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Original Article

Risk factors that increase recurrence in borderline ovarian cancers

Ozer Birge, Mehmet Sait Bakır, Ceyda Karadag, Can Dinc, Selen Doğan, Hasan Aykut Tuncer, Tayup Simsek

Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology, Antalya, Turkey

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Abstract: Objective: In this study, we aimed to compare the clinical and pathological results of borderline ovarian tumor cases that were operated on in our clinic within the last 15 years and to investigate the factors affecting recurrence. Materials and Methods: The archived files of the patients with borderline ovarian tumors, who had been operated on at the Akdeniz University Medical Faculty Gynecological Oncology Unit between 2006 and 2020 were retrospectively reviewed. A total of 48 cases were identified and included in the study. Oncological results affecting relapse were evaluated using univariate and multivariate analysis models. Disease-free survival was assessed using the Kaplan-Meier method. Results: The median follow-up period of the 48 patients included in our study was 51.5 months and while the shortest follow-up was 2 months, the longest follow-up period was 164 months. The mean age of the patients was 47.6 ± 12.5 years, and the mean BMI was found to be 27.2 ± 3.7. Of the patients, 19 (39.6%) were post-menopausal, and when all stages were included, the 10-year progression free survival (PFS) was 65%, while the 10-year overall survival (OS) was 96.6%. It was observed that 8 (16.6%) patients encountered recurrence during their follow-up. The multivariate analysis of significance found for the operation type, adjuvant chemotherapy and micro-invasion in the univariate analysis of clinical pathological characteristics with regard to recurrence, fertility-sparing surgery and micro-invasion were determined to have a significant difference in recurrence (p: 0,016, p: 0,048). Conclusion: Borderline ovarian tumors are especially seen in young patients and although their clinical prognosis is very good, a significant difference was found in recurrence in patients who had undergone fertility-sparing surgery, in whom the micro-invasion was positive and in those receiving adjuvant chemotherapy, and disease-free survival was shorter in these patients and close follow-up of these patients is recommended.

Keywords: Borderline ovarian tumors, recurrence, atypical proliferation, stromal invasion, fertility-sparing surgery, adjuvant chemotherapy

Introduction

Borderline ovarian tumors (BOT), first described by Taylor in 1929, are known as ovarian tumors with low malignant potential (LMP) or atypical proliferating ovarian tumors without stromal invasion. They were re-arranged by the FIGO in 1971 and the World Health Organization (WHO) in 1973 and included in ovarian tumors [1].

They constitute 10-15% of epithelial ovarian tumors and the most common histological types are serous and mucinous, and the more scarce histopathological types are mucinous, endometrioid, clear cell (clear type), Brenner (transitional cell) or mixed histological types [2]. The mucinous type is seen most frequently in Japan and China in particular, where the population is older, and in some other Asian countries [3].

BOT are most commonly seen in pre-menopausal young women between the ages of 30-50. The initial diagnosis is usually made at an early stage. In the early stage, the 10-year survival is approximately 83-91% [4].

Borderline ovarian tumors are mostly asymptomatic in the early stages and may mimic the complaints of invasive ovarian cancer such as abdominal swelling, and in the advanced stages, there is a palpable mass, weight loss, nausea and vomiting [5]. The tumor size can vary between 1 and 30 cm. Preoperative diagnosis is difficult, especially in small-sized tumors, and these massive lesions are often incidentally

detected after non-gynecological examination for other reasons, and can only be diagnosed intra-operatively at a rate of 85% [5].

The main treatment of borderline ovarian tumors is surgical, and in premenopausal cases, where there is a wish for fertility, the uterus and the contra-lateral ovary can be preserved. However, hysterectomy and bilateral salpingo-oophorectomy should be performed in the postmenopausal and the premenopausal period (in cases that have completed their fertility). The staging procedure includes peritoneal lavage, peritoneal and omentum biopsies and appendectomy (especially in mucinous tumors). Routine pelvic and para-aortic lymph node dissection is controversial. However, this procedure is recommended for cases with enlarged lymph nodes or invasive tumors detected on frozen examination [6, 7].

In early-stage cases in particular, the laparoscopic approach as a minimally invasive method, should be performed by experienced teams in proper centers; however, detailed information should be given to the patients considering the risk of cyst rupture and associated early recurrence [6, 7].

