Original Article

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The Relationship of Tumor Marker Panel with Tumor Size and Histopathological Results in Borderline Ovarian Tumor

Borderline Over Tümöründe, Tümör Belirteç Paneli ile Tümör Boyutu ve Histopatolojik Sonuçların İlişkisi

Canan SATIR ÖZEL[1], Eda GÜNER ÖZEN[2], Oğuz Devrim YARDIMCI[1], Ergül DEMİRÇİVİ[1], Abdulkadir TURGUT[3]

[1]Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İzmir City Hospital, Clinic of Obstetrics and Gynecology, İzmir, Türkiye
[3]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye

ABSTRACT

Objective: This retrospective, cross-sectional, and single-center study aimed to explore the correlation between preoperative tumor marker panel levels, tumor size, and histopathological features in borderline ovarian tumors (BOTs).

Methods: Sixty-seven patients, with confirmed pathologic results indicating BOTs, were included. The patients were categorized into two groups based on the type of surgery performed (comprehensive surgery and fertility-sparing surgery). The evaluation encompassed parameters such as tumor size, tumor laterality, histopathological tumor type, and other clinicopathological features.

Results: Preoperatively, 32 patients (47.7%) exhibited high cancer antigen (CA) -125, 13 patients (19.4%) high CA 19-9, 3 patients (4.4%) high CA 15-3, 7 patients (10.4%) high carcinoembryonic antigen (CEA), and 2 patients (2.9%) high alpha-fetoprotein (AFP) levels. A statistically significant correlation was observed between tumor size and elevated CEA values (p=0.010). However, no significant correlations were found between tumor size and CA-125, CA 19-9, CA 15-3, and AFP levels. Histopathological types showed a significant correlation with mean tumor diameter; serous, mucinous, and seromucinous (mixed) types had mean tumor diameters of 10.14±4.58 cm, 19.35±9.23 cm, and 10.67±6.17 cm, respectively (p=0.001).

ÖZ

Amaç: Bu retrospektif, kesitsel ve tek merkezli çalışmanın amacı borderline over tümörlerinde (BOT) preoperatif tümör belirteç paneli düzeyleri ile tümör boyutu ve histopatolojik özellikler arasındaki ilişkiyi araştırmaktır.

Yöntemler: Patoloji sonuçları BOT lehine doğrulanan 67 hasta çalışmamıza dahil edildi. Hastalar kapsamlı cerrahi ve fertilite koruyucu cerrahi uygulananlar olarak iki gruba ayrıldı. Tüm hastalar tümör boyutu, tümör lateralitesi, tümörün histopatolojik tipi ve diğer klinikopatolojik özellikler açısından değerlendirildi.

Bulgular: Ameliyat öncesi hastaların 32'sinde (%47,7) yüksek kanser antijen (CA) -125, 13'ünde (%19,4) yüksek CA 19-9, 3'ünde (%4,4) yüksek CA 15-3, 7'sinde (%10,4) yüksek karsinoembriyonik antijen (CEA) ve 2'sinde (%2,9) yüksek alfa-fetoprotein (AFP) düzeyleri mevcuttu. Tümör boyutu ile yüksek CEA değerleri arasındaki ilişki istatistiksel olarak anlamlıydı (CEA değerleri <4 cm, 4,1-10 cm ve >10 cm tümör boyutları için sırasıyla 4,95±4,48, 2,27±3,07 ve 5,17±16,45, p=0,010). Tümör boyutu ile CA-125, CA 19-9, CA 15-3 ve AFP düzeyleri arasında anlamlı bir ilişki bulunmadı. Histopatolojik tipler ile ortalama tümör çapı arasında istatistiksel olarak anlamlı bir korelasyon saptandı ve ortalama tümör çapı (cm) seröz, müsinöz ve seromüsinöz

Address for Correspondence: Eda Güner Özen, University of Health Sciences Türkiye, İzmir City Hospital, Clinic of Obstetrics and Gynecology, İzmir, Türkiye
E-mail: edaguner92@gmail.com **ORCID ID:** orcid.org/0000-0003-1102-9741

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ABSTRACT

Conclusion: Elevated tumor marker levels, especially CEA, may indicate larger tumor sizes, with mucinous BOTs being more associated with larger diameters. However, preoperative increases in tumor marker levels do not reliably predict histopathological typing for clinicians.

