European Journal of Gynaecological Oncology

Original Research

Recurrence of borderline ovarian tumors: clinical and pathological risk factors

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DOI:10.31083/j.ejgo.2021.03.2312

Submitted: 11 November 2020 Revised: 27 December 2020 Accepted: 12 January 2021 Published: 15 June 2021

Objective: The objective of this study was to determine the impact of several clinic pathologic factors on the rate of recurrence of borderline ovarian tumors (BOT). *Method*: Patients, who were diagnosed in our clinic between October 1996 and April 2016 with a final diagnosis of BOT, were retrospectively investigated. Only patients with a primary diagnosis of BOT were included. A total of 147 patients were diagnosed with BOT and underwent surgical treatment. The pathological reports, medical records and operation notes of the included patients were obtained from the gynecological oncology electronic database system. *Results*: While 51.7% of all our patients had BOTs of serous histology, 34.6% had mucinous BOTs and 13.6% had seromucinous BOTs, and their bilaterality was 11.8%, 2% and 5%, respectively. After treatment, the clinical conditions of 96 patients could be followed and recurrence was observed in six (6.3%) of them. The median follow-up time was 66 months (range: 12–266 months). The median time to recurrence was 46 months (range: 14–100 months). For non-recurrence and recurrence cases, the median age was 42.0 years (range: 17–86) years and 29.0 years (range: 18–32 years), respectively a statistically significant difference (p = 0.005). Thirteen percent of the patients who underwent conservative surgery had recurrence, whereas no recurrence was observed in patients without conservative surgery (p = 0.009). While no recurrence was observed in patients who were surgically staged as stage 1, recurrences developed in cases with stage 2 and 3 disease (p = 0.040). In this cohort histologic type, surgical staging, presence of implants, size of the tumor, presence of micropapillary variants, and lymphadenectomy were not associated with recurrence. *Conclusion*: We found the recurrence of BOT is associated with younger age at diagnosis and conservative surgery. Although we found no statistically significant association of BOT recurrences with surgical staging, among those who were surgically stage recurrences only occured in patients with stage 2 or 3 disease.

Keywords

Borderline ovarian tumors; Cancer; Neoplasm; Recurrence; Risk factors; Surgery

1. Introduction

Borderline ovarian tumors (BOTs) account for 15–20% of all ovarian tumors [1]. As a low-grade malignant biological behavior, BOT is typically characterized by nuclear abnormalities, increased mitotic activity and no stromal invasion [2].

Compared to invasive epithelial ovarian cancers, BOTs occur more commonly at a younger age, during the time of optimum fertility [3]. BOT patients generally have a good prognosis. Their five- and ten- year survival rates are successively 95% and 92%, and the overall recurrence rates reported in the literature range between 7% to 16% [4, 5]. Although it was first described many years ago, there is no consensus on the necessity for surgery and the stage at which it should be used. The management of the condition can vary depending on the particular surgeons in attendance.

The objective of this study was to determine the impact of several clinicopathological factors on the rate of recurrence.

2. Methods

Patients, who were diagnosed in our clinic between October 1996 and April 2016 with a final diagnosis of BOT were, retrospectively investigated. Ethical approval was obtained from the Scientific Research Ethics Committee of Çanakkale Onsekiz Mart University (2011-KAEK-27/2020-E.2000035624).

Those who were histologically diagnosed with serous, mucinous, or seromucinous type BOT at any age were included in our study. They were all diagnosed for the first time. Those with other mixed histology and those with concurrent invasive cancer diagnosis were excluded from the study.

Table 1. Clinico-pathologic features and histologic subtypes.

	Pathology		
	Serous type n (%)	Mucinous type n (%)	Seromucinous type n (%)
	76 (51.7%)	51 (34.6%)	20 (13.6%)
Bilateral tumors			
Yes	9 (11.8)	1 (2.0)	1 (5.0)
No	67 (88.2)	50 (98.0)	19 (95.0)
Stage			
1	39 (72.2)	20 (95.2)	13 (100.0)
2–3	15 (27.8)	1 (4.8)	0 (0.0)
Staging operation			
Yes	54 (71.1)	21 (41.2)	13 (65.0)
No	22 (28.9)	30 (58.8)	7 (35.0)
Conservative surgery			
Yes	36 (47.4)	19 (37.3)	8 (40.0)
No	40 (52.6)	32(62.7)	12(60.0)
Micropapillary variant			
Yes	12 (15.8)	0 (0.0)	0 (0.0)
No	64 (84.2)	51 (100.0)	20 (100.0)
Invasive implant			
Yes	2 (2.6)	0 (0.0)	0 (0.0)
No	74 (97.4)	51 (100.0)	20 (100.0)
Noninvasive implant			
Yes	11 (14.5)	2 (3.9)	0 (0.0)
No	65 (85.5)	49 (96.1)	20 (100.0)

A total of 147 patients were diagnosed with BOT and underwent surgical treatment. All the patients were operated in our gynecology oncology department. The pathological reports, medical records and operation notes of the included patients were obtained from the gynecological oncology electronic database system.

