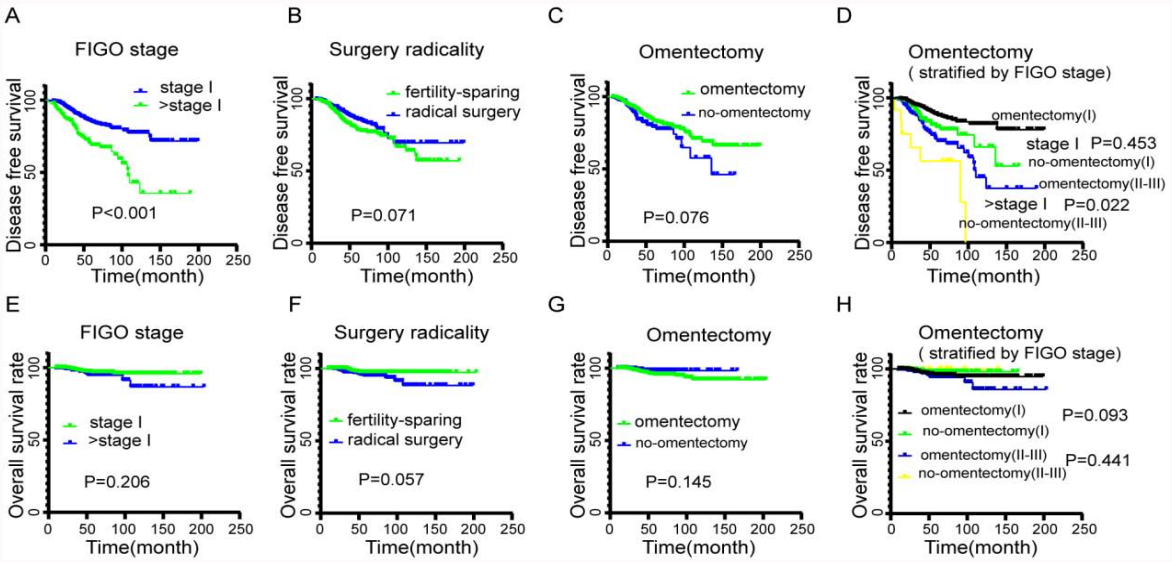

Figure 2: The DFS and OS of patients with BOTs.
a/e. Comparing DFS and OS rates between different FIGO stage (FIGO stage I and >FIGO stage I); b/f. Comparing DFS and OS rates between fertility-sparing surgery and radical surgery; c/g. Comparing DFS and OS rates between with/without omentectomy; d/h. Comparing DFS and OS rates between with/without omentectomy stratified by FIGO stage.

factors for the recurrence of BOTs. Meanwhile, in the multivariate analysis, performance of surgical staging or not, omentectomy and lymphadenectomy were not independent prognostic factors for recurrence. Only performance of radical surgery and adjuvant chemotherapy were risk factors for the recurrence of BOTs.

Each of the latter staging procedures, if not carried out, had no negative impact on DFS in univariate and multivariate analysis (p=0.505 *vs.* p=0.800, respectively) (Table S2). Overall, patients had a 5-year OS rate of 97.4%, and a 5-year DFS rate of 88.3%. The 5-year OS rate was 96.4% for complete staging surgery patients and 98.6% for incomplete staging surgery patients. It supported that only the 5-year DFS rate of complete staging surgery was slightly higher than those of incomplete staging surgery patients (p>0.05, Table 1, Figure 2B).

Discussion

Borderline Ovarian Tumors (BOTs) with low malignant potential carry a favorable prognosis [11]. Therefore, the role of comprehensive surgical staging in patients with BOTs is a controversial issue [12,13]. In our large dataset of 901 cases showed that complete staging surgery is associated with lower recurrence in patients of advanced stage II-III BOTs but not stage I. Our study also showed that without omentectomy in staging surgery was associated with a higher recurrence rate but limited mortality, even when diagnosed at advanced stage. We also found that lymphadenectomy in staging surgery has no effect on recurrence and survival in patients with BOTs. Moreover, this study showed that macroscopically normal-appearing ovary or peritoneal surfaces rarely contain microscopic disease. This study also found that lymph node and omentum involvement rate is rare if the tumor is confined in the ovary.

Despite comprehensive staging surgery is recommended for all patients with BOTs, it is unfeasible in daily practice. In our study, 70.9% of the patients were received inadequately staging surgery during initial operation because of several clinical factors, such as a lack of effective preoperative diagnostic tools, limited value of intraoperative frozen sections, desire to fertility preservation. Finally, complete staging procedures were performed in 53% patients either at primary surgery or at a later staging operation. Similar results have been described by other authors, only 12% to 41% of patients with BOT undergo complete surgical staging [14]. According to current guidelines, many patients underwent cystectomy first, require re-staging procedures. Complete surgical staging was defined as the set of procedures that follow standard guidelines for staging surgery, in order to determine whether implants are present which would be identified high-risk patients for invasive recurrence. However, for BOTs, the role of comprehensive staging surgery in BOT remains controversial, particularly in the absence of visible disease [12,14,15].