Keywords: Borderline ovarian tumors, tumor size, tumor markers

ÖZ

(mikst) tipler için sırasıyla 10,14±4,58, 19,35±9,23 ve 10,67±6,17 bulundu (p=0,001).

Sonuç: Özellikle CEA için yüksek tümör belirteç seviyeleri, daha büyük tümör boyutuna işaret edebilir. Büyük tümör çapı daha çok müsinöz tip borderline over tümörleri ile ilişkilidir. Ancak ameliyat öncesi tümör belirteçlerinden herhangi birinin düzeyindeki artış histopatolojik tiplemeyi öngörmede klinisyenler için sağlıklı bir yol sağlamamaktadır.

Anahtar Kelimeler: Borderline over tümörleri, tümör boyutu, tümör belirteçleri

Introduction

Ovarian cancer ranks fifth in cancer-related deaths among women, surpassing other cancers of the female reproductive system in mortality (1). Borderline ovarian tumors (BOTs) account for 10-20% of all epithelial ovarian cancers (2) and share similar risk factors with invasive epithelial ovarian cancers (3). Unlike invasive cancers, BOTs lack stromal invasion, though approximately 10% may exhibit microinvasion areas (4). Patients with BOTs may be asymptomatic or present with symptoms such as pelvic pain, distension, dyspareunia, or the discovery of an adnexal mass during routine pelvic examinations. Tumor size in BOTs, like other ovarian tumors, can vary. BOTs lack a specific sonographic appearance, and measurements of tumor markers are nonspecific (5). While a high cancer antigen (CA) -125 level in serum may raise suspicion of ovarian cancer, it is not a reliable indicator for detecting BOTs. Elevated CA19-9 and carcinoembryonic antigen (CEA) levels are typically observed in stage 1b and higher stages (6). The association between BOTs and elevated levels of CA15-3 and alpha-fetoprotein (AFP) lacks substantial evidence from large-scale studies.

The majority of borderline ovarian tumor cases are of serous or mucinous histology. Rarely, endometrioid, clear-cell, mixed (seromucinous), or transitional cell (Brenner) borderline tumors are identified (7). Surgical intervention stands as the primary treatment for BOTs. In young women, the treatment goal is complete tumor removal. For patients who have completed their fertility, the recommended optimal treatment involves total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Complete staging may necessitate pelvic and paraaortic lymph node dissection and omentectomy. Fertility-sparing surgery is an option for suitable patients.

This study aims to investigate the correlation between preoperative levels of a tumor marker panel, tumor size, and histopathological features in BOTs. It involves measuring the levels of a panel of serum tumor markers, including CA-125, CA 15-3, CA 19-9, CEA, and AFP.

Methods

BOTs are characterized by nuclear atypia, epithelial stratification, formation of microscopic papillary projections, cellular pleomorphism, and increased mitotic activity without stromal invasion (12). This study retrospectively examined pathology results from patients treated at the Obstetrics and Gynecology department of a tertiary hospital between 01.01.2011 and 01.04.2022. A total of 67 patients diagnosed as having BOTs, including a tumor marker panel comprising CA-125, CA 19-9, CA 15-3, CEA, and AFP, were included in the study. Patient anamnesis provided information on age, obstetrical history, menopause status, complaints at the time of admission, and smoking.

Normal upper limits for tumor marker values were established as 35 U/mL for CA-125, 34 U/mL for CA 19-9, 26.2 U/mL for CA 15-3, 5 ng/mL for CEA, and 7 ng/mL for AFP. Patients with elevated preoperative serum CA 15-3 levels underwent mammography or breast sonography to rule out related breast diseases.

Patients were categorized based on the surgical procedures performed, either comprehensive or fertility-sparing surgery. Comprehensive surgical staging included peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, bilateral pelvic and paraaortic lymph node dissection, and appendectomy. Fertility-preserving surgery was defined as operations in which the uterus and at least one ovary were preserved.

All patients underwent evaluation for tumor size, tumor laterality, histopathological type, and other clinicopathological features. Tumor size was determined based on the largest diameter reported in the pathological examination, with tumors classified into three groups as <4 cm, 4.1-10 cm, and >10 cm. Staging followed the 2014 International Federation of Gynecology and Obstetrics classification (1).

To ensure the study's integrity, patients with concurrent conditions (e.g., endometrioma, pelvic inflammatory disease) that might lead to elevated CA 125 levels were also excluded.

Ethical permission was obtained from İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Ethics Committee for ethical compliance (approval no: 2022/0354, date: 01.06.2022).

