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Epithelial borderline ovarian tumors: clinicopathological characteristics, management options, and diagnostic role of intraoperative consultation

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Summary

Aim: The objective of the present study was to evaluate clinicopathological and surgical features, accuracy of frozen section in patients with serous and mucinous borderline ovarian tumors (BOTs) treated in this clinic. *Materials and Methods:* A retrospective analysis of all patients treated for BOTs at Ankara Oncology Education and Research Hospital between 2008 and 2015 was performed. Data were obtained from hospital records and from the patients by phone. Fifteen patients were identified. *Results:* The mean age at diagnosis was 38.20 ± 7.37 (27-50) years. Sixty percent of the patients in this study were under 40 years of age. At the time of diagnosis, 93.4% of the patients had Stage I disease and 6,6% of the patients had advanced-stage disease. All patients underwent surgery. Serous histology was found in 73.3% of the patients. Forty-six percent of patients underwent fertility-sparing surgery (FSS) and 53.3% radical surgery. *Conclusion:* BOTs have perfect prognosis, and FSS may be applied to patients at reproductive ages desiring to protect their fertility.

Key words: Borderline ovarian tumors; Fertility-sparing surgery; Frozen section.

Introduction

Borderline ovarian tumors (BOTs) constitute 10-20% of all epithelial origin ovarian tumors. They were defined as a distinct entity from epithelial ovarian cancers (EOCs) by International Federation of Gynecology and Obstetrics (FIGO) in 1961 and by World Health Organization (WHO) in 1973 [1, 2]. They are distinguished from EOCs by their certain features. BOTs occur ten years earlier than EOCs, at an average age of 45 years. In addition, 75% of BOTs and 20% of EOCs are discovered as FIGO Stage I at the time of diagnosis. Prognosis is better than in patients with BOTs than patients with EOCs. The five-year survival rate is around 95-97% for Stage I BOTs and 65-87% even in Stage II and III BOTs [2]. The non-specificity of symptoms, the lack of appropriate diagnostic tools, and the inability of tumor markers to contribute to differential diagnosis make preoperative diagnosis difficult. Although these tumors were defined many years ago, optimal staging and management of BOT are still controversial. The diagnostic value of intraoperative frozen section is also low in BOTs, as it is known that frozen section has a potential sampling error. Nearly 55% of BOTs are serous and 40% of BOTs are mucinous. Histological tumor types such as endometrioid, clear cell, and Brenner tumor are rarely seen [1, 3]. The standard treatment for BOTs is surgical. The standard surgical treatment is bilateral salpingo-oophorectomy, hysterectomy, and surgical staging (peritoneal washing, omentectomy, removal of suspicious lesions, and multiple peritoneal biopsies if there is no suspicious lesion). If histological diagnosis is mucinous BOT, and appendectomy should also be added to staging. However, fertility-sparing surgery (FSS) has been widely accepted and applied because BOT is usually seen in women of reproductive age and reproductive function is required to be protected. FSS means that at least one ovary and the uterus are preserved [3, 4]. However, the patient must be informed and give written approval about that this is not a standard treatment.

The aim of this study is to evaluate clinical, pathological, and survival results of patients with serous and mucinous BOTs treated in this clinic, accuracy of frozen section, and to review the literature on the subject.

Materials and Methods

Fifteen patients were treated due to BOT at Ankara Oncology Education and Research Hospital between 2008 and 2015, and evaluated retrospectively. Medical and surgical follow-up and recurrence information of the patients were obtained by the hospital's electronic registration system and by telephone from the patients. Age at diagnosis, histological subtype, tumor size, primary surgery, staging procedure, postoperative treatment, follow-up, recurrence findings, and current situation of the patients were recorded. The patients were restaged according to 2014 FIGO ovarian cancer staging system. Histological classification was made according to WHO histological classification of tumours of the ovary. After frozen section examination was made, conservative or radical surgical treatment was per-