Micro-invasion to the stroma of the ovary, peritoneal areas or other abdominal areas may be seen in very few borderline ovarian tumors. Micro-invasion in BOTs was first described by Tavassoli et al. in 1988, and it was reported as the widest invasion of the tumor of up to 3-5 mm in each or more involvement areas [8, 9].

Although BOTs are slowly growing tumors, the recurrence rate is around 11%, and 20-30% of cases with recurrence may undergo invasive malignant transformation [10]. There are many recent studies showing the greatest risk for tumor recurrence as different factors are involved such as stage, stromal micro-invasion, peritoneal invasive implants, micro-papillary pattern, adjuvant chemotherapy, capsule rupture and fertility-sparing surgery, especially in laparoscopic operations [11-13].

In this study, we aimed to discuss the clinical and histopathological features of the patients with borderline ovarian tumors that were surgically treated in our clinic through analysis of the factors affecting the recurrence by revealing the treatment methods applied under the light of literature.

Materials and methods

The data of 48 patients with BOT at the Akdeniz University Gynecological Oncology Clinic between 2006 and 2020 were retrospectively analyzed after having obtained approval from the ethics committee of our hospital (decision number: KAEK-764). Informed consent was obtained from all participants.

Patients who had all stages of BOT, but not a second primary tumor, were included in the study, and patients with borderline and invasive ovarian tumors without epithelial histology were excluded.

All patients were evaluated with regard to age at diagnosis, gravida, parity, body mass index (BMI), pre-operative CA-125 levels, tumor size in the pathology report, presence of micro-invasion and micro-papillary structure, smoking status, menopause status, additional systemic disorders, use of oral contraceptives, fertility request, tumor stage, surgery method, surgical treatment modality, adjuvant therapy application, follow-up protocol, survival, recurrence, recurrence number and death.

It was observed that the definition of micro-invasion in the pathology reports of the cases evaluated by pathologists in the field of gynecology were cases with a stromal invasion of up to 5 mm, and 12 (25%) of 48 cases were found to be positive for micro-invasion.

In the pre-operative evaluation of the cases, trans-vaginal ultra-sonography (USG), pelvic examination, tumor markers, cervical smear, endometrial sampling, and abdominal computed tomography (CT) and/or pelvic magnetic resonance (MRI) imaging methods were used when necessary.

When the patient files were analyzed, it was observed that the operation had been performed with laparoscopy and laparotomy, and the patients who were infertile and/or had not completed fertility, and those who had requested fertility-sparing surgery, had been given detailed information about the future risks and their consent had been obtained.

Surgical treatment was modified according to the fertility desire of the cases as well as the frozen examination results and the extent of the tumor intra-operatively. While total hyster-

ectomy, bilateral salpingo-oophorectomy ± bilateral pelvic-paraaortic lymph-adenectomy, omentectomy, cytology and/or appendectomy and peritoneal biopsy were performed in cases with no desire for fertility, the patients with the desire for fertility had undergone unilateral salpingo-oophorectomy or cystectomy, unilateral lymph-adenectomy, peritoneal biopsy, omental biopsy and/or appendectomy and cytology. The patients who had bilateral ovarian tumor and fertility desire had undergone bilateral cystectomy (if possible) or unilateral salpingo-oophorectomy + contralateral cystectomy.

All patients were staged intra-operatively and it was seen that the diagnosis of tumor, histology, regional lymph node evaluation, evaluation of biopsies obtained from all areas and cytology were performed by expert pathologists in a single pathology center in the post-operative pathological evaluation.

The cases were staged according to the FIGO (International Federation of Gynecology and Obstetrics) 2014 system [14]. While Stage 1A-1B Grade 1-2 was considered low risk in early ovarian cancer, Grade 3 Stage 1C and above was considered high risk. Adjuvant platinum-based chemotherapy treatment was planned for all cases considered at risk by the multi-disciplinary oncology council.

The patients were invited for routine controls every 3 months in the first post-operative year, every 6 months in the next 3 years, and thereafter. During the controls, a comprehensive physical examination, a gynecological examination and a pelvic/trans-vaginal ultra-sonography (USG) were performed and the serum CA-125 level and complete blood count were examined at each visit. Computed tomography (CT), chest radiography and the laboratory tests were performed every year. Recurrences were detected by imaging methods and pathological evaluations were made for those deemed necessary.

