Borderline epithelial ovarian tumors: a single center experience

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Summary

Aim: To evaluate the clinical outcomes of the patients treated for borderline ovarian tumor (BOT). *Materials and Methods:* In this retrospective study, records of the patients between November 2001 and December 2012 who underwent surgery and whose final pathological diagnosis were BOT were retrieved. *Results:* During the study period, 78 patients were diagnosed as BOT. The pathological diagnoses of the tumors were serous in 26 (33.3%) and mucinous in 52 patients (66.6 %), respectively. Accuracy of frozen section diagnosis was observed in 63 of 89 patients (70.7%). Sixty-eight women (87.1%) underwent complete staging procedure. According to final pathological diagnoses, Stage IA, IB, and IC were found in 52 (67%), five (6.5%), and seven (9%) patients, respectively. FIGO Stages IIC and IIIC were found in one case in each (1.25%). Remaining 12 patients were classified as unstaged (15%). The median follow-up time was 63 months. The authors observed only one recurrence (1.3%) and that patient died of disease. *Conclusion:* The survival rate in patients with BOTs confined to the ovary is excellent. Surgical staging procedure can be omitted in the patients with grossly apparent Stage I mucinous tumors.

Key words: Borderline ovarian tumor; Surgical staging; Clinical outcome.

Introduction

Borderline ovarian tumors (BOT) account for 10-15% of all ovarian cancers [1]. These epithelial tumors are accepted as carcinoma of low malignant potential as they act between benign and malignant fashion in terms of pathological features and clinical behavior [2].

Pathologically, the tumor is characterized by cellular proliferation of the epithelium, increased mitotic activity, and nuclear atypia; however the obvious criterion to differentiate it from malignancy is the absence of stromal invasion [3, 4].

In contrast to ovarian cancer, the majority of BOTs (80-90%) are diagnosed in the early stages and survival rate is excellent (98%). Also, median age at diagnosis is 40 years (27% of the patients are younger than 40 years of age) compared with about 60 years for women with invasive carcinoma [1, 5].

Standard treatment of BOT is same as ovarian cancer: surgical resection of all macroscopic disease and proper surgical staging [6]; however conservative surgery is an option in the treatment of younger patients with BOT for preserving reproductive function and hormone production [7]. Most patients referred to tertiary centers after primary surgery have had incomplete surgery, and completion of surgical staging is a controversial event as there is no consensus on the clinical management of these patients [8-10].

In this retrospective study, the authors aimed to evaluate the clinical outcomes of the patients treated for BOT and who were followed at their clinic.

Materials and Methods

After Institutional Review Board approval was obtained for this retrospective study, records of the consecutive patients between November 2001 and December 2012 who underwent surgery and whose final pathological diagnosis were BOT were retrieved from the gynecologic oncology database at the Department of Obstetrics and Gynecology, Kanuni Sultan Suleyman Research and Teaching Hospital. Data were obtained from patients' files and follow-up charts. Pathology and radiology reports, and laboratory results were thoroughly reviewed. Collected data included patient's age, parity, menopausal status, presenting symptom, pattern of sonography, serum CA-125 and CA 19-9 levels, risk of malignancy index (RMI) score, operative procedure, frozen-section and final pathology report, presence of recurrence, and overall survival.

Ultrasound examinations were performed in all patients at most one week before the surgery. Serum samples were collected preoperatively, and serum CA-125 and CA 19-9 levels were measured. An ultrasound scoring system that was described by Jacobs *et al.* had been used and following features were determined as suggestive of malignancy: the presence of a multilocular cyst, solid areas, bilateral lesions, presence of ascites, and evidence of metastases (scored as 0 for no finding, 1 for one finding, and 3 for two or more abnormal findings). Then, risk of malignancy index (RMI) score that utilises the ultrasound findings, menopausal status, and serum CA 125 levels was calculated with the attribution of 1 for premenopausal status and 3 for postmenopausal status (M), versus ultrasound score (U) and the absolute values of CA 125 (U/ml) serum levels: U x M x CA 125. RMI scores of $\leq$ 200 were determined as low risk, and >200 as high risk for malignant lesions [11].

