ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Clinicopathologic Evaluation of Borderline Ovarian Tumours: A Tertiary Centre Experience

Borderline Over Tümörlerinin Klinikopatolojik Değerlendirilmesi: Üçüncü Basamak Hastane Deneyimi

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ABSTRACT

Objective: *Borderline ovarian tumours (BOTs) are rare tumours in the intermediate category of benign and malignant ovarian neoplasms. This study presents the clinicopathological features of the cases diagnosed with BOT in the pathology department.*

Material and Methods: *The 139 patients were selected retrospectively. Haematoxylin&eosin slides were re-evaluated according to the 2020 World Health Organization classification. The data of the patients were obtained from the hospital archive.*

Results: *The mean age was 44.8. Intraoperative consultation was performed on 114 patients, and 86 of them (75.4%) were diagnosed with BOT. The most common histology was serous, followed by mucinous and seromucinous (54.8%, 32.5%, and 7.6%, respectively). Serous histology was observed in 16 of 18 bilateral BOT patients and mucinous histology was not seen. Mean tumour sizes were 10.4 cm in serous BOTs, 18.5 cm in mucinous BOTs and 12.4 cm in seromucinous BOTs. Mean CA-125 levels were 180.2 U/ml (N: 35 U/ml) in serous BOTs, 49.5 U/ml in mucinous BOTs and 35.4 U/ml in seromucinous BOTs. Mean CA-19.9 levels were 85.6 U/ml (N: 35 U/ml) in serous BOTs, 54.4 U/ml in mucinous BOTs and 93 U/ml in seromucinous BOTs. The recurrence rate was 10.9% (n=15), and no disease-related death was seen.*

Conclusions: *Serous BOT is the most common subtype, especially since most bilateral BOT has serous histology. Interestingly, the mean CA-19.9 level of seromucinous BOTs was higher than serous and mucinous BOTs. The prognosis can be excellent since the recurrence was observed in very few patients, and no disease-related death was detected.*

Key words: *borderline ovarian tumour; Brenner tumour; neoplasms, cystic, mucinous, and serous; ovarian neoplasms; recurrence*

ÖZET

Amaç: *Borderline over tümörleri (BOT), benign ve malign over neoplazmlarının ara kategorisinde yer alan, nadir sıklıkta görülen tümörlerdir. Bu çalışmada, patoloji bölümünde BOT tanısı alan olguların klinikopatolojik özelliklerinin sunulması amaçlanmıştır.*

Gereç ve Yöntem: *Patoloji bölümünde tanı alan 139 hasta retrospektif olarak seçildi. Vakaların hematoksilen&eozin boyalı lamları 2020 Dünya Sağlık Örgütü sınıflandırmasına göre yeniden değerlendirildi. Hastaların verileri hastane arşivinden elde edildi.*

Bulgular: *Ortalama yaş 44,8 idi. İntraoperatif konsültasyon yapılan 114 hastanın 86'sına (%75,4) BOT tanısı konuldu. En sık görülen histolojik alt tip serözdü, bunu müsinöz ve seromüsinöz takip ediyordu (%54,8, %32,5 ve %7,6). On sekiz bilateral BOT hastasının 16'sında seröz histoloji gözlendi; müsinöz histoloji görülmedi. Ortalama tümör boyutları seröz BOT'larda 10,4 cm, müsinöz BOT'larda 18,5 cm ve seromüsinöz BOT'larda 12,4 cm idi. Ortalama CA-125 düzeyleri seröz BOT'larda 180,2 U/ml (N: 35 U/ml), müsinöz BOT'larda 49,5 U/ml ve seromüsinöz BOT'larda 35,4 U/ml idi. Ortalama CA-19,9 düzeyleri seröz BOT'larda 85,6 U/ml (N: 35 U/ml), müsinöz BOT'larda 54,4 U/ml ve seromüsinöz BOT'larda 93 U/ml idi. Rekürrens oranı %10,9 idi (n=15) ve hastalığa bağlı ölüm görülmedi.*

Sonuç: *Seröz BOT en yaygın alt tipti ve özellikle bilateral BOT'ların büyük çoğunluğu seröz histolojiye sahipti. İlginç bir şekilde, seromüsinöz BOT'ların ortalama CA-19,9 seviyesi seröz ve müsinöz BOT'lardan daha yüksekti. Çok az hastada rekürrens gözlendiğinden ve hastalığa bağlı ölüm tespit edilmediğinden, prognozun mükemmel olduğu söylenebilir.*