Different surgical procedures used are described as follows: surgical staging was performed, including abdominal washing, infracolic omentectomy, appendectomy and peritoneal biopsies in the right and left paracolic gutters, with or without lymphadenectomy. This was carried out at the discretion of the surgeon and in accordance with the time of the diagnosis of the tumor (intraoperative and postoperative).

While non-conservative surgery (radical surgery) means the removal of both ovaries with or without the uterus, conservative surgery defines the operation in which at least one ovary is partially protected. This definition includes unilateral salpingo-oophorectomy (USO), USO with contralateral cystectomy, unilateral cystectomy and bilateral cystectomy with or without surgical staging.

Pathologists were experienced in gynecologic pathology and meticulously evaluated all pathological specimens. The definitions and details of the pathologic criteria are as follows: micropapillary was characterized by micropapillary structures of at least 5 mm in the longest dimension [6]; microinvasion was defined as the presence of microscopic foci of stromal invasion, less than 10 mm^2 in the area [7]; and, according to whether or not they were breaking through the basal lamina, peritoneal implants were divided into invasive and non-invasive types [8]. During the evaluation, lymph node involvement was defined by the presence of previously classified pathological markers, which mostly composed of simple unbranched papillary structures, similar to the BOT histology, as in previous studies [9].

Patients were staged according to the 2014 FIGO (International Federation of Gynecology and Obstetrics) staging system for ovarian carcinoma [10]. Follow-up with patients occurred once every 3 months in the first 2 years, and every 6 months thereafter. At the time of follow-up, patients received a routine gynecological examination, testing for cancer markers with ultrasound. If cancer biomarkers and/or ultrasound tests were found to be abnormal, then patients would be examined by computer tomography. Overall survival (OS) was defined as the time from the date of surgery to the date of death, last follow-up, or censoring. The period from surgery to recurrence or last visit was defined as progression-free survival (PFS).

We classified "recurrence" as that which occurred on the same ovary, on the contralateral ovary or both ovaries. We also defined recurrence as "borderline" if it was purely borderline and as "invasive recurrence" where evidence of histological features of adenocarcinoma was observed.

Statistical analysis

The data in this study were analyzed using the statistical software package SPSS 20.0 (IBM, Armonk, NY, USA). Number, percentage, median, minimum and maximum values were used in the presentation of the data. The relation-

Table 2. Relationship between age, tumor size, blood cancer markers and histology of BOT.

Variables	Pathologic types	Median (Min–Max)	*p*
Age (year)	Serous	40.0 (18–67)	0.229
	Mucinous	45.0 (17–83)	
	Seromucinous	42.0 (20–61)	
Tumor size (cm)	Serous	9.0 (3–30)	**0.001***
	Mucinous	20.0 (4–45)	
	Seromucinous	9.0 (4–25)	
CA125	Serous	48.6 (3–983)	**0.016***
	Mucinous	25.5 (2–375)	
	Seromucinous	55.3 (8–358)	
CA 19–9	Serous	12.0 (2–2162)	**0.003***
	Mucinous	19.0 (2–9865)	
	Seromucinous	14.0 (1–434)	

Min, Minimum; Max, Maximum; *p*, Kruskal Wallis Analysis of Variance and Dunn test.

*tumor size mucinous > serous >, mucinous > seromucinous.

CA125 level serous > mucinous, seromucinous > mucinous.

CA 19–9 level mucinous > serous.

p results include statistical significance (p meaning : $p < 0.05$).

Table 3. Presence of implant, bilaterality according to presence of micropapillary variants.

	Micropapillary variant yes	Micropapillary variant no	*p*
	n (%)	n (%)	
Implant			
Yes	4 (33.3)	11 (8.1)	0.022
No	8 (66.7)	124 (91.8)	
Bilateral tumors			
Yes	4 (33.3)	7 (5.2)	0.006
No	8 (66.7)	128 (94.8)	

n, Number; %, Column percentage; *p*, Fisher's exact chi-square test.

