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Borderline ovarian tumors: twenty years of experience at a tertiary center

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ABSTRACT

Aims: To investigate whether there is a difference between serum tumor markers panel (CA 125, CA 19-9, CA 15-3, and carcinoembryonic antigen (CEA)) and tumor size and histopathology in well-staged patients with borderline ovarian tumors (BOTs).

Methods: Over the past 20 years (January 2001 to January 2021), the results of four tumor markers (CA 125, CA 19-9, CA 15-3, and carcinoembryonic antigen (CEA)) have been clinically analyzed for for this retrospective cohort study of 156 patients who underwent surgery and were diagnosed with histopathology consistent with a borderline ovarian tumor.

Results: The average age of patients with borderline ovarian tumors was determined to be 51.67 (4.726) years. Before the first surgery, high CA 125 levels (>35 U/l) were found in 53 patients (34%), high CEA levels (>4 ng/ml) were found in 24 patients (15.4%), high CA 19-9 levels (>37 U/ml) were found in 29 patients (18.6%), and high CA 15-3 (>30 ng/ml) levels were found in 12 patients (7.7%). The average CA 125 levels in tumors with serous histopathology [372.8 (1805.2)] were higher than those in tumors with mucinous histopathology (p=0.006). There was no statistically significant difference in tumor markers between tumors smaller than 8 cm and larger than 8 cm [(CA 125 p=0,257), (CEA p=0.9), (CA 19-9 p=0.295), (CA 15-3 p=0.404)].

Conclusion: Our primary outcome of the study is an increase in CA 125 levels, which indicates serous histopathology. Our secondary outcome is the higher levels of tumor markers, but it does not suggest larger tumors.

Keywords: Borderline epithelial ovarian tumors, tumor markers, CA 125

INTRODUCTION

Borderline epithelial ovarian tumors (BOTs) make up 10-20% of all epithelial ovarian tumors and are primarily derived from ovarian epithelial lesions. They are considered a type of carcinoma with low-grade malignant potential.[1] The histologic diagnosis of BOT is determined by the presence of epithelial cellular proliferation features such as stratification of the epithelial lining of the papillae, multi-layering of the epithelium, mitotic activity, and nuclear atypia, in the absence of stromal invasion. The lack of obvious stromal invasion is the primary diagnostic criterion for BOT.[2] A significant portion of BOTs have serous and mucinous histological types. In addition, a small percentage of BOTs can be of clear cell, endometrioid, mixed, transitional, or Brenner type. Approximately 30% of serous borderline tumors are bilateral and frequently have peritoneal implants as a form of extraovarian invasion. Most peritoneal implants are non-invasive, with invasive peritoneal implants seen in approximately 30-35% of cases. Surgical resection is typically considered sufficient. In contrast, bilaterality and extraovarian spread is less frequently observed in mucinous borderline tumors.[3]

It is known that these tumors, which are more commonly seen in young women, have a better prognosis compared to malignant ovarian tumors.[4] Most patients present with asymptomatic adnexal mass. The main goal of treatment for these tumors in young women is to surgically remove the tumor completely. Unilateral oophorectomy is sometimes used as a conservative treatment for Stage I tumors that are limited to only one ovary in young women. For women who have completed their childbearing, the best treatment option is a combination of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies, and examination of fluid collected during the surgery for any abnormal cells. In cases of mucinous tumors, it is also recommended to perform an

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appendectomy. While lymph node removal is not typically recommended as part of the surgical treatment for BOTs, studies have shown that even when there is involvement of the lymph nodes, the survival and recurrence rates remain similar.[5] Currently, there is a lack of research showing the benefits of adjuvant treatments like chemotherapy or radiotherapy for patients with advanced stage BOT or invasive peritoneal implants. It is known that patients with advanced stage BOT respond well to cisplatin-based adjuvant chemotherapy regimens, however, it does not significantly improve on long-term survival.[6]

With this information in mind, we aimed to investigate the relationship between tumor markers, tumor size, and histopathology in patients diagnosed with BOT who underwent surgery in our clinic over the past 20 years.

