Comparison of tumor markers and clinicopathological features in serous and mucinous borderline ovarian tumors

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Summary

Objective: The aim of this study was to assess tumor markers and clinicopathological findings of patients with serous and mucinous borderline ovarian tumor (BOT) features. *Methods:* The study consisted of 50 patients that were diagnosed with and treated for BOT between 2005- 2010 in three centers. CA125, CA19-9, and CA125+CA19-9 levels and clinicopathological features were compared in serous and mucinous histotypes. In serous and mucinous BOTs, correlations between tumor markers and demographics such as age, menopausal status, parity, clinical findings (stage, relapse, adjuvant chemotherapy, cytology, lymph node involvement and tumoral morphology (cystic-solid content, papilla, septation) were evaluated. *Results:* There were no significant differences between serous and mucinous tumors in the clinicopathological features such as stage, tumor markers, age, menopausal status, or cytology. In serous BOTs we found a significant relation between elevated CA125+ CA19-9, CA19-9 and recurrence ($p < 0.05$). Also there was a significant relation between elevated CA125+ CA19-9, CA19-9 and cytology positivity ($p < 0.05$). We found a significant relation in serous BOTs between elevated CA125+CA19-9, adjuvant chemotherapy and lymph node metastases ($p < 0.05$). Also In mucinous BOTs with papilla formation we found a significant relation between elevated CA125 and CA125+ CA19-9 ($p < 0.05$).There was significant relation between cytology positivity and elevated CA19-9 in mucinous BOTs ($p < 0.05$). *Conclusion:* Serum tumor markers of serous and mucinous BOTs were different in relation to their clinicopathological features. This may reflect differences of serous and mucinous BOTs.

Key words: Borderline ovarian tumor; Serous; Mucinous borderline ovarian tumor; Tumor markers.

Introduction

Borderline ovarian tumors (BOTs) were first described by Taylor in 1929 [1] and were introduced in 1971 by FIGO as a category of epithelial ovarian tumors [2]. BOT is a different form of both benign epithelial ovarian tumor and invasive epithelial ovarian cancer and accounts for 10-15% of all epithelial ovarian tumors. Clinically BOTs are diagnosed in earlier stage such as Stage I, affect mainly young reproductive women, have low potential for malignancy, including indolent behavior, longer patient survival, and later recurrence as compared with invasive epithelial ovarian tumors [3-6].

The most common histological types of BOTs are serous (65%) and mucinous (35%) tumors [3, 5]. Besides different histological appearances, these subtypes seem to have different etiologies and behavior patterns [6]. There is a clear association between the tumor marker and the histotypes of tumor. Elevated cancer antigen (CA) 125 in serous tumors was significantly more frequent than CA19-9, and elevated CA19-9 levels in mucinous types was more frequent, as shown in several studies [7-9].

Associations between serum tumor markers and clinical and sonographic parameters such as age, premenopausal status, tumor size, stage, and recurrance have been evaluated in many studies, and these have also been compared between serous and mucinous tumors [7-13].

To our knowledge, comparison of serum tumor markers and clinicopathologic features in serous and mucinous subtypes separately, has not been studied yet.

The aim of the present study was to review the clinical characteristics and serum tumor markers CA125 and CA19-9 of patients with BOT with special emphasis on serous and mucinous histology.

Materials and Methods

Fifty patients with BOTs diagnosed and treated in three gynecologic oncology centers between 2005-2010 were studied retrospectively. To be included in the study, a patient had to have complete information about preoperative tumor marker status; CA125, CA19-9. The levels of CA125 were considered positive when ≥ 35 ng/ml and CA19-9 levels were considered positive when ≥ 37 ng/ml [10]. Other tumor markers were not included, because they were not present in the patient records of all BOTs.

Other study characteristics that were analyzed in relation to tumor markers such as demographic characteristics, histotypes, ultrasonographic (US) features, surgery and follow-up were complete in the files. Also, other BOT histotypes such as Brenner, clear cell and endometriod-type BOTs were excluded. Then, both serous and mucinous groups were divided into three subgroups: elevated CA125, elevated both CA125 and CA19-9, and elevated CA19-9.