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formed according to the age of the patients and their fertility desires and complete staging was applied. Conservative surgery (CS) was defined as cystectomy or unilateral salpingo-oophorectomy (USO). Radical surgery (RS) was defined as total abdominal hysterectomy with bilateral salpingo-oophorectomy (BSO). Cytological examination, omentectomy, multiple peritoneal biopsies, and appendectomy were defined as complete staging procedure (CSP). Unlike epithelial ovarian tumors, lymph node dissection (LND) was not considered as part of complete staging procedure and was not routinely performed. However, it was applied to the patients predicted to have clinical or radiological involvement.

Results

Fifteen BOTs were evaluated out of 155 ovarian cancer patients. The mean age at diagnosis was 38.20 ± 7.37 (27-50) years. Frozen section was made in 14 (93.3%) patients. Frozen section was reported as benign in six (42.8%) patients, as borderline in seven (50%) patients, and as malignant in one (7.2%) patient. Eleven (73.3%) patients had serous BOT and four (26.7%) patients had mucinous BOT according to paraffin follow-up results. Seven (46.7%) patients underwent FSS and eight (53.3%) patients underwent radical surgery. While one (14.3%) patient underwent cystectomy and six (85.7%) patients underwent USO in the FSS group, eight patients underwent TAH+BSO in the RS group. Of the patients with RS, all underwent LND. Thirteen (86.7%) underwent omentectomy and seven (46.7%) underwent appendectomy. While one (7.7%) of the patients with omentectomy had non-invasive implants, none of the patients with appendectomy had metastasis. Only one patient underwent pelvic LND and other patients underwent bilateral pelvic and para-aortic LND (BPPLND). Eleven (73.3%) patients had serous BOT and four (26.7%) patients had mucinous BOT. Nine (60%) patients had unilateral BOT and six (40%) patients had bilateral BOT. Eight of the (8/9) unilateral tumors were found in the right ovary and all of the bilateral tumors were detected to be serous BOT. The mean tumor diameter in serous and mucinous tumors was 9.64 ± 1.27 (4-16) and 13.50 ± 4.73 (5-27), respectively. When the distribution of the patients was evaluated according to their stage, nine (60%) had Stage IA disease, two (13.4%) had Stage IB disease, three (20%) had Stage IC2 disease, and one (6.6%) had Stage IIIB disease. When the Ca 125 test results of 13 patients were evaluated, the mean Ca 125 value was 298.47 ± 679.57 (6.6-2,295). In subgroup analysis, this value was 421.15 ± 266.13 (7.4-2,295) and 22.45 ± 13.57 (6.6-63) for serous and mucinous BOT, respectively. Platinum-based chemotherapy was given as adjuvant treatment in one patient with non-invasive implants. Recurrence developed in one (6.7%) of the patients who had a mean follow-up of 40.9 ± 24.6 (6-92) months. The patient with recurrence was treated surgically. At the time of the study, all of the patients including one with disease are alive. Clinical details of the patients are shown in Table 1, while the pathological and surgical data are shown in Table 2.

Table 1. — *Clinical details of patients with BOT.*

	Number of patients	%
Age (years)		
≤ 40	9	60
> 40	6	40
First surgery		
Radical surgery	8	53.3
Fertility-sparing surgery	7	46.7
USO	6	85.7
Cystectomy	1	14.3
Tumor implantation (n=1/15)		
Non-invasive	1	6.7
Invasive	-	-
Peritoneal cytology (n=15)		
Negative	15	100
Malignant	0	0
Lymphadenectomy (n=8/15)		53.3
Pelvic	1	12.5
Pelvic-para-aortic	7	87.5
Stage at the time of diagnosis (FIGO 2009)		
IA	9	60
IB	2	13.4
IC	3	20
IIIB	1	6.6
Frozen section pathology (n=14/15)		93.3
Benign	6	42.8
Borderline	7	50
Malignant	1	7.2
Pathology		
Borderline	15	100
Adjuvant treatment		
CT	1	6.7
Recurrence		
Yes	1	6.7