Given the retrospective nature of the study and the analysis of anonymized data, the ethics committee waived the requirement for informed consent.

Statistical Analysis

The study employed a range of statistical tests, including the Kruskal-Wallis test, chi-square analysis, ANOVA test, Fisher's exact test, and Mann-Whitney U test. The predetermined cut-off value for statistical significance was set at $p<0.05$.

Results

Sixty-seven cases were identified, and their demographic characteristics are presented in Table 1. The mean age at diagnosis for the 67 patients included in the study was 43 (range: 18-86). Preoperatively, 32 patients (47.7%) exhibited elevated CA-125 levels, 13 (19.4%) had elevated CA 19-9 levels, 3 (4.4%) showed elevated CA 15-3 levels, 7 (10.4%) had elevated CEA levels, and 2 (2.9%) had elevated AFP levels. Bilateral tumors were observed in 7 patients. The diagnosed borderline tumors comprised 32 (47.8%) serous, 23 (34.3%) mucinous, 9 (13.4%) seromucinous (mixed), 2 endometrioid, and 1 Brenner tumor. Tumor size was less than 4 cm in 8 patients (11.9%), between 4.1-10 cm in 21 patients (31.3%), and more than 10 cm in 38 patients (56.7%). No recurrence was detected in the follow-up until September 2022.

The lymph node involvement rate was 1.5% (1/67), and positive peritoneal washing cytology was observed in 5 patients (7.4%). Micropapillary invasion was present in 8 patients (11.9%), and only 1 patient (1.5%) had borderline interpretation on omental histopathologic examination. The distribution of surgical stage and histological subtype of BOTs is given in Table 2 and there is no significant difference between the groups.

The mean preoperative tumor marker levels concerning tumor size are outlined in Table 3. A significant correlation was found between tumor size and high CEA values ($p=0.010$), with CEA values for tumor sizes <4 cm, 4.1-10 cm, and >10 cm being 4.95±4.48, 2.27±3.07, and 5.17±16.45, respectively. However, no significant correlation was found between tumor size and CA-125, CA 19-9, CA 15-3, and AFP levels.

Table 4 illustrates a significant correlation between histopathological types and mean tumor diameter (cm) (10.14±4.58, 19.35±9.23, and 10.67±6.17 for serous, mucinous, and seromucinous types, respectively; $p=0.001$).

The mean preoperative tumor marker values concerning histopathology are summarized in Table 5. No significant correlation was found between preoperative CA-125, CA 19-9, CA 15-3, CEA, and AFP values and histopathological types. Although not statistically significant, CA-125 levels were approximately 2 times higher in serous compared to mucinous borderline tumors, and CEA levels were approximately 4 times higher in mucinous compared to serous borderline tumors. Four extreme values (>1000 U/mL) for the CA19-9 variable were excluded from the analysis.

Table 1. Demographic data

	Average ± SD or number (percentage)
Age	43.01±15.71
Pregnancy history	
Pregnant	2.52±2.67
Parity	2.15±2.43
Obstetrics history	
SVD	1.72±2.51
CS	0.43±0.76
D&C	0.37±0.80
Menopause status	
Premenopausal	46 (68.7)
Postmenopausal	21 (31.3)
Presenting complaint	
Asymptomatic	21 (31.3)
Pelvic pain	30 (44.8)
Abdominal distention	9 (13.4)
Abnormal uterine bleeding	5 (7.5)
Nausea and vomiting	2 (3.0)
Type of surgery	
Comprehensive	38 (56.7)
Fertility-sparing	29 (43.3)
FIGO staging	
Unstaged	12 (17.9)
1a	41 (61.1)
1b	6 (9.0)
1c	5 (7.4)
2b	2 (3.0)
3b	1 (1.5)
Tumor laterality	
Right	32 (47.8)
Left	28 (41.8)
Bilateral	7 (10.4)
Tumor size (cm)	
<4	8 (11.9)
4.1-10	21 (31.3)
>10	38 (56.7)
Histopathology	
Serous	32 (47.8)
Mucinous	23 (34.3)
Mixed (seromucinous)	9 (13.4)
Endometrioid	2 (3.0)
Brenner	1 (1.5)
Preoperative CBC parameters	
Hemoglobin	12.13±1.50
Hematocrit	36.97±4.11
Platelet	275.64±70.89
White blood cell	7.27±2.47
C-reactive protein	1.79±2.92