Tumor marker groups were compared for other parameters

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such as tumor size, age, menopausal status, US features, cytology positivity, etc. Patients were staged according to classification of ovarian carcinomas established by the International Federation of Gynecology and Obstetrics [14]. Pathologically, BOTs are characterized by features of malignant epithelial ovarian tumors, including stratification of epithelial lining of the papillae, formation of microscopic papillary projections, epithelial pleomorphism, atypicality, and mitotic activity, without invasion of stroma [15]. Cystic tumors were defined as cysts with clear fluid, and solid contents were defined as dense echogenic fluid. Papillae were defined as small tissues in the cyst wall, septae were defined as walls inside the cyst (but septa and papilla were not further separated into small, large or thin-thick). Peritoneal implants were classified as non-invasive or invasive depending on the absence or presence of stromal invasion of the peritoneum, respectively. Surgery was considered conservative when the uterus and at least a portion of one ovary were preserved. Staging was considered complete when all peritoneal surfaces were carefully inspected and peritoneal washing, multiple random or oriented biopsies, omentectomy and appendectomy in cases of a mucinous tumor were performed.

Statistical analysis

Statistical analysis was performed with the SPSS software (Chicago, USA) 15 version for Windows. Quantitative variables were compared by using Mann-Whitney U test; categorical variables were compared by using the chi-square test.

Results

We studied a total of 50 patients with BOTs: 30 (60%) serous and 20 (40%) mucinous. Demographics and clinicopathological characteristics of the study are shown in Table 1. The mean ages of BOT cases were 42.7 ± 15.7 and 41.1 ± 12.1 years, serous and mucinous, respectively. Ages of patients with serous BOTs were similar with mucinous tumors.

There were no differences between parity, menopause status, tumor features, tumor contents, tumor bilateralism, rate of positive peritoneal cytology, presence of peritoneal implants, surgical approach, the choice of surgical staging, lymph node metastases, adjuvant chemotherapy, and recurrence in BOTs. Tumor size was 11.0 ± 6.64 for serous and 13.8 ± 9.3 for mucinous BOTs, and tumor size was similar between mucinous and serous BOTs (tumor size 5-10 cm and ≥ 10 cm). Forty-four (88%) patients had Stage I and six (12%) had Stage II-III in BOTs. According to FIGO stage there were no differences between Stage I and II-III.

Mean CA125 levels were 191.1 ± 165.9 in serous BOTs and 163.9 ± 124.2 in mucinous BOTs. Mean serum CA125 was not significant between serous and mucinous BOTs (191.1 ± 145.9 vs 163.9 ± 94.2, respectively). The elevated CA125 rate was 18 cases (60%) of serous and nine (45%) of mucinous, respectively. Also, mean CA19-9 levels were 38.7 ± 43.3 in serous BOTs and 48.1 ± 34.3 in mucinous BOTs. The elevated CA19-9 rate was 26% (8 cases) and 50% (10 cases) for serous and mucinous tumors, respectively. There were no differences between serous and mucinous BOTs according to high and normal value of CA125, CA 19-9 and CA125+CA19-9.

Correlations between tumor markers and clinical features according to histotypes are shown in Table 2. When the serous tumor group and mucinous group were evaluated by elevated CA125, CA125+CA 19-9 and CA19-9 tumor markers and the marker associations with clinicopathological features, there was no correlation between menopausal status, age, parity, tumor size, cystic features, the presence of septum in the tumor, bilaterality and implant positivity for either serous or mucinous tumors. In serous BOTs there was a significant correlation between elevated CA125+CA19-9 stage, adjuvant chemotherapy and lymph node metastases ($p < 0.05$). This correlation was also present in mucinous tumors; the presence of papilla was correlated with CA125+CA19-9, and CA19-9 ($p < 0.05$). In serous BOTs, there was a significant correlation between elevated CA125+CA19-9, and CA19-9 tumor markers and recurrence ($p < 0.05$). Also there was a significant correlation between CA19-9 tumor markers and cytology positivity ($p < 0.05$).

Discussion

Serous and mucinous BOTs are the most frequent histotypes of BOTs, accounting for more than 95% . Besides different histological appearances, these subtypes seem to have different etiology and behavior [6], and are assumed to differ from each other in various aspects such as the rate, tumor characteristics and tumor markers.

Information on the association of preoperative tumor markers and findings for BOT is very limited and dependent on case series.

The most important issue for serous and mucinous BOTs was the difference in tumor markers. Elevated CA125 was significantly more frequent in serous tumors than CA19-9 and, elevated CA19-9 was more frequent in mucinous types [7-9].