Table 4. Tumor stage status according to tumor diameter.

Tumor size (cm)	FIGO stage		*p*
	Stage 1 n (%)	Stage 2–3 n (%)	
3–10	30 (71.4)	12 (28.6)	0.041
10, 1–20	31 (88.6)	4 (11.4)	
>20	11 (100.0)	0 (0.0)	

n, Number; %, Column percentage; *p*, Fisher's exact chi-square test.

ship of categorical variables was tested with chi-square. In cases where the expected frequencies fell below 5, Fisher's exact chi-square test was applied. Kruskal Wallis and Mann Whitney U nonparametric tests were preferred for comparison tests, since there was no normal distribution in measurement variables (such as age, CA125). Nonparametric Dunn test was performed to determine between which groups significant differences were obtained from the Kruskal Wallis test result. The cases where *p* value was less than 0.05 were considered to be statistically significant.

3. Results

A total of 147 patients who had been given a final diagnosis of BOT in our hospital were identified. The mean age of the patients at the time of diagnosis was 41.5 years (range 17–83). The most common symptoms are groin pain 42.7%, abdominal swelling 27.9%, menstrual irregularities 13.9% and incidental findings 9%. Bilateralite ratios of 11.8%, 2% and 5% were found in serous, mucinous and seromucinous BOT, respectively. The surgical staging was performed on 88 patients (88/147), of whom 81.8% were categorized as stage 1 (72/88), 2.3% were stage 2 (2/88) and% 15.9 were stage 3 (14/88). Micropapillary variants were present in 12 of 147 cases in our sample group, and all of these micropapillary variants were serous, 2 of them were diagnosed microinvasively. The implant was seen in 15 patients, of which 13 were non-invasive and 2 invasive. In the non-invasive implant group, 11 of them were serous and 2 were categorized as mucinous histologic type. In the invasive implant group, all of them were serous. While age did not differ significantly between the pathology groups, the tumor diameter was significantly larger in mucinous type compared to the others (p = 0.001). The mean CA125 value was significantly higher in the other types (serous and seromucinous) than mucinous type (p = 0.016), while CA19-9 was statistically significantly higher in mucinous type than serous type (p = 0.003). The clinical features of these patients at baseline are summarized and illustrated in Tables 1 and 2. The implants were mostly in the omentum (24.2%), while the second most common location was in the same-sided or bilateral tubes (15.1%). Implant and bilateralite frequency was statistically significantly higher in patients with the micropapillary variant (Table 3). Consideration was also given to the correlation between the diameter of the tumor and the stage assigned to it. While the tumor diameter was less than 10 cm, our rate of diagnosis at stage 1 was 71.4%, while this rate was found to be 88.6% when the tumor diameter was between 10 and 20 cm. However, above 20 cm in diameter, all were categorized as stage 1 (p = 0.041) (Table 4). 66 patients underwent conservative surgery, of whom 40 had unilateral salpingo-oophorectomies and 26 had unilateral or bilateral cystectomy. The mean ages of the patients for whom conservative surgeries were performed or not were 30 and 50 years, respectively. A total of 8 patients received adjuvant platinum-based chemotherapy. The reasons for the use of adjuvant chemotherapy were nodal involvement in 4 patients, the presence of invasive implant in 2 patients and stage 3b in 2 patients.

Recurrence: The postoperative conditions of 96 patients could be evaluated in terms of recurrence. The median follow-up time was 66 months (range: 12–266 months). Six patients had a recurrence (6.3%). The median time to recurrence was 46 months (range: 14–100 months). All the cases of recurrence were found in patients who had undergone conservative surgery. Four of them underwent unilateral cystectomy and the remaining 2 underwent USO operations. All the recurrences recorded in patients who had

Table 5. Details of patients who had recurrences.

Primary pathology (BOT)	Age	Surgery	Stage	Implant	Recurrence time (Month)	Recurrence location	Recurrence pathology	Preoperative CA125
Serous BOT	32	Bilateral Cystectomy	2a	-	31	Bilateral ovary	Serous BOT	18.1
Serous BOT	18	USO	-	-	33	Contralateral ovary	Serous BOT	488.0
Serous BOT	19	USO	-	-	100	Contralateral ovary	Serous BOT	-
Serous micropapillary BOT	29	Cystectomy	-	-	41	Contralateral ovary	Serous BOT	40.1
Mucinous BOT	29	Cystectomy	-	-	58	Bilateral ovary	Mucinous BOT	-
Serous microinvasive Micropapillary BOT	29	Cystectomy	3c	Invasive implant	14	Same ovary	Malign serous	983.0

BOT, Borderline ovarian tumor.