Statistical analysis was performed using the SPSS 23.0 (IBM, USA) program, and all descriptive statistics were carried out. For the descriptive statistics, the mean, standard deviation, median, min-max values and frequencies were used according to the normality distribution. Different categorical variables were analyzed using the chi-square and the Fisher Exact tests. When the theoretical frequency in Chi-square test was less than 5, the Chi-square test of continuity correction was used. The Fisher's exact test was used when there was more than 20 percent of the data above 5. The Student t test and the Mann-Whitney U test were used to compare the parametric and the non-parametric data, respectively. The measuring data were expressed by mean ± standard deviation (x ± sd) and compared by the t test of independent samples. The measuring data were expressed by median (min-max), and the median (min-max) was compared using the Mann-Whitney U test of independent samples. The disease-free survival (DFS) and the overall survival (OS) were calculated using the Kaplan Meier method. The univariate logistic regression was used to predict factors affecting the recurrence. Variables that were significant in the univariate analysis underwent the multivariate logistic regression analysis to find an independent factor. When the *p* values in all tests were less than 0.05, it was considered to be statistically significant.

Results

Demographic and clinical features

The median follow-up period of 48 cases included in our study was 51.5 months, while the shortest follow-up was 2 months, and the longest follow-up period was 164 months (**Table 1**). The ten-year progression-free survival (PFS) was 65%, while the 10-year overall survival (OS) was found to be 96.6%.

Eight out of 48 cases (16.6%) had relapse, and no recurrence was detected in 40 cases (83.6%). Considering the average age, it was 43.6 ± 12.2 in the group with relapse and 48.4 ± 12.5 in the group without relapse, and there was no significant difference between the two groups (P: 0.876). When the cases were evaluated in terms of gravida and parity, the median values were 3 (1-5) and 2 (1-4), respectively, and it was observed that they had no effect on recurrence (P: 0.563, P: 0.202, respectively). When the cases were evaluated in terms of the body mass index, the mean value was 27.0 ± 3.2 in the non-recurrence group and 28.3 ± 5.8 in the recurrence group, and a significant difference was found for both groups (P: 0.037).

Table 1. Clinical and pathological characteristics of the cases [n (%)] (x ± sd) (min-max)

		Recurrence (-) n: 40	Recurrence (+) n: 8	Totale n: 48	*P-Value*
Average age (years)		48,4 ± 12,5	43,3 ± 12,2	47,6 ± 12,5	0,876
Median gravida		3 (0-8)	3 (1-5)	3 (0-8)	0,563
Median parity		2 (0-5)	2 (1-4)	2 (0-5)	0,202
Average BMI (Kg/m^2)		27,0 ± 3,2	28,3 ± 5,8	27,2 ± 3,7	0,037
Preop CA-125 (U/ml)	-<35	26 (54,2%)	5 (10,4%)	31 (64,6%)	1,000
	-≥35	14 (29,2%)	3 (6,2%)	17 (35,4%)	
Pathological tumour diameter (cm)	-<10	13 (27,1%)	4 (8,3%)	17 (35,4%)	0,428
	-≥10	27 (56,2%)	4 (8,3%)	31 (64,6%)	
Smoke	-Yes	19 (39,6%)	6 (12,5%)	25 (52,1%)	0,249
	-No	21 (43,8%)	2 (4,2%)	23 (47,9%)	
Menopause	-Yes	17 (35,4%)	2 (4,2%)	19 (39,6%)	0,457
	-No	23 (47,9%)	6 (12,5%)	29 (60,4%)	
Comorbid disease	-Yes	22 (45,8%)	3 (6,2%)	25 (52,1%)	0,454
	-No	18 (37,5%)	5 (10,4%)	23 (47,9%)	
OCP	-Yes	2 (4,2%)	2 (4,2%)	4 (8,3%)	0,124
	-No	38 (79,2%)	6 (12,5%)	44 (91,7%)	
History of İnfertility	-Yes	3 (6,2%)	0 (0%)	3 (6,2%)	1,000
	-No	37 (77,1%)	8 (16,7%)	45 (93,85)	
Operation Type	-FSS	9 (18,8%)	6 (12,6%)	15 (31,2%)	0,008
	-CS	31 (64,6%)	2 (4,2%)	33 (68,8%)	
Surgical procedure by	L/S	5 (10,4%)	1 (2,1%)	6 (12,5%)	1,000
	L/T	35 (72,9%)	7 (14,6%)	42 (87,5%)	
FIGO stage	Stage 1	32 (66,7%)	4 (8,3%)	36 (75%)	NA
	Stage 2	3 (6,2%)	2 (4,2%)	5 (10,4%)	
	Stage 3	4 (8,3%)	2 (4,2%)	6 (12,5%)	
	Stage 4	1 (2,1%)	0 (0%)	1 (2,1%)	
Histology	Serous	20 (41,7%)	4 (8,3%)	24 (50%)	NA
	Musinous	16 (33,3%)	3 (6,2%)	19 (39,6%)	
	Clear cell	1 (2,1%)	1 (2,1%)	2 (4,2%)	
	Seromusinous	3 (6,2%)	0 (0%)	3 (6,2%)	
Microinvasion	-Yes	7 (14,6%)	5 (10,4%)	12 (25%)	0,017
	-No	33 (68,8%)	3 (6,3%)	36 (75%)	
Micropapillary pattern	-Yes	17 (35,4%)	5 (10,4%)	22 (45,8%)	0,442
	-No	23 (47,9%)	3 (6,2%)	26 (54,2%)	
Adjuvant Chemotherapy	-Yes	13 (27,1%)	6 (12,5%)	19 (39,6%)	0,045
	-No	27 (56,2%)	2 (4,2%)	29 (60,4%)	
Number of recurrence	1 times		5 (62,5%)	5 (62,5%)	0,986
	2 times		3 (37,5%)	3 (37,3%)	
Patient status	Alive	40 (83,3%)	7 (14,6%)	47 (97,9%)	0.167
	Dead	0 (0%)	1 (2,1%)	1 (2,1%)	
Follow-up (months)				51,5 (2-164)	