All the patients were operated for the indication of an adnexal mass, and frozen-section analysis was performed for most of the cases. Detailed and informed consent was taken from each patient for the extent of the surgery (radical or conservative). The present clinic follows the international guidelines for the treatment of BOT [12]. Accordingly, the standard treatment of BOT includes removal of all macroscopic disease and proper surgical staging: peritoneal washings, multiple peritoneal biopsies, omentectomy and, occasionally, lymphadenectomy (only when bulky lymph

Table 1. — *The clinico-pathological characteristics of the patients treated for borderline ovarian tumor.*

	n (%)
Total number of patients	78
Median age (years)	44 (16-84)
Menopausal status	21 (27 %)
Median parity	2
RMI score >200	14 (18 %)
Tumor markers	
Median CA-125 level (U/ml)	27,4
Elevated CA-125 level (>35 U/ml)	30 (38.4 %)
Median CA-199 level (U/ml)	13,91
Elevated CA-199 level (>35 U/ml)	14 (18 %)
Tumor histology	
Serous	26 (33.3 %)
Mucinous	52 (66.6 %)
Bilaterality	5 (8 %)
Median tumor size (mm)	100 (40-500)
Median size (mm) - histology	
Serous	85
Mucinous	110
Staging	
1A	52 (67 %)
1B	5 (6.5 %)
1C	7 (9 %)
2C	1 (1.25 %)
3C	1 (1.25 %)
Unstaged	12 (15 %)
Treatment	
TAH + BSO + surgical staging	51 (65 %)
TAH + BSO	4 (5 %)
Oophorectomy + surgical staging	17 (22 %)
Oophorectomy	6 (8 %)
Median follow up (months)	63 (3-136)
Recurrence	1 (1.3 %)
Dead of disease	1 (1.3 %)

TAH + BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy
RMI= risk of malignancy index, RMI score of ≤ 200, >2 00 were determined as low risk and high risk for malignant lesions, respectively.

Table 2. — *Frozen section diagnosis compared with permanent pathology.*

Pathology	Benign	Borderline	Malign	Total
Frozen				
Benign	0	9	0	9
Borderline	4	63	11	78
Malign	0	2	0	2

low-up of the patients consisted of clinical examination, transvaginal sonography, and serum tumor markers. Magnetic resonance imaging (MRI) was also performed when recurrence was suspected after initial evaluation.

Results

During the study period, 78 patients were diagnosed as BOT, accounted for 15% of all ovarian cancers (n=520) treated at the present hospital. The clinico-pathologic characteristics of the patients are summarized in Table 1. The median age of the patients was 44.0 years (range 16-84 years); 21 patients (32%) were postmenopausal. The main presenting symptom was abdominal pain in 45 patients (57.6%). The median pre-operative value of CA-125 was 27.4 U/ml (range, 0-223 U/ml) with 38.4% (n=30) of the patients being above the upper limit (> 35 U/ml), whereas the median preoperative value of CA 19-9 was 13.9 U/ml (range, 0-233 U/ml) with 18% (n=14) of the patients being above the upper limit (> 35 U/ml). Post-surgery levels of CA-125 and CA 19-9 returned to normal range in all of the patients. Upon calculating RMI scores for each of the patients, the median RMI score was 45.0, and 14 patients (18%) were classified as high risk.

The pathological diagnoses of the tumors were serous in 26 patients (33.3 %) with two of them included micro-papillary pattern, and were mucinous in 52 patients (66.6%). The frozen section results are shown in Table 2. Agreement between frozen section diagnosis and final pathology was observed in 63 of 89 patients (70.7%). Among the 78 patients with frozen section proven BOT, under-diagnosis, and over-diagnosis occurred in nine of 74 (12.2%) and two of 74 patients (2.7%), respectively. In the present study, median tumor diameter was 100 mm (range, 40-500 mm) with the mucinous tumors (range, 60-500 mm) being larger than serous tumors (range, 40-200 mm) ($p < 0.05$). Also, five patients had bilateral disease (8%).