Anahtar kelimeler: *borderline over tümörü; Brenner tümörü; neoplazmlar, kistik, müsinöz ve seröz; over neoplazmları; rekürrens*

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Introduction

Borderline ovarian tumour (BOT) is a neoplasm characterized by cellular proliferation with mild nuclear atypia but without stromal invasion[1]. It is classified as an intermediate between benign and malignant ovarian epithelial tumours. It has six subgroups distinguished by epithelial cell type, commonly comprising serous, mucinous, and less commonly endometrioid, clear cell, seromucinous, and Brenner BOT[2,3]. Compared with ovarian carcinoma, BOTs are portrayed clinically by a younger age at diagnosis and better overall survival[4,5]. BOTs can exist either unilaterally or bilaterally[6]. The majority of them belong to serous and mucinous subtypes[2,3]. Although it is stated that BOTs do not make stromal invasion, they can be associated with microinvasion, intraepithelial carcinoma, lymph node involvement, and peritoneal implants [1,7].

At diagnosis, most BOTs are stage I according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system. The main treatment is surgical same as for malignant ovarian tumours. Fertility-sparing surgery that preserves the uterus and at least part of one ovary is preferable for young women. Hysterectomy and bilateral salpingo-oophorectomy could be performed in people who have completed their fertility. Routine lymph node dissection is controversial because there is no difference in the recurrence or survival rate of whether lymphadenectomy is performed or not[8,9]. Follow-up with tumour markers such as CA-125, CEA and CA-19.9 could have a role in the postoperative period because of elevated in 25–60% of patients at diagnosis[10].

The study aims to retrospectively analyse the clinical and histopathological features of BOTs diagnosed in our centre and investigate their compatibility with the literature.

Material and Methods

Ethics committee approval was received for this study from the university's ethics committee (Approval date: 14/03/2021, number: 0110). Written informed consent was obtained from patients who participated in this study. We retrospectively examined the patients with BOT diagnosed in the pathology department between January 2006 and December 2017. The cases were reviewed by two pathologists (SDA and SY) on haematoxylin and eosin-stained slides and reclassified according to the 2020 World Health Organization (WHO) classification. The presence of epithelial proliferation <10% of the tumour and the invasion ≥5 mm in the greatest dimension in any single focus were accepted as exclusion criteria. Stromal microinvasion was defined as <5 mm invasion in the greatest dimension, and these cases were included in the study. In serous BOT cases, the implants were evaluated as non-invasive and invasive implants (low-grade serous carcinoma).

Statistical Analysis

From the hospital database, the patient's age, tumour side (right/left/bilateral), mean tumour size, the levels of pre-operative CA-125 (Cancer Antigen-125), CA-19.9 (Cancer Antigen-19.9), intraoperative consultation (frozen procedure) pathology records, type of surgical treatment, presence of implants, lymph node status, presence of recurrence and results of malignant transformation were noted. All data were collected with Microsoft Excel (Redmond, WA, USA).

Results

A total of 139 patients were included in the study. Clinicopathological parameters of all patients were given in Table 1. The mean age at diagnosis was 44.9 (range: 12–80). The mean age by histological type was 43.1, 45.3, and 45.3 years in serous, mucinous, and seromucinous BOTs, respectively. Forty-eight tumours (35.8%) were localized on the right side and 68 (50.7%) tumours were on the left side. Bilateral tumours were observed in 18 (13.4%) patients. The tumour localization of 5 patients could not be reached because they were consultation cases. The histologic types of BOTs according to localizations were given in Table 2. Patients with 18 bilateral tumours were added separately when calculating the mean tumour size and there was a total of 157 tumours. The tumour size of 13 patients could not be reached, therefore the tumour size of 144 tumours was calculated. The mean tumour size was 13.4 cm (range: 0.8–35). Of 129 patients whose preoperative CA-125 level was reached, 39 (30.2%) had high levels (≥35 U/ml). Of 126 patients whose CA-19.9 level was reached, 29 (23%) had high levels (≥35 U/ml). The comparison of the number of tumours, the mean age, the mean tumour size, and the levels of CA-125 and CA-19.9 at serous, mucinous and seromucinous BOTs were made in Table 3.