METHODS

The study was carried out with the permission of Okmeydanı City Hospital Clinical Researches Ethics Committee (Date: 26.12.2022, Decision No: 364). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Over the past 20 years (January 2001 to January 2021), 156 patients who underwent surgery and were diagnosed with histopathology consistent with a borderline ovarian tumor have been clinically analyzed for retrospective cohort study. All patients were evaluated for tumor size, FIGO stage, histopathology, and other clinicopathologic characteristics. They were staged according to surgical findings and the FIGO criteria (2014), and their histological types were determined using the WHO system (2003). Pathological specimens were evaluated by experienced gynecologic pathologists, and patients were divided into 3 histological types: serous, mucinous, and endometrioid. Serous borderline tumors with complex micropapillary structures and a filigree pattern were diagnosed as micropapillary lesions. Microinvasion was defined as a stromal invasion limited to an area of no more than 10 mm^2. The aim of this study is to determine the levels of serum tumor markers including CA 125, CA 15-3, CA 19-9 and CEA, in patients with borderline ovarian tumors and investigate whether there is a difference in the frequency of histopathology types according to tumor size.

The serum levels of CA 125, CA 19-9, CA 15-3 and CEA were analyzed using an automatic microparticle enzyme immunoassay (MEIA). The cutoff limits for normal tumor marker values were taken as 35 U/ml for CA 125, 37 U/ml for CA 19-9, 30 U/ml for CA 15-3 and 4 ng/ml for CEA. Preoperative CA 125, CA 19-9, CA 15-3 and CEA levels were available for all patients.

All patients with high preoperative serum CA 15-3 levels underwent either mammography or breast ultrasound to rule out any related breast conditions. Patients with high CA 19-9 and CEA levels were also evaluated for possible gastrointestinal origin through upper and lower endoscopies. Currently, there is a standardized procedure for measuring ovarian tumors during surgery. The largest diameter of the ovarian tumor is measured at the time of the initial operation and recorded.

Statistical Analysis

Statistical analysis was conducted using SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to check if the data followed a normal distribution. The Student's t-test was applied for normally distributed data and mean (standard deviation (SD)) were used as a descriptive statistical method. For data that did not follow a normal distribution, the Mann-Whitney U test was applied, and the median (as well as the 25th and 75th percentiles) were used as descriptive statistics. The Chi square test was used for categorical data and n(%) was used as descriptive statistics. A p-value of <0.05 was considered statistically significant.

RESULTS

The average age of patients diagnosed with borderline ovarian tumors at the time of diagnosis was 51.67 (4.726). 47.4% of the cases were postmenopausal. 21.1% of the patients were nulliparous, 78.9% were multiparous.

Histopathologically, there were 76 cases of serous (48.7%), 77 cases of mucinous (49.4%), and 3 cases of endometrioid type BOT. 115 cases were stage 1a (73.7%), 10 cases were stage 1b (6.4%), 22 cases were stage 1c (14.1%), 2 cases were stage 2a (1.3%), 4 cases were stage 3a (2.6%), and 3 cases were stage 3c (1.9). The distribution of surgical stage and histological subtype of BOTs are given in **Table 1**.

Table 1. The distribution of surgical stage and histological subtype of BOTs

Stage		Serous (n:76) (49.3%)	Mucinous (n:77) (48.7%)	Endometrioid (n:3) (2%)	Total
1a	Count	48	64	3	115
	%	41.7%	55.7%	2.6%	100.0%
1b	Count	5	5	0	10
	%	50.0%	50.0%	0.0%	100.0%
1c	Count	15	7	0	22
	%	68.2%	31.8%	0.0%	100.0%
2a	Count	2	0	0	2
	%	100.0%	0.0%	0.0%	100.0%
3a	Count	4	0	0	4
	%	100.0%	0.0%	0.0%	100.0%
3c	Count	2	1	0	3
	%	66.7%	33.3%	0.0%	100.0%
Total	Count	76	77	3	156
	%	48.7%	49.4%	1.9%	100.0%

At the time of the initial surgery, 53 patients (34%) had high CA 125 levels (>35 U/l), 24 patients (15.4%) had high CEA levels (>4 ng/ml), 29 patients (18.6%) had high CA 19-9 (>37 U/ml) and 12 patients (7.7%) had high CA 15-3 (>30 ng/ml) levels.