Initial surgical procedures for patients with BOT are also shown in Table 1. Of the 68 women (87.1%) who had undergone complete staging, 17 (21.8%) and 51 (65.3%) received conservative and non-conservative treatment, respectively. Of the ten women (12.8%) who had undergone incomplete staging, six (7.7%) and four (5.1%) received conservative and non-conservative treatment, respectively. Despite having benign intraoperative pathological report, one patient underwent hysterectomy and BSO with complete staging due to clinical suspicion of a

nodes were observed). Appendectomy should also be carried out for mucinous type of BOT. Initial surgery was accepted as an incomplete staging procedure in all other circumstances. Also, conservative surgery was defined as a surgical procedure in which uterus, and at least a part of one ovary, are preserved [8,9]. Thus, preserving uterus plus unilateral salpingo-oophorectomy and unilateral ovarian cystectomy, with or without contralateral ovarian cystectomy, were all defined as fertility-sparing surgeries. Surgical treatment was accepted as non-conservative if bilateral salpingo-oophorectomy (BSO) with or without hysterectomy was performed.

All pathologic specimens were reviewed by the senior gynecopathologists in the present center. After the final pathology was reviewed by the same pathologist, tumors were classified according to the World Health Organization system and were staged according to the International Federation of Gynecology and Obstetrics system [13].

After completion of the primary treatment, patients were examined every three months during the first two years, every six months during the next three years, and yearly thereafter. The fol-

malignant ovarian tumor that was confirmed by final pathology. In one patient who was 16 years of age and had unilateral serous BOT with non-invasive implants in the pelvic peritoneum and omentum (Stage IIIC), conservative surgery, and complete surgical staging was performed. Patient received four-cycles adjuvant chemotherapy.

According to final pathological diagnoses, Stage IA, IB, and IC were found in 52 (67%), five (6.5%), seven (9%) patients, respectively. FIGO Stage IIC and IIIC were also found in one case each (1.25%). Remaining 12 patients were classified as unstaged (15 %). In the latter group, median tumor diameter was 115 mm (range, 50-400 mm) with five patients (41.6 %) had a tumor diameter greater than 200 mm. The pathological diagnoses included serous in two patients (16.6 %), and mucinous in ten patients (83.3%). The median preoperative values of CA-125 and RMI score were 27.4 U/ml and 16.0, respectively.

In the present study population, median follow-up time was 63 months (range, 3-136 months). The authors observed only one recurrence (1.3 %). The patient was a 46-years-old, premenopausal, multiparous woman who had hysterectomy and BSO and full surgical staging procedure. Final pathology was reported as Stage IA serous BOT with micropapillary pattern. Six months later from initial surgery, peritoneal carcinomatosis developed, and patient received chemotherapy. After nine months of follow-up, the patient died of disease complication (1.3%). All other patients were alive.

Discussion

In the present study, the authors aimed to evaluate the clinical outcomes of the patients treated for BOT and followed at their center and secondarily, to discuss the necessity of surgical staging procedure in the management of BOT.

The relevance of ultrasonography and serum tumor markers in the preoperative assesment of patients with BOT is controversial. Although ultrasonography may be helpful in making a differential diagnosis between benign and malignant masses, it is not useful in the diagnosis of BOT. Similarly, serum CA-125 levels are not specific and not always elevated in the diagnosis of BOT [14]. In the present study, high levels of serum CA-125 (> 35 U/ml) and CA 199 (> 35 U/ml) were detected in only 38.4% and 18% of the patients, respectively. As RMI was superior to any individual criterion in diagnosing adnexal masses, the authors evaluated RMI scores of BOT, and classified 18% of the patients in this study as high risk. In the study of Chia *et al.*, an RMI score of > 200 identified 91% of invasive ovarian cancer whereas the rate was 58% in the case of BOT [15]. Also, Andersen *et al.* showed limited value of RMI score in the prediction of BOT [16]. Because the preoperative assesment of BOT is not sufficient enough to make an accurate diagnosis, intraoperative histopathological diagnosis has a critical role in the clinical management of BOT. Unfortunately, frozen-

section diagnosis is not always reliable [17]. In the study of Kim *et al.*, agreement between frozen section diagnosis and permanent pathology was reported in 63 of 101 patient (62.4%). Among the 76 patients with frozen section proven BOT, under-diagnosis and over-diagnosis occurred in 10.5% and 6.6% of the patients, respectively [18]. In accordance with the literature, the present study showed an accuracy rate of 70.7%. Also, under-diagnosis and over-diagnosis of BOT occurred in nine of 74 (12.2 %) and two of 74 patients (2.7%), respectively.