Intraoperative consultation was performed on 114 of 139 (82%) patients. The sensitivity of the frozen

Table 1. *Clinicopathological parameters of all patients*

	Number of patients (%)
Total number of patients	139
Mean age, years (range)	44.9 (12–80)
Mean tumour size, cm (range)	13.4 (0.8–35)
Laterality (n=134)	
– Right	48 (35.8%)
– Left	68 (50.7%)
– Bilateral	18 (13.4%)
Histologic type, per tumour (n=157)	
– Serous	68 (43.3%)
– Serous micropapillary/cribriform	10 (6.4%)
– Serous microinvasive	8 (5.1%)
– Mucinous	42 (26.8%)
– Mucinous + intraepithelial carcinoma	5 (3.2%)
– Mucinous microinvasive	4 (2.5%)
– Seromucinous	12 (7.6%)
– Brenner	2 (1.3%)
– Endometrioid microinvasive	3 (1.9%)
– Clear cell microinvasive	1 (0.6%)
– Serous + endometrioid	1 (0.6%)
– Seromucinous + endometrioid	1 (0.6%)
Frozen procedure results (n=114)	
– Benign	20 (17.5%)
– Borderline	86 (75.4%)
– Malignant	2 (1.8%)
– Could not be decided	6 (5.3%)
Stage (n=139)	
– IA	91 (65.5%)
– IB	7 (5%)
– IC	26 (18.7%)
– IIIA1	3 (2.2%)
– IIIB	1 (0.7%)
– IIIC	11 (7.9%)
Tumour implants (n=45)	
– Non-invasive	5 (11.1%)
– Invasive	3 (6.7%)
– Absence	37 (82.2%)
Lymph node involvement (n=48)	
– Presence	7 (14.6%)
– Absence	41 (85.4%)
Recurrence (n=137)	
– Presence	15 (10.9%)
– Absence	122 (89.1%)
Malignant transformation (n=137)	
– Presence	4 (2.9%)
– Absence	133 (97.1%)

Table 2. *The histologic types of borderline ovarian tumours according to primary localizations*

Tumour localizations	Histologic type	Number of patients (%)
Right	Serous	21 (43.6%)
	Serous micropapillary/cribriform	3 (6.3%)
	Serous microinvasive	1 (2.1%)
	Mucinous	17 (35.4%)
	Mucinous + intraepithelial carcinoma	2 (4.2%)
	Mucinous microinvasive	1 (2.1%)
	Seromucinous	2 (4.2%)
	Endometrioid microinvasive	1 (2.1%)
Total: 48 (100%)		
Left	Serous	23 (33.8%)
	Serous micropapillary/cribriform	3 (4.4%)
	Serous microinvasive	3 (4.4%)
	Mucinous	23 (33.8%)
	Mucinous + intraepithelial carcinoma	3 (4.4%)
	Mucinous microinvasive	2 (2.9%)
	Seromucinous	7 (10.3%)
	Brenner	2 (2.9%)
	Seromucinous + endometrioid	1 (1.5%)
	Clear cell microinvasive	1 (1.5%)
Total: 68 (100%)		
Bilateral (n=18)	Serous	11 (61.1%)
	Serous micropapillary/cribriform	1 (5.6%)
	Serous microinvasive (right side) + Serous micropapillary/cribriform (left side)	2 (11.1%)
	Serous microinvasive (right side) + Serous (left side)	1 (5.6%)
	Seromucinous	1 (5.6%)
	Serous + endometrioid (right side) + Serous (left side)	1 (5.6%)
	Endometrioid microinvasive	1 (5.6%)
Total: 18 (100%)		

procedure was 75.4%. It was determined that two of the patients who underwent the frozen procedure were overdiagnosed, and 20 of them were underdiagnosed. Of the 2 cases overdiagnosed in the frozen procedure, 1 was signed out as serous BOT and 1 as mucinous BOT on the permanent pathology report. Of the 20 cases underdiagnosed in the frozen procedure, 15 were signed out as mucinous BOT, 3 as serous, 1 as seromucinous BOT and 1 as Brenner BOT on the permanent pathology report. Immunohistochemical stainings