BMI: Body Mass Index; OCP: Oral Contraceptive Pills; FSS: Fertility Sparing Surgery; CS: Complete Surgery; L/S: Laparoscopy; L/T: Laparotomy.

The cases evaluated for CA-125 pre-operatively were divided into two groups with values below 35 and above 35 as reference. While the CA-125 value was 35 U/ml and above in 17

cases (35.4%), it was found to be below 35 U/ml in 31 cases (64.6%) and no significant difference was found for either of the two groups (P: 1.00) (**Table 1**).

The smoking rate of the patients was 52.1% (25), and when evaluated for the menopausal status, 39.6% (19) were post-menopausal cases and 25 cases (52.1%) had co-morbid diseases. No statistically significant difference was found in terms of smoking, menopausal status and co-morbid diseases when 8 cases with recurrence were compared with 40 cases without recurrence (P: 0.249, P: 0.457, P: 0.454, respectively). Four cases (8.3%) had been using oral contraceptives for protection from pregnancy and 3 cases (6.2%) were being followed-up and treated for infertility. It was observed that oral contraceptive use and infertility history were not significant in terms of recurrence (P: 0.124, P: 1.00, respectively) (**Table 1**).

Surgery features

In our routine clinic, after providing detailed information about laparotomy and laparoscopy to all our cases, 42 cases (87.5%) had undergone laparotomy after having been informed. Again, when a comparison was made with 6 cases (12.5%) that had undergone laparoscopy with their consent and information, no significant difference was found in terms of recurrence (P: 1.00). Recurrence was detected in 6 (12.6%) out of 15 (31.2%) cases operated with open surgery and fertility-sparing surgery, and 2 (4.2%) out of 33 (68.8%) patients who had undergone complete surgery, and a significant difference was determined between the two groups in terms of recurrence (P: 0.008). After evaluation of the post-operative pathology reports, when we divided the cases into two groups according to tumor diameter as below 10 cm and 10 cm and above, 31 (64.6%) had a tumor of 10 cm and above; however, 4 (8.3%) cases in each group were determined to have recurred and there was no significant difference between the groups (P: 0.428) (**Table 1**).

Pathological and clinical features

Four (8.3%) recurrent cases and 32 (66.7%) non-recurrent cases, 36 (75%) cases in total, were found to have Stage 1 according to the FIGO staging. The most common histopathological type was the serous type in all groups and the least common was the clear cell type with one (2.1%) in each of the recurrent and non-recurrent group. Nineteen cases were of mucinous type and of these, 3 (6.2%) were in the recurrence group. In the abdomen exploration, the appendices of 19 mucinous borderline cases were palpated and evaluated, and of these, only 3 underwent appendectomy and the pathology results of all three were normal appendix tissue. No difference was found between the groups with regard to the histopathological features (**Table 1**).