In the present series, most patients had early stage disease (82.5%), advanced stage (FIGO II/III) only occurred in 2.5%. If the unstaged group (15%) was excluded, rate of early stage patients became 96.7% which was higher than the literature [19, 20]. In a large retrospective Norwegian study of 370 women with BOT; Stage I, II, and III were diagnosed in 84%, 6%, and 10%, of the patients, respectively. None had Stage IV disease [20]. In the present study, mucinous tumors (66.6%) were more common than serous ones (33.3%). Interestingly, although studies in Western countries have reported the serous type as the most common histologic finding (60% - 74%), studies in Eastern countries reported the mucinous type to be the most common (68% - 76%) [8, 18, 20]. Mucinous tumors are more likely to be Stage I than are serous tumors (84% as compared with 67%) [21]. The present authors' rare incidence of advanced stage disease may be attributable to the main histologic type of BOT (mucinous) as its larger size resulted patients to become symptomatic earlier.

Overall survival for the patients with BOT is excellent. In a study by De Iaco *et al.*, of the 168 patients treated for BOT, 16% of the patients recurred, but none of the relapsed patients died of disease [22]. Also, Trillsch *et al*. reported a five-year overall survival rate of almost 100% in early stage disease (FIGO I/II) and between 86% and 92% in advanced stage (FIGO III/IV) [23]. In the present study, 98.7% of the patients were alive, on a median follow-up time of 63 months. Although patient prognosis is excellent following treatment for BOT, there appears to be a sub-group of tumors that have potential to either recur or become more aggressive as an invasive carcinoma. In a recent review by Morice *et al.*, patients who had invasive peritoneal implants (in serous BOT) and residual disease after surgery were defined as high-risk group in whom disease is likely to evolve to invasive cancer. Other factors such as micropapillary pattern, microinvasion, intraepithelial carcinoma, and use of cystectomy were controversial [24]. However, in the present study, the only recurrence and dead of disease (1.3%) occurred in a patient who had serous BOT with micropapillary pattern.

Traditionally, all the patients with frozen proven BOT should be surgically staged, however, it is a fact that most patients referred to tertiary centers after primary surgery have had incomplete surgery. Because the malignancy is not suspected at the initial operation, intraoperative exploration of the abdomen would be mostly lacking. Therefore,

should these patients be re-operated? Camatte *et al.* suggested that incomplete staging has no effect on survival, even if the recurrence rate is increased [8]. In the present study, based on benign frozen pathology, incomplete surgery was performed in ten patients (12.8%), but none of them recurred. Snider *et al.* upstaged five out of 27 women with Stage I disease. None of the 12 women with mucinous BOT were upstaged, whereas five out of 13 women with serous BOT were upstaged. Mucinous BOTs grossly confined to one ovary are unlikely to be upstaged at a restaging procedure [25]. Also, Leake *et al.* suggested that for serous BOT with micropapillary pattern, it is reasonable to perform complete surgical staging as an initial or reoperation procedure because of the high probability of lymphnode involvement and recurrence [26]. In accordance with the literature, none of the patients with grossly apparent Stage I tumors were upstaged after the permanent pathology and the only poor outcome was observed in a patient with serous BOT with micropapillary pattern

The present study had some limitations: retrospective nature of the study, follow-up period, rare incidence of specific pathologic features (microinvasion, micropapillary pattern, etc.), and advanced surgical stages weakened the results.

Conclusion

The survival rate in patients with BOTs confined to the ovary is excellent. Surgical staging procedure can be omitted in the patients with grossly apparent Stage I mucinous tumors.

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