The mean of CA 125 in tumors with serous histopathology [372.8 (1805.2)] was significantly higher than the mean of patients with mucinous BOT [44.75 (56.11)] (p=0.006). No statistical difference was observed between histopathological subtypes in terms of other tumor markers.

When looking at the FIGO stage, 27.8% of patients with Stage 1 BOTs had high CA 125 levels. When dividing the patients into two groups, early-stage (Stage 1) and advanced stage (Stage 2 and above), the percentages of patients with CA 125 levels <35 and >35 were found to be statistically significant between the groups (p=0.033). No statistically significant difference was found when evaluating the other tumor markers.

When the tumor size is divided into two groups, smaller than 8 cm and 8 cm or larger, there was no statistically significant relationship between the tumor markers and the tumor volume [(CA 125, p=0.257), (CEA, p=0.9), (CA 19-9, p=0.295), (CA 15-3, p=0.404)].

In nulliparous women, the average level of CA 125 was found to be significantly higher than in multiparous women (p=0.022).

In multiparous women, the average level of CEA was found to be higher than in nulliparous women (p=0.03). There was no significant difference found between nulliparous and multiparous women in terms of CA 19-9 (p=0.077) and CA 15-3 (p=0.39).

When looked at in terms of parity, there was no significant difference in stages between nulliparous and multiparous patients (p=0.865).

In patients with borderline ovarian tumors, 41.1% of unilateral tumors were of the serous histopathology, 56.6% were of the mucinous histopathology, and 2.3% were of the endometrioid histopathology. 85.2% of bilateral tumors were of the serous histopathology and 14.8% were of the mucinous histopathology. Unilateral tumors were more often of the serous histopathology, while bilateral tumors were more often of the mucinous histopathology (p<0.001). The results are summarized in **Table 2**.

Table 2. Unilateral and bilateral frequency in serous, mucinous and endometriod tumors

		Serous	Mucinous	Endometrioid	Total
Unilateral	Count	53	73	3	129
	%	41.1%	56.6%	2.3%	100.0%
Bilateral	Count	23	4	0	27
	%	85.2%	14.8%	0.0%	100.0%
Total	Count	76	77	3	156
	%	48.7%	49.4%	1.9%	100.0%
Chi-square p<0.001					

Positive peritoneal cytology was detected in 27 (17.3%) patients with BOTs. Peritoneal washing cytology results were positive in 45.3% of patients with high preoperative CA 125 tumor marker levels (p<0.001). The difference between high preoperative tumor markers and positive peritoneal cytology was not statistically significant. It was observed that 48.1% of the BOT patients with positive peritoneal cytology were of the serous histopathological type and 48.1% were of the mucinous histopathological type. There was no statistically significant difference in histopathological type rates between cytology positive and negative groups (p=0.759).

Patients with advanced-stage disease or who are finished childbearing are treated with radical surgery consisting of peritoneal washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, complete peritoneal resection of macroscopic lesions, or multiple peritoneal biopsies; in case of mucinous BOTs, patients also are treated with an appendectomy. Fertility-sparing surgery including unilateral salpingo-oophorectomy or cystectomy, was performed in 40 patients who desired to preserve early-stage fertility.