After the pathological examination, micro-invasion was found to be positive in 12 (25%) cases, and 5 (10.6%) out of 8 patients in the recurrence group were positive for microinvasion, whereas in the group without recurrence, 7 (14.6%) out of 40 cases were found to be positive, and a significant difference was determined between the two groups (P: 0.017). In addition, it was found to be positive in 22 of the cases evaluated in terms of micro-papillary structure, in 5 (10.4%) patients in the recurrence group, and in 17 (35.4%) patients in the non-recurrence group; however, there was no significant difference between the groups (P: 0.442) (**Table 1**).

Six (12.5%) out of 19 patients (39.6%) who had been evaluated post-operatively and received adjuvant chemotherapy were from the recurrence group and a significant difference was determined when compared with the non-recurrence group (P: 0.045) (**Table 1**).

During the follow-up of 8 patients with recurrence, a second recurrence was detected in 3 (37.5%). These cases had re-operation, and their follow-ups are still ongoing, and all are alive.

During the 51.5 (2-164) months of follow-up of 48 cases, recurrence developed in 8 cases and age, body mass index, smoking status, menopausal status, use of oral contraceptives, status of surgery performed by laparotomy or laparoscopy, micro-invasion obtained from the pathology report, micro-papillary pattern positivity, complete or fertility-sparing surgery status, whether they received adjuvant chemotherapy or not, tumor size, pre-op Ca-125 levels and the Figo staging, the presence of fertility-sparing surgery, adjuvant chemotherapy and micro-invasion were found to be significant

Table 2. Univariate and multivariate logistic analysis of factors affecting recurrence in borderline epithelial ovarian cancer

		Univariate				Multivariate			
		OR	CI %95		*P*-Value	OR	CI %95		*P*-Value
			Lower	Upper			Lower	Upper	
Age (year)		0,96	0,90	1,03	0.296				
BMI (Kg/m^2)		1,09	0,89	1,33	0,384				
Smoke	No	1							
	Yes	3,31	0,59	18,4	0,171				
Menopause status	No	1							
	Yes	0,36	0,08	2,51	0,364				
Surgical procedure by	L/T	1							
	L/S	1	0,10	9,92	1,000				
OCP	No	1							
	Yes	6,33	0,74	53,8	0.091				
Microinvasion	No	1				1			
	Yes	7,85	1,51	40,8	*0,014*	7,95	1,01	62,2	0,048
Micropapillary pattern	No	1							
	Yes	2,25	0,47	10,7	0,308				
Operation Type	CS	1				1			
	FSS	10,33	1,77	60,30	*0,009*	14,15	1,62	123,1	*0,016*
Adjuvant Chemotherapy	No	1				1			
	Yes	6,23	1,10	35,20	*0,038*	6,38	0,77	52,9	0,086
Pathological tumour diameter (cm)	-<10	1							
	-≥10	0,48	0,10	2,23	0,351				
Preop CA-125 (U/ml)	-<35	1							
	-≥35	1,11	0,23	5,36	0,893				
FIGO stage	Stage I	1							
	≥ Stage II	4,0	0,81	19,5	0,087				

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; OCP: Oral contraceptive pills; FIGO: International Federation of Gynecology and Obstetrics.

(OR (odds ratio)): 10.33 (95% CI: 1.77-60.3) P: 0.009, OR: 6.23 (95% CI: 1.10-35.20) P: 0.038 and OR: 7.85 (95% CI: 1.51-40.8) P: 0.014, respectively). Stage and oral contraceptive use were evaluated as borderline significant (OR: 4.0 (95% CI: 0.81-19.5) P: 0.087 and OR: 6, respectively. 33 (95% CI: 0.74-53.8) P: 0.091, respectively). No significant difference was found between the micro-papillary pattern positive and negative cases (P: 0.308) (**Table 2**).

In the multivariate analysis, fertility-sparing surgery and micro-invasion were found to be independent prognostic risk factors that significantly increased recurrence (OR: 14.15 (95% CI: 1.62-123.1) P: 0.016 and OR: 7.95 (95% CI: 1.01-62.2) P: 0.048, respectively). However, when evaluated in terms of adjuvant chemotherapy, it can be stated that there was a borderline significant difference (OR: 6.38 (95% CI: 0.77-52.9) P: 0.086) (**Table 2**).