Discussion

BOT has been accepted a premalignant disease as the precursor of invasive ovarian cancers at long-term. Therefore, they have been treated with RS and adjuvant chemotherapy as invasive ovarian cancer. Today, BOT is characterized by atypical epithelial proliferation without stromal invasion and is considered a different entity from invasive ovarian cancers [1, 2, 5]. There is no prospective randomized study to guide us in the treatment of patients with BOT in today. However, it is understood that as experiences with BOT increase, patients with BOT have a younger age, are at an earlier stage at the time of diagnosis, have a later recurrence, and a higher life expectancy compared to patients with invasive ovarian cancer [6, 7].

In this study out of 155 ovarian cancer patients, 15 BOTs were evaluated. This single-center study also showed similar results to those described in the literature. BOTs occur ten years earlier than invasive ovarian cancer. The mean age of the patients in our study was 38.20 ± 7.37 (27-50) years. Sixty percent of the patients in this study were under 40 years of age. This finding supports the fact that the incidence of BOT is higher in young adults.

Table 2. — *Pathologic and surgical data of patients with BOT.*

P. #	Age (years)	Frozen	Paraffin	Histology	Surgery	Implants	Stage	AT	Recurrence	Status(A/E)	MD (months)
1	27	Benign	BOT	Serous	FSS	-	IA	-	-	A	92
2	40	BOT	BOT	Serous	FSS	-	IA	-	-	A	40
3	38	Benign	BOT	Serous	Radical	-	IB	-	+(24 months)	A	64
4	38	Malignant	BOT	Mucinous	Radical	-	IA	-	-	A	6
5	33	BOT	BOT	Serous	Radical	-	IC	-	-	A	25
6	34	BOT	BOT	Serous	FSS	-	IA	-	-	A	58
7	29	BOT	BOT	Serous	FSS	-	IB	-	-	A	67
8	47	-	BOT	Serous	Radical	-	IC	CT	-	A	42
9	48	Benign	BOT	Mucinous	Radical	-	IA	-	-	A	46
10	27	BOT	BOT	Serous	Radical	Non-invasive	IIIB	-	-	A	35
11	50	BOT	BOT	Serous	Radical	-	IC	-	-	A	42
12	35	Benign	BOT	Serous	FSS	-	IA	-	-	A	14
13	43	BOT	BOT	Serous	FSS	-	IA	-	-	A	10
14	41	Benign	BOT	Mucinous	FSS	-	IA	-	-	A	13
15	43	Benign	BOT	Mucinous	FSS	-	IA	-	-	A	6

BOTs are diagnosed histopathologically. The definitive diagnosis of BOTs is made by examining permanent sections after the operation [8]. Intraoperative frozen section examination is a method used in order to avoid incomplete or excessive surgery and to direct the treatment properly in cases with the distinction between benign and malignant tumors cannot be performed preoperatively. Although the overall accuracy of frozen section for the ovarian masses is adequate, its efficiency lessens in the differentiation between benign and borderline or borderline and invasive ovarian cancers [9]. Moreover, invasive ovarian cancers can be correctly diagnosed over 90% with this method. However, this rate was not as high as expected in BOTs.The accuracy, sensitivity, and specificity of frozen section examination in BOTs were 60-78%, 45-87%, and 98%, respectively. In particular, the margin of error was increasing in the presence of mucinous histology [10-13]. Several authors searched the accuracy of frozen section and defined various factors for misdiagnosis in BOTS. Basaran *et al.* found that intraoperative frozen section had an overall accuracy of 62.7%, sensitivity of 71.2%, and positive predictive value of 84.1% in their study [9]. In the present limited study, there was no agreement between frozen and permanent histopathology in four patients with mucinous BOT. Frozen section diagnosis was reported as benign in three of these patients and as malignant in one of these patients. However, overall agreement between frozen and permanent sections was 73% in serous BOTs.