DISCUSSION

The Carbohydrate Antigen 125 (CA125) was first identified in the early 1980s.[7] CA 125, also known as Cancer Antigen 125 or Tumor Antigen 125, is a mucin-type glycoprotein produced by the MUC16 gene and found on the surface of cells. In laboratory tests, a variety of tumor markers (including CA125, CA19-9, CA15-3, CEA, AFP, LDH, hCG, VEGF, OVX1, immunosuppressive acidic protein, inhibin, sFas, human kallikrein, hK10 and macrophage-colony stimulating factor etc.) have been examined to determine their ability to identify ovarian carcinoma in women.[8]

In studies, CA 125 levels were found to be higher in patients with serous borderline ovarian tumors.[9] There are numerous publications in the literature that support this statement.[10] In our study, CA 125 levels were higher in serous BOT tumors than in mucinous tumors (p=0.006). The difference in terms of CA 125 tumor markers in early and advanced BOTs was statistically significant (p=0.033). There are publications supporting this data in the literature.[11,12] In terms of parity, high CA125 levels were found in nulliparous women,[13] and the mean of CA 125 was found to be higher in nulliparous women in the current study (p=0.022). On the other hand, there are publications that correlate CA 125 levels with peritoneal cytology and peritoneal implants.[10,13] In our study, on the contrary, there was no difference in cytology positivity between patients with high and normal tumor markers.

CA19-9 is a monosialoganglioside that is commonly found in various types of mucinous tumors in the gastrointestinal tract such as the pancreas and biliary tract.[14] Measurement of serum CA19-9 is important in identifying and determining the progression of colorectal, pancreatic, and biliary tract cancers. Elevated levels of serum CA19-9 may indicate the presence of mucinous BOTs.[15] In similar studies, high CA 19-9 levels in serous and mucinous BOTs were found to be 51.5% and 44.7%, respectively,[12] and in another study, they were found to be 44.24% and 36.4%, respectively.[16] In our study, on the contrary, there was no difference in CA 19-9 between mucinous and serous BOTs. Studies have associated high levels of CA 19-9 with larger tumor size.[13] In our study, no relationship was found between tumor sizes and CA 19-9 tumor markers.

CEA, a naturally occurring high molecular weight glycoprotein found in fetal tissues, is often used as a marker for gastrointestinal malignancies. Published studies have shown that high CEA levels are associated with advanced stage and tumor size, with specific nuances.[12,13] On the contrary, there are also publications that do not associate high CEA levels with the stage of FIGO.[17] No association between CEA levels and the stage of FIGO was found in the current study. The CA 15-3 test is used to measure the presence of the MUC-1-encoded glycoprotein, which is commonly known as polymorphic epithelial mucin. This protein is expressed at the surface of most glandular epithelial cells. It is widely used as a marker for breast cancer, but it can also be present at high levels in patients with ovarian cancer.[18] In a similar study, CA 15-3 levels were found to be normal in patients with BOT.[19] In our study, no difference was observed between serous and mucinous BOTs in terms of CA 15-3.

Although in current applications, tumor markers are used to evaluate treatment response and recurrence, they can be helpful in the diagnosis and management of BOTs. We acknowledge the limitations of this study, in particular the small number of women, and not examining the possible inflammatory and proliferative markers on high tumor markers levels. Future prospective studies with large sample size in well-staged patients with BOTs examining the tumor markers levels are needed.