Clinical characteristics of recurrent borderline cases

When 8 cases with relapse were analyzed, the longest follow-up period was 164 months and the shortest follow-up period was 45 months, the age range was between 32-64, the stages were between stage 1A-3C, the tumor diameter was between 3-13.5 cm, all histological types were included, but they were mostly of serous histology; micro-invasion was negative in 3 cases, micro-papillary pattern was negative in 3 cases, fertility-sparing surgery was performed in 6 cases, and only 2 cases did not receive adjuvant chemotherapy. In the follow-up of the

cases, the shortest recurrence time was 13 months, and the longest recurrence time was 102 months, and only 1 (2.1%) case whose age was 50 years old, with stage 3c, had serous epithelial, micro-invasion and the micro-papillary structure were found to be positive and recurrence was detected at 13 months and the patient was followed-up and treated, but died at the 47th month (**Table 3**).

Discussion

Borderline ovarian tumors are slowly growing lesions with an excellent prognosis, which constitute 10-15% of epithelial ovarian tumors with atypical epithelial proliferation without stromal invasion, and 75-80% of which are detected in stage I, especially at a younger age than epithelial ovarian cancers. In fact, BOTs differ greatly from epithelial ovarian tumors in terms of the age of first occurrence and prognosis, their treatment is surgical and fertility-sparing surgery may be preferred, especially in young patients with a desire for fertility [12, 15].

Although they show nuclear abnormality and increased mitotic activity like ovarian cancers, their destructive effects are not observed, since they do not demonstrate stromal invasion and stromal growth [16].

Pathological features are valuable in terms of tumor prognosis. The stage of the disease at the time of diagnosis, conservative surgery, capsule rupture, cystectomy especially in laparoscopic surgery, and the remaining post-operative residual tumor and invasive peritoneal implants are poor prognostic factors [12, 17, 18]. In a meta-analysis examining the data of 6362 patients, which comprises the largest series of the literature, 78.9% of the cases were diagnosed with BOT in FIGO Stage I [19]. In a multi-center study conducted by Boyraz G. et al., the rate of Stage 1 was reported to be 82.6%, and this rate was reported to be between 80-90% in other studies, consistent with this study [13, 20, 21]. In our study, the rate of Stage 1 borderline ovarian tumors was 75% (36), and we suggest that the low number of cases compared to the number of cases in the literature may be significant.

The mean age of the patients in our study was 48.4 years; 29 cases were pre-menopausal, and 19 cases were post-menopausal. When the recent literature was examined in line with the data obtained in our study, it was seen that the patients were between the ages of 40-50 and most of them were pre-menopausal [12, 13, 20, 21].

According to the definitive pathology results, 24 cases were of serous type, 19 cases were of mucinous type, 2 cases were clear cell, and 3 cases were of mixed type (serous + mucinous). While the mean tumor diameter was below 10 cm in 35.4% of the cases and above 10 cm in 64.6%, no statistically significant difference was found between the two groups (P = 0.428). In the study of Houck et al. conducted with 140 patients, the mean age was 52.3 years, and the mean tumor diameter was 13.7 cm (10.2 cm in serous tumors, 20.1 cm in mucinous tumors), 57.1% of the cases were serous, 33.5% were mucinous, and 9.4% were of other histological types [22].

In the literature, the vast majority of the cases with borderline ovarian tumors are mucinous or serous tumors, but clear cell, endometrioid, mixed, transitional or Brenner type tumors have been detected in 4-5% of the cases. It has been reported that serous histological subtypes constitute 43%-53%, while the mucinous subtypes constitute 42%-52% [23]. In our study, the serous (57%) and mucinous (33.5%) types were the most common and their frequencies were similar, and endometrioid, Brenner or transitional histology was not found. We believe that other rare types can be detected with an increase in the number of cases.

There was no clear correlation between Ca-125 elevation and recurrence, and when we took the values above 35 U/ml as reference, we found an elevation in 3 (6.2%) patients who relapsed, and no significant difference was found (P: 1,000). In many studies, it has been stated that elevated Ca-125 is more sensitive at a rate of 83%, especially in advanced stage tumors and 67% in serous type tumors [17, 18, 22].