USO were found in the contralateral ovary. Among the patients who developed recurrence after cystectomy, two were ipsilateral, one was contralateral and one was in the bilateral ovary. A total of six patients experienced recurrence: two of them had micropapillary variant and one had an invasive implant. While there was no recurrence in our patients who underwent surgical staging and followed up as stage 1; recurrence was seen in two patients, one in stage 2 and one in stage 3. During the operation frozen section was examined in all patients with recurrence. One of our patient's result was reported as malignant, and complementary surgery (bilateral salpingooophorectomy + hysterectomy and peritoneal biopsies) was applied to this patient. Conservative surgery was also applied to our other patients. According to the histopathology results after the investigation of the recurrences, five cases belonged to the same histologic type and one was a stage 1 serous carcinoma (Table 5). In our study, four of six patients with recurrent disease had preoperative CA125 levels, and this value was above 35 in three of them. None of the patients who experienced recurrence died of BOT and all have since been completely free of the disease.

Factors associated with recurrence in BOT: We used the univariate X-square test to evaluate the recurrent risk factors of BOT, and Tables 6 and 7 indicate that there were three main causes: age, conservative surgery, and stage.

4. Discussion

Despite a good prognosis, even with recurrence, there has been a little concern about the optimal management of BOT cases and a lack of clarity on best strategies. BOT often occurs in younger patients during childbearing years. In the literature, 54% of the BOTs are women under the age of 40 [11]. Stage 1 patients have a very good prognosis [12]. Therefore, conservative treatment becomes important. Therefore, conservative surgery is a feasible option for many of these women. Many published studies explored risk factors for recurrence in patients with BOT; however, the conclusions are still controversial. Identification of clinicopathological variables predicting recurrence and survival may assist in the selection of optimum treatments for BOT. The effect of fertility-preserving surgery on the probability of recurrence remains inconclusive. Several studies report no impact of fertility-preserving surgery on recurrence and no difference in overall survival between patients who underwent fertility-sparing surgery and those who did not [13–15]. Others studies reported an association with worse outcomes for fertility preserving surgery [16–18]. Plett *et al.* [19] diagnosed 80.2% of 352 patients when they were in stage 1 and reported the recurrence risk as 5.1% in these cases. They stated that the most important risk factor in terms of recurrence was stage and conservative surgery. A recent meta-analysis on this subject by Huang *et al.* [20] also concluded that the recurrence rate would be increased after conservative surgery when compared with radical surgery. Recurrence rates in our study were compatible with the literature, and conservative ovarian surgery was applied to all patients with recurrence. Conservative surgery can be performed in different ways and can also have an impact on the outcome. Many authors stated that they preffered to perform adnexectomy instead of cystectomy in cases of unilateral BOT because the recurrence rate was reported to be higher after cystectomy due to the frequent multifocal nature of the disease [21, 22]. However, Marchette *et al.* [23] reported that there was no statistically significant difference between the 10-year recurrence rates of the groups undergoing USO or cystectomy in their study including 535 cases where they performed fertility-sparing surgery. In the same study, they added that stage and bilaterality were important risk factors for recurrence. There is no consensus on the necessity for surgical staging. This is because there is no difference between the survival rates of patients having staging surgery or not. Another controversy regarding staging surgery is whether it should include lymphadenectomy. Current data demonstrate that lymph node metastasis does not worsen OS [24, 25]. Guvenal *et al.* [26] reported that staging surgery and lymphadenectomy did not affect survival in their study involving 539 patients with a multicenter. Other studies also report that lymphadenectomy did not improve PFS or OS for BOT [15, 27, 28]. However, Ureyen *et al.* [29] found that positive lymph node metastasis was significantly associated with worse PFS in patients with serous BOT. It cannot be denied that there are some benefits of lymphadenectomy, such as helping to define the precise

Table 6. Reccurence of BOT according surgical procedure and pathological characteristics.