CONCLUSION

Our primary outcome of the study is an increase in CA 125 levels, which indicates serous histopathology. Our secondary outcome is the higher levels of tumor markers, but it does not suggest larger tumors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Okmeydanı City Hospital Clinical Researches Ethics Committee (Date:26.12.2022, Decision No:364).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Yilmaz E, Sahin N, Koleli I, et al. Retrospective analysis of borderline ovarian tumors:outcomes at a single center. *Acta Clin Croat.* 2019;58(1):29-36.
2. Morris CR, Liu L, Rodriguez AO, Cress DR, Snipes K. Epidemiologic features of borderline ovarian tumors in California:a population-based study. *Cancer Causes Control.* 2013;24(4):665-674.
3. Rasmussen CB, Jensen A, Albieri V, Andersen KK, Kjaer SK. Increased risk of borderline ovarian tumors in women with a history of pelvic inflammatory disease: a nationwide population-based cohort study. *Gynecol Oncol.* 2016;143(2):346-351.
4. Matsuo K, Machida H, Mandelbaum RS, et al. Mucinous borderline ovarian tumor versus invasive well-differentiated mucinous ovarian cancer:Difference in characteristics and outcomes. *Gynecol Oncol.* 2019;153(2):230-237.
5. Solmaz Hasdemir P, Guvenal T. Borderline ovarian tumors:a contemporary review of clinicopathological characteristics, diagnostic methods and therapeutic options. *J BUON.* 2016;21(4):780-786.
6. Tropé C, Davidson B, Paulsen T, Abeler VM, Kaern J. Diagnosis and treatment of borderline ovarian neoplasms: the state of the art. *Eur J Gynaecol Oncol.* 2009;30(5):471-482.
7. Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest.* 1981;68(5):1331-1337.
8. Van Haaften-Day C, Shen Y, Xu F, et al. OVX1, macrophage-colony stimulating factor, and CA-125-II as tumor markers for epithelial ovarian carcinoma:a critical appraisal. *Cancer.* 2001;92(11):2837-2844.
9. Gotlieb WH, Soriano D, Achiron R, et al. CA 125 measurement and ultrasonography in borderline tumors of the ovary. *Am J Obstet Gynecol.* 2000;183(3):541-546.
10. Fotopoulou C, Sehouli J, Ewald-Riegler N, et al. The value of serum CA125 in the diagnosis of borderline tumors of the ovary:a subanalysis of the prospective multicenter ROBOT study. *Int J Gynecol Cancer.* 2015;25(7):1248-1252.
11. Rice LW, Lage JM, Berkowitz RS, et al. Preoperative serum CA-125 levels in borderline tumors of the ovary. *Gynecol Oncol.* 1992;46(2):226-229.

12. Tamakoshi K, Kikkawa F, Shibata K, et al. Clinical value of CA125, CA19-9, CEA, CA72-4, and TPA in borderline ovarian tumor. *Gynecol Oncol.* 1996;62(1):67-72.
13. Ayhan A, Guven S, Guven ES, Kucukali T. Is there a correlation between tumor marker panel and tumor size and histopathology in well staged patients with borderline ovarian tumors? *Acta Obstet Gynecol Scand.* 2007;86(4):484-490.
14. Dede M, Gungor S, Yenen MC, et al. CA19-9 may have clinical significance in mature cystic teratomas of the ovary. *Int J Gynecol Cancer.* 2006;16(1):189-193.
15. Engelen MJ, de Bruijn HW, Hollema H, et al. Serum CA 125, carcinoembryonic antigen, and CA 19-9 as tumor markers in borderline ovarian tumors. *Gynecol Oncol.* 2000;78(1):16-20.
16. Chen X, Fang C, Zhu T, Zhang P, Yu A, Wang S. Identification of factors that impact recurrence in patients with borderline ovarian tumors. *J Ovarian Res.* 2017;10(1):23.
17. May J, Skorupskaite K, Congiu M, et al. Borderline ovarian tumors: fifteen years' experience at a scottish tertiary cancer center. *Int J Gynecol Cancer.* 2018;28(9):1683-1691.
18. Yedema KA, Kenemans P, Wobbes T, et al. Carcinoma-associated mucin serum markers CA M²6 and CA M²9:efficacy in detecting and monitoring patients with cancer of the breast, colon, ovary, endometrium and cervix. *Int J Cancer.* 1991;47(2):170-179.
19. Schutter EM, Davelaar EM, Van Kamp GJ, Verstraeten RA, Kenemans P, Verheijen RH. The differential diagnostic potential of a panel of tumor markers (CA 125, CA 15-3, and CA 72-4 antigens) in patients with a pelvic mass. *Am J Obstet Gynecol.* 2002;187(2):385-392.