The main treatment for BOTs is surgery. Less aggressive surgery is logical due to the young age of the patients and the low recurrence rates of the tumors or their long-life periods. If the patient is young and has a desire for fertility, cystectomy or oophorectomy can be applied; in patients who have completed their fertility,

Table 3. Clinical characteristics of recurrent borderline ovarian tumours

Patients name	Age	Stage	Histology	Microinvasion	Micropapillary pattern	Surgical procedure by	Type of surgery	Tumour diameter (cm)	Adjuvant chemotherapy (3-6 cycle C+P)	PFS (mo)	Follow-up (mo)	Status
M.K.	56	2B	Serous	No	No	L/T	FSS	6,5	Yes	102	164	Alive
A.B.	46	3C	Serous	Yes	Yes	L/T	FSS	11	Yes	10	141	Alive
E.Y.	32	1B	Mucinous	Yes	Yes	L/T	FSS	10	Yes	60	129	Alive
S.A.	32	1C1	Serous	No	Yes	L/S	FSS	3	Yes	75	117	Alive
E.G.	55	2A	Mucinous	Yes	No	L/T	CS	9	Yes	50	58	Alive
Ö.T.	33	1A	Clear cell	Yes	Yes	L/T	FSS	10	No	37	50	Alive
G.U.	50	3C	Serous	Yes	Yes	L/T	CS	4	Yes	13	47	Dead
B.S.	35	1A	Musinous	No	No	L/T	FSS	13,5	No	14	45	Alive

L/T: Laparotomy; L/S: Laparoscopy; FSS: Fertility Sparing surgery; CS: Complete surgery; C+P: Carboplatin + paclitaxel; mo: month.

total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) are appropriate. There are different opinions on surgical staging. Many authors have reported the importance of staging in terms of prognostic factors. Although some authors report that the tumor is bilateral, that there is presence of an exophytic involvement and that masses being larger than 10 cm should be considered when making a surgical staging decision, some others have reported that advanced stage disease and a high recurrence risk should be considered [24, 25]. In our study, laparoscopy was performed in 6 cases (12.5%) and laparotomy was performed in 42 cases (87.5%). As surgical procedures, fertility-sparing surgery was performed in 15 cases (31.2%) and complete staging surgery was performed in 33 cases (68.8%) (**Table 1**). Fertility-sparing surgery was performed in 6 out of 8 patients with recurrence and complete staging surgery in 2, and a significant difference was found between the two groups in terms of recurrence (P: 0.008).

The recurrence rates were reported to be 3%, 10% and 5.2% in Turkey, Sweden and North Vietnam, respectively, in patients diagnosed with BOT, and the overall survival rates were 97.9% and above. However, there are studies in the literature reporting high recurrence rates of 37.5% and 50% among cases with micro-invasion [18, 26-28]. In our study, the recurrence rates were found to be 16.6%, and 41.6% in cases with micro-invasion, consistent with the literature.

No significant difference was found between age, gravida, parity, pre-operative Ca-125 levels, FIGO stage, type of surgery, lymph node involvement, micro-invasion and micro-papillary structure between the cases with and without recurrence; however, the tumor-free survival was reported to decrease in the presence of micro-papillary structure and/or invasive peritoneal implants and in patients under 30 years of age who had undergone fertility-sparing surgery. In serous borderline ovarian tumors in particular, it was recommended to plan fertility-sparing surgery after thorough evaluation of the contra-lateral ovary [18, 26, 27].

When the literature was reviewed in terms of recurrence, it was reported in many studies that the recurrence rates are higher in patients undergoing fertility-sparing surgery [11, 13, 21]. For example, in a meta-analysis, after the evaluation of around 2000 cases, the recurrence rates were reported to be higher in fertility-sparing surgery, but survival was not affected, and in cases of recurrence, repeated surgery could be performed successfully [29]. In another study, a significant difference was found in terms of recurrence when complete surgery and fertility-sparing surgery were compared, and the recurrence rates were found to be between 0-20% and 12-58%, respectively [30]. In another study, no recurrence was found in the long-term follow-up of 11 patients who had undergone unilateral salpingo-oophorectomy and multiple biopsies from the contra-lateral ovary and other peritoneal areas (48 ± 9,02 months) [12]. In our study, FSS was performed in 6 out of 8 patients with recurrence and the univariate and the multivariate analysis revealed a significant difference in FSS compared to complete surgery (CS) in terms of recurrence, and it was observed that performing FSS was an independent prognostic risk factor in terms of recurrence (P: 0.016).

With regard to the operation performed by laparoscopy or laparotomy, no significant difference was found in our study in terms of recurrence, but when the literature was examined, it was suggested that laparotomy should be preferred, since it should not be forgotten that the risk of recurrence increases as a result of rupture of the mass, peritoneal spread of tumor cells and trocar metastases during the operation. In addition, there are publications reporting 8 trocar metastases in the postoperative period after laparoscopy [31-33].