SD: Standard deviation, SVD: Spontaneous vaginal delivery, CS: Cesarean section, D&C: Dilatation and currettage, CBC: Complete blood count, FIGO: International Federation of Gynecology and Obstetrics

Table 2. Distrubution of surgical stage and histological subtype of borderline ovarian tumors

		Histology*			p-value
FIGO staging	Number of patient	Serous (n=32)	Ucinous (n=23)	Mixed (seromucinous) (n=9)	
IA	41	19 (46.3%)	18 (43.9%)	4 (9.8%)	0.361
IB and higher	13	8 (61.5%)	2 (15.4%)	3 (23.1%)	
Unstaged	10	5 (50.0%)	3 (30.0%)	2 (20.0%)	

*Endometrioid type was detected in 2 patients and Brenner tumor was detected in 1 patient. These patients were excluded from the analysis, FIGO: International Federation of Gynecology and Obstetrics

Table 3. The mean preoperative tumor markers levels with regard to tumor size

	Tumor size (cm)			
Tumor markers	<4 (n=8)	4.1-10 (n=21)	>10 (n=38)	p-value
CA-125 (U/mL)	95.35±133.71	58.81±77.47	103.37±194.96	0.651
CA 19-9 (U/mL)*	36.04±50.60	23.04±50.06	25.25±27.64	0.334
CA 15-3 (U/mL)	17.49±11.21	13.46±5.65	13.56±5.84	0.800
CEA (ng/mL)	4.95±4.48	2.27±3.07	5.17±16.45	0.010
AFP (ng/mL)	3.99±2.91	2.87±2.20	2.60±1.17	0.599

*Four extreme values (>1000 U/mL) for the CA19-9 variable were excluded from the analysis, CA: Cancer antigen, CEA: Carcinoembryonic antigen, AFP: Alpha-fetoprotein

Table 4. The mean and subcategorized tumor size with regard to histopathology

	Histopathology			
	Serous (n=32)	Mucinous (n=23)	Mixed (seromucinous) (n=9)	p-value
Tumor size (cm, mean)	10.14±4.58	19.35±9.23	10.67±6.17	**0,001**
Tumor size (cm)				0.058
<4	2 (33.3%)	2 (33.3%)	2 (33.3%)	
4.1-10	14 (66.7%)	3 (14.3%)	4 (19.0%)	
>10	16 (43.2%)	18 (48.6%)	3 (%8,1)	
Tumor laterality				0.319
Unilateral	28 (49.1%)	22 (38.6%)	7 (12,3)	
Bilateral	4 (57.1%)	1 (14.3%)	2 (28.6%)	

Table 5. The mean preoperative tumor marker levels with regard to histopathology

	Histology			
Tumor markers	Serous (n=32)*	Mucinous (n=23)**	Mixed (seromucinous) (n=9)	p-value
CA-125 (U/mL)	126.72±199.55	60.7±123.16	34.38±31.99	0.069
CA 19-9 (U/mL)	18.80±22.26	36.89±53.71	10.96±6.96	0.270
CA 15-3 (U/mL)	14.24±5.68	12.5±6.85	14.91±4.5	0.235
CEA (ng/mL)	1.97±2.13	8.36±21.22	2.48±1.75	0.264
AFP (ng/mL)	2.73±1.82	2.78±1.41	3.58±2.83	0.830

Four extreme values (>1000 U/mL) for the CA19-9 variable were excluded from the analysis, CA: Cancer antigen, CEA: Carcinoembryonic antigen, AFP: Alpha-fetoprotein

Discussion

Tumor markers are substances found in tissues, blood, bone marrow, or other body fluids that may serve as indicators of cancer within the relevant system. For ovarian cancer, numerous markers are known and under study, including CA-125, CA 19-9, CA 15-3, CEA, AFP, hCG, lactate dehydrogenase, vascular endothelial growth factor, human epididymis protein 4, inhibin, sFas, kallikrein, hK10, mesothelin, macrophage colony-stimulating factor, osteopontin, and soluble EGF receptor. Among these, CA-125 is the most well-known and widely used in clinical practice, especially in the diagnosis, treatment, and follow-up of epithelial ovarian cancers. Protocols often recommend assessing serum CA-125 at diagnosis and during the follow-up of borderline tumors (8).