Several studies have reported an association of surgical staging with prognosis in BOT. In our study, complete surgical staging was associated with a reduced recurrence risk only in advanced stage BOT, nor in stage I, although no significant association with overall survival was observed. When focusing on recurrence rate in all patients by staging procedure in our study, we found that patients who had received complete staging surgery suffered compared relapses rate than those with incomplete staging surgery. Otherwise, stratifying our analysis according to FIGO stage revealed more details about patient survival. We found that only in advanced stage, complete staging surgery had the advantage in the reduced relapses risk (26% *vs.* 44.8%, P=0.027). Overall survival rates were also similar in completely and incompletely staged patients (p=0.445). Especially on stage I BOTs incomplete staging surgery was not related to poor prognosis. Similar results have been described by other authors [14-17]. Shim et al. [14] reported in the fixed-effects model-based meta-analysis indicated a reduced recurrence risk among complete surgical staging patients. However, no significant between-group difference in mortality was observed. In a series of 539 patients with borderline tumors [16], survival rates were also similar in completely and incompletely staged patients. When staged group was evaluated according to its completeness, no differences were found between completely and incompletely staged patients as well. Gokcu et al. [17] reported 53.9% (395/733) of patients were staged completely, the OS

no difference was found between completely and incompletely staged patients. They find that whether performance of surgical staging were not independent risk factors for the recurrence of BOTs.

However, in the recent subgroup analysis of the ROBOT study by Trillsch et al. [18], individual staging procedures were found to influence the prognosis of serous BOT patients, as each skipped staging procedure increased the risk of recurrence. Romeo et al. [19] reported incomplete staging surgery as a major predictor of relapse of borderline ovarian tumor, in their study 10.9% of patients experienced a recurrence who had been diagnosed with stage I disease and had received incomplete staging surgery.

This apparent discrepancy could be explained by a bias of analysis in these studies which included BOTs both stages of the disease and the different pathologic type. Meanwhile, the sample sizes were insufficiently large to clarify the prognostic role of surgical staging for this rare tumor. Studies have confirmed that serous BOTs have a disproportionally higher frequency of extra-ovarian disease compared to mucinous BOTs. All patients in ROBOT study by Trillsch et al. were serous BOT. It concluded that surgical staging correlated with prognosis.

One explanation for why the OS is not different between the complete staging and incomplete staging groups could be that recurrences are often surgically salvageable with a good prognosis, and higher recurrence rates have not translated into higher mortality, a key difference from invasive disease. In the presumed stage I, normal-like tissue only has implant rarely, and complete staging surgery has not effect on recurrence or prognosis. The validity of comprehensive staging surgery is the most debatable issue at present [10-16,18-20]. In the multivariate analysis of our study, comprehensive surgical staging appears not to be a prognostic factor in BOT patients.

It has also been reported that omentectomy in early-stage BOT may not improve patient's prognosis and therefore might not be required. Bendifallah et al. [15] concluded complete staging including peritoneal cytology, random peritoneal biopsies and omentectomy could be omitted for presumed stage I BOTs. Lee et al. [21] even questioned the need to perform omentectomy in patients of early-stage epithelial ovarian cancer in a retrospective review. They reported that the benefits of omentectomy for normal-appearing tissue in apparent early-stage epithelial ovarian cancer are minimal. Guidelines from the French national college of obstetricians and gynecologists recommended omentectomy to achieve a complete surgical initial staging when a BOT is diagnosed with extemporaneous histology or suspected on the basis of preoperative imagery [2]. De Decker et al. [22] reported that o implants were seen upon microscopic examination in patients with mucinous borderline tumors of the ovary. Only two patients (3%) developed a recurrence. They concluded that staging procedures in the case of an mBOT may be omitted because of no extra-ovarian disease was found [22]. In our study, omentectomy in advanced stage can decreased the relapsed rate, but no effect on long-term survival in women with BOT. If there is a precise and reliable description of a normal omentum, the need for a secondary staging operation could be discussed with the patient because the risk for invasive implants is negligible, and in the event of a recurrence, it can be treated surgically with excellent results.

The need of complete surgical staging including lymph node sampling or dissection is controversial. Routine lymphadenectomy often leads to late morbidity of lymphedema and may affect the reproductive ability. On the other hand, a large retrospective study from the Surveillance, Epidemiology, and End Results Program (SEER) has reported that the prevalence of lymph node metastasis in BOT was rare, they revealed that the lymph node involvement was not appear as a prognosis factor for advanced-stage BOT after adjusting with FIGO stages [23,24]. Qian et al. [25] reported that lymph node metastasis did not seem to be correlated to a worse prognosis of SBOT. Data from our work and the previous study showed that lymphadenectomy were not a risk factor associated with disease-specific survival [25-27]. Because metastasis to the lymph nodes is not known to affect survival or recurrence, lymphadenectomy is not necessary.

In summary, this present study showed that advanced FIGO stage II-III, performance of surgical staging or not, omentectomy, lymphadenectomy were not independent prognostic factors for recurrence in BOT. Comprehensive surgical staging are not beneficial in management of borderline ovarian tumors. Previous studies and our study showed that ovaries and peritoneal surfaces with a macroscopically normal appearance rarely contain a microscopic focus of BOT. we found no difference between the survival rates of staged and unstaged patients. So, re-staging procedures following incomplete primary surgery should be omit in stage I BOT.

Although our retrospective analysis was inherently limited by a lack of multicenter verification and prospective randomization, our study demonstrated that, BOT has excellent survival outcomes and conservative surgery and incomplete surgery in early stage is associated with few long-term complications. Complete staging surgery recommended in advanced stage. Therefore, our conclusions provide improved BOT management options for young women, and we recommend conservative surgery for the treatment for younger patients and earlier stage patients with BOT.

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