Table 3. *The comparison of the number of tumours, the mean age, the mean tumour size, and the levels of CA-125 (Cancer Antigen-125) and CA-19.9 (Cancer Antigen-19.9) at serous, mucinous and seromucinous borderline ovarian tumours*

	Serous (including micropapillary/ cribriform and microinvasive)	Mucinous (including intraepithelial carcinoma and microinvasive)	Seromucinous	All
Number of tumours (%)	86 (54.8%)	51 (32.5%)	12 (7.6%)	157 (100%)
Mean age, years	43.1	45.3	45.3	44.9
Mean tumour size, cm	10.4	18.5	12.4	13.4
Number of high CA-125 level/ number of tumours (%)	21/86 (24.4%)	14/51 (27.5%)	3/12 (25%)	39/157 (24.8%)
Mean CA-125 level, U/ml	180.2	49.5	35.4	128.6
Number of high CA-19.9 level/ number of tumours (%)	9/86 (10.5%)	15/51 (29.4%)	3/12 (25%)	29/157 (18.5%)
Mean CA-19.9 level	85.6	54.4	93	76.6

were applied to 6 of 51 cases diagnosed with mucinous BOT to differentiate primary/metastasis. Four cases were cytokeratin 7 positive and cytokeratin 20 negative, whereas 2 cases were cytokeratin 7 positive and cytokeratin 20 positive.

Fertility-sparing surgery was performed in 46 of 139 (33.1%) patients. Ten of these patients underwent staging surgery, and 10 underwent comprehensive staging surgery. Of the 93 (66.9%) patients who did not have fertility-sparing surgery, 47 had staging surgery, and 10 had comprehensive staging surgery. Appendectomy was performed in 33 patients. Two of the patients who underwent appendectomy were diagnosed with low-grade mucinous neoplasia, and the BOT in these two cases had a serous histologic type. Non-invasive tumour implants were diagnosed in 5 patients (11.1%) and invasive implants were diagnosed in 3 patients (6.7%) in serous BOTs cases. Disseminated peritoneal adenomucinosis was detected in 4 of 23 mucinous BOT cases for which omental/peritoneal sampling was performed. All patients were staged based on the FIGO staging system 2020. Of all 139 patients, 124 (89.2%) had FIGO stage I disease, and 15 (10.8%) had stage III disease.

The mean follow-up period was 75.3 months. Recurrence was observed in 15 patients during follow-up. Of these patients, 8 had serous BOT, 2 had serous micropapillary/cribriform BOT, 2 had mucinous BOT, 2 had seromucinous BOT, and 1 had seromucinous + endometrioid BOT. Of these patients who developed recurrence, 3 of them had a malignant transformation, and 1 had recurrent disease with borderline histology. Six patients died of other reasons, and none of the patients died of disease.

Discussion

Borderline ovarian tumours generally have a good prognosis between benign and malignant tumours. It occurs at a younger age than ovarian carcinoma and has a low stage at the time of diagnosis. In this study of 139 patients, we examined borderline ovarian tumours diagnosed in our department. The mean age was slightly higher than in previous studies and was 44.9 years, ranging from 12 to 80 years; 61 of these patients (43.9%) were <40 years. And the mean age was found to be 38 years and above in studies[8,9,11,12]. When we compared the mean age according to the histological types, it was seen that serous BOT occurred slightly younger than mucinous and seromucinous BOTs. In the literature, a major part of the cases with BOTs are serous and mucinous subtypes. Consistent with previous studies, the most common histological type in the present study was a serous type, followed by mucinous and seromucinous types, respectively[8,9,11,12].

Although BOT is known to generally proceed with a favourable prognosis, differentiating between benign and malignant lesions at diagnosis is also important for correct surgical treatment. Hence, the accurate diagnosis is based on histopathological examination, which highlights the matter of intraoperative consultation (frozen procedure). The diagnostic criteria of BOT require adequate sampling to determine 10% atypical proliferation features without invasion. In our study, 114 of 139 (82%) patients underwent the frozen procedure, and the accuracy rate was reported at 75.4%. In studies, the accuracy rates of BOT diagnosis in the frozen procedure range between 55.5% and 79%[13–17]. In the permanent pathology reports, a mucinous BOT diagnosis was given to 15 of 20 cases considered benign

in the frozen procedure. This result, which is not unexpected, is consistent with the literature[13]. Reasons such as less sampling, sampling errors and misinterpretation may lead to under or overdiagnosis[18,19]. Pathologists should pay attention to some details that might help to reduce the inconsistency of frozen procedures, such as understanding the histologic limitations of the frozen procedure and routing to permanent pathology diagnosis when needed.