Most authors suggest that fertility preservation should be done in Stage 1 disease. However, there are also studies showing that conservative surgery, especially cystectomy, increases recurrence risk [2, 14-16]. In the present study, recurrence developed in one patient with bilateral serous BOT and underwent RS and complete staging. No recurrence was observed in the patients who underwent FSS (USO/cystectomy). In this study, no relationship was observed between FSS and recurrence risk. However, the fact that the mean follow-up time (40.9 ± 24.6 months) in the current study was relatively short for a disease with late recurrence behavor such as BOT, also a point to be kept in mind in terms of recurrence rates.

The standard treatment for BOTs is surgical approach. Although the extent of surgery and the limits of staging are still controversial, the standard surgical treatment accepted in routine practice is bilateral salpingo-oophorectomy, hysterectomy, and surgical staging (peritoneal washing, omentectomy, removal of suspicious lesions, and multiple peritoneal biopsies if there is no suspicious lesion) [3, 4, 17]. Appendectomy should be added to staging in mucinous BOT [18]. There has been no concensus about lymph node dissection because it is not considered prognostically important and does not contribute to life expectancy. Moreover, it is not considered a mandatory component of standard staging [18, 19]. However, the rate of lymph node metastasis (LNM) is around 15% in serous BOTs, and this rate is below 5% in patients considered to be limited to the ovaries during surgery [19, 20]. In the present study, 53.3% of the patients underwent LND. While the rate of LND was 87.5% in the RS group, it was 14,3% in the FSS group. In addition, LNM was not detected in the patients in both groups undergoing LND.

Stage is one of the important prognostic factors in BOTs. Stage at the time of diagnosis is earlier in BOTs than invasive ovarian cancers [2, 19]. In the present study, at the time of diagnosis, 93.4% of the patients had Stage I disease (Stage IA=60%, Stage IB=13,4%, Stage IC=20%), and 6,6% of the patients had advanced-stage disease. This rate was 90.9% and 100% for serous and mucinous BOTs, respectively. Serous BOTs are the most common borderline tumors and the rate of bilateral involvement in this type is as high as 25-50% [21, 22]. In this study, 73.3% of the patients had serous BOT and 26.7% of the patients had mucinous BOT. While the rate of bilateral BOT was 40%, all of the bilateral tumors were serous BOT. Bilaterality was seen predominantly in serous tumors; however, it was seen that mucinous tumors were larger than serous tumors in terms of tumor size. These results were also consistent with the literature.

BOTs spread through the peritoneum and form peritoneal implants. Although most of these implants are non-invasive, 15% of them can be invasive. Implants are more frequently seen in serous BOTs. They can be seen in the small and large intestines and are rarely seen in the pelvic peritoneum, omentum, the pouch of Douglas, and uterine tubal serosa. The presence of implant increases recurrence risk, without the type of tumor [22-26]. In this study, non-invasive implants were seen in one patient with serous BOT. No recurrence was observed in this patient, who has been followed for 35 months. There are studies with shorter follow-up durations indicating that non-invasive implants had better prognosis than invasive implants. However, it has been shown that non-invasive implants had adverse effects on prognosis with the publication of studies with longer follow-up durations in today. In a review study, while relapse rate was 36% and tumor mortality rate was 25% in patients with invasive implants, these rates were 18% and 6% in patients with non-invasive implantation, respectively [24, 25].

As a conclusion, BOTs have a perfect prognosis, and FSS may be applied to patients at reproductive ages who desire to protect their fertility. Although in many studies survival rates close to 99% were reported, it is a reality that these rates are independent from surgery type, and most of them have low follow-up periods (< 5 years). For this reason, it must be kept in mind that there might be late recurrences, and long-term follow-up must be recommended in such patients.

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