BOTs are staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system (9). Most patients with BOTs are diagnosed at FIGO stage 1. Disease spread beyond the pelvis is rare at the time of diagnosis, with abdominal spread being an exception (10). Serum CA-125 antigen levels are higher in cases of serous BOTs and correlate with tumor size and FIGO stage, particularly in serous BOTs. However, a normal level of serum CA-125 antigen does not rule out a BOT (11). In this study, the preoperative serum CA-125 level was elevated in 62% of patients with serous BOTs, and it was also elevated in 50% of patients with tumor sizes both less than 4 cm and greater than 10 cm. Conversely, it was elevated in 42.9% of patients with tumor sizes between 4.1-10 cm. Previous research with 123 patients showed higher preoperative CA-125 levels in those with advanced stage disease compared to those with stage 1 disease (12). In the present study, serum CA-125 levels were elevated in 7.5% of stage 1 patients, while the rate increased to 21.4% in patients with stage 1b and above.

In a study involving 60 patients, none of the tumor markers, including CA-125, CA 15-3, CA 19-9, and CEA, showed a linear correlation with tumor size. However, when grouping the tumor size as <4 cm, 4.1-10 cm, and >10 cm, the mean values of CA-125 and CA 19-9 were found to increase significantly with larger tumor sizes (13). In contrast, in our study among tumor markers, which included CA-125, CA 15-3, CA 19-9, CEA, and AFP, a statistically significant correlation was observed only between the preoperative elevation of CEA values and the increase in tumor size.

The CEA is commonly used as a tumor marker in gastrointestinal system malignancies in contemporary medical practice. A study investigating tumor markers in mucinous ovarian tumors found CEA to be a reliable marker for differentiating between benign, borderline, and malignant tumors (14). In our study, among patients with elevated CEA level, 80% had mucinous histological types, while 20% had a mixed type (seromucinous) BOT.

In another study involving 44 patients with mucinous type BOTs, the preoperative serum CA19-9 level was more frequently elevated than CA-125 and CEA levels. (14). Similarly, in our study, CA19-9 was the most commonly elevated tumor marker in 23 patients (39.1%) with mucinous BOTs.

The comprehensive staging procedure for patients who do not desire future pregnancy includes total hysterectomy and bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and pelvic and para-aortic lymph node dissection. In contrast, more conservative surgery may be considered for patients who wish to preserve fertility. Epidemiological data indicate that approximately one-third of patients with BOTs are younger than 40 years (5). A significant proportion of young patients express the desire to preserve at least one ovary to maintain fertility or avoid menopausal symptoms (15). It's crucial to inform these patients that available data suggest a higher recurrence rate after conservative treatment (10% to 20%) compared to radical surgery (approximately 5%) (16,17). Notably, this higher recurrence rate has not translated into a higher mortality rate, as demonstrated in the largest series to date, the German ROBOT study. (18). In our study, 31.3% of the 67 included patients were nulliparous, with 65.5% of the 29 patients who underwent fertility-sparing surgery belonging to this group.

From a clinical perspective, we believe, based on the results of this study and existing literature, that preoperative discrimination using CA-125 levels is particularly challenging, especially between patients with stage 1 ovarian cancer and those with serous and/or advanced-stage BOTs. Elevated tumor marker levels, especially for CEA, may indicate a larger tumor size. A larger tumor diameter is more associated with mucinous BOTs. However, the preoperative elevation of any tumor markers does not offer a reliable method for clinicians to predict histopathological typing. Larger studies involving a greater number of patients are needed to address these complexities comprehensively.

Study Limitations

The study's retrospective design and the small sample size constitute its limitations.

Conclusion

In conclusion, elevated tumor marker levels, particularly for CEA, may indicate a larger tumor size. A larger tumor diameter is more associated with mucinous BOTs. However, the preoperative rise in the level of any tumor markers does not offer a reliable method for clinicians to predict histopathological typing.

Ethics

Ethics Committee Approval: Ethical permission was obtained from İstanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Ethics Committee for ethical compliance (approval no: 2022/0354, date: 01.06.2022).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: O.D.Y., A.T., Concept: C.S.Ö., E.G.Ö., E.D., Design: C.S.Ö., E.G.Ö., O.D.Y., A.T., Data Collection or Processing: C.S.Ö., E.G.Ö., E.D., Analysis or Interpretation: C.S.Ö., E.G.Ö., O.D.Y., E.D., Literature Search: C.S.Ö., E.G.Ö., O.D.Y., E.D., A.T., Writing: C.S.Ö., E.G.Ö., A.T.

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