In our study, the mean tumour size was slightly lower in the serous subtype compared to the mucinous and seromucinous subtypes. In addition, mucinous BOTs had a mean tumour size of 18.5 cm, higher than the mean size of all tumours (13.4 cm). In the study of Houck et al., the mean diameter of overall tumours was 13.7 cm, 10.2 cm for serous, and 20.1 cm for mucinous[15]. In the literature, a major part of the cases with BOTs are serous and mucinous subtypes. Consistent with previous studies in the present study, the most common histological type was a serous type, followed by mucinous and seromucinous types, respectively[8,9,11,12]. In a systematic review of 6362 cases, 78.9% of patients with BOT are diagnosed at FIGO stage I (20). In our study, 89.2% of our patients had stage I disease, which is more frequent than the literature. This result supports that patients with BOT have better survival than patients with ovarian cancer.

In our study, it was seen that high CA-125 levels were in 24.4% of serous BOTs, with a mean of 180.2 U/ml, 27.5% of mucinous BOTs, with a mean of 49.5 U/ml, 25% of seromucinous BOTs with a mean of 35.4 U/ml, while it was in 24.8% of all tumours with a mean of 128.6 U/ml. Although three studies, one from Türkiye, showed higher CA-125 levels in serous and mucinous BOTs than in our results, our mean CA-125 levels were slightly higher than the study of Gotlieb et al.[5,11,21]. In our patients with mucinous BOTs, CA-19.9 levels were more elevated than in patients with serous BOTs, and this result supports the other studies[21,22]. The mean CA-19.9 level was higher in seromucinous BOTs than in serous and mucinous BOTs. A case report was diagnosed as a seromucinous BOT derived from endometriosis due to the increase in CA-19.9 levels in the follow-up after the bilateral salpingo-oophorectomy because of peritoneal cysts[23]. It was reported that the CA-19.9 level decreased after the second operation.

In the present study, there were 10 patients with serous micropapillary/cribriform BOT, and one had bilaterality. Recurrence was observed in 2 of these 10 patients. The incidence of serous micropapillary/cribriform BOT was 6.4% in all tumours in our study and 11.6% in serous BOTs. Studies in the literature find different incidences, such as 1% and 25%[8,24]. Stromal microinvasion was defined as <5 mm invasion in the greatest dimension[25]. The effect of microinvasion on recurrence and prognosis is controversial in the literature. Studies indicate that microinvasion does not affect the patients' prognosis as few cases have been reported[5,26,27]. In this study, there were 8 patients with serous microinvasion BOT; none had a recurrence and/or malignant transformation.

The subclassification of extraovarian disease into invasive and non-invasive implants is one of the most important prognostic indicators for serous BOTs[28]. Invasive implants were considered a poor prognostic factor in the studies[29]. In our study, 11.1% of the patients had non-invasive implants, and 6.7% had invasive implants. Recurrence was observed in 2 of 3 patients with invasive implants. The histology of these two patients was serous BOT. Lymph node involvement is not considered an adverse prognostic factor[28–30]. However, one study reported worse progression-free survival in patients with paraaortic lymph node metastases in univariate analysis[31]. Our study observed lymph node involvement in 7 of 48 patients who underwent lymphadenectomy. Recurrence was observed in only 2 of these patients. In addition, the recurrence rate was between 2.7% and 16.6% in studies from Türkiye, and in our study, the recurrence rates were found to be 10.9%, consistent with the literature[5,8,9]. There were limitations in our study. It was a retrospective study without randomized designs and had some deficits in hospital records.

Conclusion

In conclusion, we presented the study of 139 patients with borderline ovarian tumours, and no disease-related death was found. The recurrence rate was found to be low; therefore, we can say that BOTs have an excellent prognosis. This is a publication in a tertiary hospital with pathologists specialising in gynecological pathology, with a high number of cases, and detailed clinical data contributing to the literature, making this study considerable.

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