Continuing with factors affecting recurrence, it is controversial in the literature whether the micro-papillary structure has an effect on recurrence or not, and there are publications stating that it is an independent prognostic factor; in particular, Shih et al. reported that the relapse rates were higher, and the disease-free survival (DFS) was shorter during the 4-year follow-up (75.9% vs. 94.3%) [34]. In another study, the authors stated that detection of micro-papillary structure, especially in serous BOT, affected the prognosis negatively and that this was the most important pathological structure that increased the invasive recurrence [35]. In another study conducted by Sözen et al. in 2018, micro-papillary structure was reported to be an

independent prognostic factor affecting recurrence in the follow-up of 16 cases (15.5%) with recurrence, consistent with the literature [21]. In addition, other studies also stated that micro-papillary structure was highly associated with micro-invasion, invasive peritoneal implants, bilateral ovarian involvement and lymph node involvement [36, 37]. Considering the results of our study, it was seen that the micropapillary structure was not significant, but we suggest that the low number of cases compared to other significant studies may be the reason for this.

Due to the limited data on BOTs thus far, the clinical evaluation of micro-invasion in terms of recurrence and prognosis is a controversial issue in the literature, especially based on retrospective data. Some authors, who have accepted that micro-invasive BOT cases have a high risk of relapse and invasive disease and that they may have poor oncological results, have failed to show an increased recurrence frequency and a poor prognosis in micro-invasive BOT cases [9, 12, 21, 38].

In many studies, it has been stated that the presence of micro-invasion and invasive implants is the most important risk factor for the development of recurrence and that it also reduces the disease-free survival [9, 20, 34]. In 2017, in the study of Boyraz et al., one of the largest studies conducted with the participation of 6 centers and evaluating 902 BOT cases, the prevalence of micro-invasion was found to be 7.6% and the recurrence rate was 17.3%, and they stated that micro-invasion was the most important independent prognostic factor in terms of relapse and reduced disease-free survival, but they could not find its relationship with overall survival. There are studies reporting that the presence of micro-invasion is a prognostic factor, especially in BOT with serous histopathology [31, 33]. However, in a large series study in mucinous type BOTs, micro-invasion was not related to the frequency of invasive recurrence and prognosis [31, 39]. In our study, no significant difference was found in terms of histopathology, but micro-invasion was observed to be an independent prognostic factor in both the univariate analysis and the multivariate analysis, in parallel with new publications in the literature (P: 0.048).

In the literature, many studies have stated that adjuvant chemotherapy is not effective in BOTs, especially in BOTs with advanced stage or invasive implants, and that it negatively affects the prognosis and patient health due to toxic effects and complications. Therefore, it has been stated that there is no clear evidence that adjuvant chemotherapy reduces the recurrence in BOTs [40, 41]. In our study, although there was a significant difference in the univariate analysis regarding the effect of adjuvant chemotherapy on relapse (P: 0.038), multivariate analysis was performed, and it was found to be a borderline significant prognostic factor (P: 0.086).

Finally, in our study, in the univariate analysis, a 6.3-fold higher use of oral contraceptives and a 4-fold higher FIGO stage revealed a risk and a significant difference in terms of recurrence (P: 0.091 and 0.087, respectively). Although there is an insufficient amount of evidence-based data on the use of oral contraceptives in the literature, it has been stated in many studies that the relationship between advanced stage and recurrence is high and that the recurrence rates are around 40% in advanced stage BOTs. In the same studies, it was reported that the recurrence rate after conservative surgery in stage 1 BOTs was around 15% [11, 13, 15, 26, 41, 42].

When the literature was evaluated in terms of the 5- and 10-year survival, it was reported as 99% and 90% in stage 1 [23] in our study, and the 10-year survival was 96.6% when all stages were taken into account, and only one of our patients died.

In conclusion, although borderline ovarian tumors have very good prognostic results in terms of tumor prognosis and biological character compared to invasive ovarian cancers, it should be considered that disease-free survival may be short and oncological outcomes may be poor, especially since the detection of micro-invasion in the histopathological evaluation and performing fertility-sparing surgery are independent prognostic factors that increase the risk of recurrence, and long-term follow-up should be carried out carefully.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ozer Birge, Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology, Dumlupınar Boulevard, Postal Code: 07058 Campus, Antalya, Turkey. E-mail: ozbirge@gmail.com

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