	Recurrance No n (%)	Recurrance Yes n (%)	*p*	Odds ratio
Pathology diagnosis				
Serous	50 (90.9)	5 (9.1)	0.468	
Mucinous	29 (96.7)	1 (3.3)		
Seromucinous	11 (100.0)	0 (0.0)		
Staging operation				
Yes	61 (96.8)	2 (3.2)	0.177	
No	29 (87.9)	4 (12.1)		
Conservative surgery				
Yes	39 (86.7)	6 (13.3)	0.009	1.154
No	51 (100.0)	0 (0.0)		
Implant (non inv + inv)				
Yes	11 (91.7)	1 (8.3)	0.562	
No	79 (94.0)	5 (6.0)		
Tumor size (cm)				
3–10	44 (91.7)	4 (8.3)	0.843	
10, 1–20	36 (94.7)	2 (5.3)		
>20	10 (100.0)	0 (0.0)		
Bilateral tumors				
Yes	8 (88.9)	1 (11.1)	0.455	
No	82 (94.3)	5 (5.7)		
Stage				
1	50(100.0)	0(0.0)	0.040	1.182
2–3	11 (84.6)	2 (15.4)		
Micropapillaryvariant				
Yes	7 (77.8)	2 (22.2)	0.097	
No	83 (95.4)	4 (4.6)		
Lymphadenectomy				
Yes	58 (96.7)	2 (3.3)	0.193	
No	32 (88.9)	4 (11.1)		

n, Number; non inv, non invaziv; inv, invaziv; %, Line percentage; *p*, Fisher's exact chi-square test.

Table 7. Comparison of age, pre-procedure CA125 values according to relapse.

Variable	Recurrence	Median (Min–Max)	*p*
Age	No	42.0 (17–86)	0.005
	Yes	29.0 (18–32)	
CA125	No	29.2 (2–1733)	0.155
	Yes	264.1 (18–983)	

Min, Minimum; Max, Maximum; *p*, Mann Whitney U Test.

clinical-pathological stage. In this study, lymphadenectomy was found to have no impact on recurrence. Kristensen *et al.* [30], concluded that the presence of omental involvement was detected in 12% of the patients with serous BOTs and that a normal looking omentum did not exclude the presence of microscopic implants. According to our series, 8 omental metastases were detected and omentum was the most frequent site of the implants. Previous studies have suggested that preoperative blood CA125 levels may serve as a prognostic marker for BOT patients [15, 31]. In our study CA125 level was known in the cases of 4 recurrence patients, and it was above 35 in for 3 patients. Similarly, Tang *et al.* [32] showed in their study using a multivariable model that elevated preoperative serum CA125 level was an independent prognostic factor for PFS. Evidence from the largest cohort with a long time follow-up, in Germany found that advanced FIGO stage, incomplete staging, tumor residuals, and organ preservation might be independent risk factors for recurrence [33]. Although a micropapillary growth pattern was reported to be an independent prognostic factor by some authors [15], a micropapillary pattern itself is not usually accepted to be significantly associated with worse PFS than others [33, 34]. Neither micropapillary variant nor presence of implant had any impact on recurrence, according to our findings. Several reports indicate that invasive implants are associated with poor prognosis [18, 27, 34, 35]. Serous BOT with an invasive implant is considered to be low-grade serous adenocarcinoma and associated with a significantly worse prognosis [36, 37]. However, this study included only two BOT patients who had invasive implants, and one of them experienced recurrence at the fourteenth month, which developed into Grade 1 serous carcinoma. Limitations of our research were firstly related to the fact that the study was retrospective and that the follow-up period was 66 months because we know that the recurrence risk of BOTs continues even in 10 years of follow-up [23]. In addition, another factor that may affect the results of our study is the surgical technique used. We did not include the surgical technique (laparotomy or laparoscopy) data in the evaluation criteria. In conclusion, histologic type, staging during operation, presence of implants, size of the tumor, presence of micropapillary variants, and lymphadenectomy are not correlated with recurrence. There are three main causes of recurrence: Age, conservative surgery and stage.

Author contributions

HOS, AY, MB, KO, HO conceived and designed the project. HOS, AY, MB, EP, KO, HO searched the literatures. HOS, AY, MB, EP, KO, HO analyzed the data. HOS, EP, wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All required ethical approvals were obtained from Çanakkale 18 Mart University Clinical Research Ethics Committee (approval number: 2011-KAEK-27/2020-E.2000035624).

Acknowledgment

We would like to express my gratitude to all those who helped me during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Patient consent for publication

Not required.

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