Elevated CA125 rates were present in 36-70% of serous BOTs, and 22-52% of mucinous BOTs [6-11]. On the contrary, elevated CA19-9 rates in 8-27% of serous, and 30.4-65% of mucinous BOTs were reported [10, 16].

In another study, median value of CA125 of 142 mucinous BOT cases was 38.0 while the median value of CA19-9 was 49.5 [17]. We found tumor markers (elevated CA125 and CA19-9 levels) in serous and muccinous BOTs to be similar, but this similarity was not statistically significant. In the literature, serum tumor markers and clinicopathological relation assessment studies are few.

The studies, especially on tumor markers and stage, tumor size, recurrence and this relation were compared by multivariant analyses [16, 18].

In one study, associations between clinical, sonographic and serum tumor marker parameters (CA125, CA19-9, CEA, CA15-3) were analyzed [13]. The study showed that patients who had at least one abnormal serum tumor marker were more likely to have large tumors, bilateral tumors and ascites. Women with normal and abnormal tumor markers did not differ in terms of their mean age, familial history of cancer, parity (including nulliparity), menopausal status, presenting symptoms, or the use of

Table 1. — *Demographics and analyses of clinicopathological characteristics in borderline ovarian tumors*.

Characteristics	Total (n = 50)	Serous (n = 30)	Mucinous (n = 20)	*p* value
Mean age (year)	42.08 ± 14	42.73 ± 15.75	41.10 ± 12.169	NS*
Age				
< 40 years	22 (44%)	15 (50%)	7 (35%)	NS **
≥ 40 years	28 (56%)	15 (50%)	13 (65%)	
Parity				
Nulliparous	22 (44%)	12 (40%)	10 (50%)	NS **
Multiparous	28 (56%)	18 (60%)	10 (50%)	
Menopause status				
Premenopausal	36 (72%)	22 (73.3%)	14 (70%)	NS **
Postmenopusal	14 (28)	8 (26.7%)	6 (30%)	
Tumor features				
Papillary absent	24 (48%)	16 (53.3%)	8 (40%)	NS **
Papillary positive	26 (52%)	14 (46.7%)	12 (60%)	
Tumor contents				
Cystic	41 (82%)	26 (86.7%)	15 (75%)	NS **
Semi-solid	9 (18%)	4 (13.3%)	5 (25%)	
Tumor bilateralism				
Unilateral	33 (66%)	18 (60%)	15 (75%)	NS **
Bilateral	17 (34%)	12 (40%)	5 (25%)	
Mean tumor size	12.12 ± 7.88	11.0 ± 6.64	13.80 ± 9.37	NS **
Tumor size				
5-10 cm	32 (64%)	21(70%)	11(55%)	NS **
> 10 cm	18 (36%)	9 (30%)	9 (45%)	
FIGO stage				
I	44 (88%)	25 (83,3%)	19 (95%)	NS **
II-III	6 (12%)	5 (16,6%)	1 (5%)	
Cytology				
Positive	9 (18%)	5 (5%)	4 (20%)	NS **
Negative	41 (82)	25 (83.3%)	16 (80%)	
Implant				
Positive	6 (12%)	5 (16.7%)	1 (5%)	NS **
Negative	44 (88%)	25 (83.3)	19 (95%)	
Surgical approach				
Laparoscopy	7 (14%)	5 (16.7%)	2 (10%)	NS **
Laparotomy	43 (86%)	25 (83.3%)	18 (90%)	
Choice of surgical staging				
Fertility-sparing	11 (22%)	6 (20%)	5 (25%)	NS **
Comprehensive	39 (78%)	24 (80%)	15 (75%)	
Lymph node metastases				
Positive	1 (2%)	1 (3.3%)	0	NS **
Negative	49 (98)	29 (96.7%)	20 (100%)	
Adjuvant chemotherapy				
Yes	4 (8%)	3 (10%)	1 (5%)	NS **
No	46 (92%)	27 (90%)	19 (95%)	
Recurrence				
Yes	4 (8%)	3 (10%)	1 (5%)	NS **
No	46 (92%)	27 (90%)	19 (95%)	
Mean CA125 (U/ml)	171.2 ± 115.5	191.1 ± 165.9	163.9 ± 124.2	NS *
CA125 - High	27 (54%)	18 (60%)	9 (45%)	NS **
Normal	23 (46%)	12 (40%)	11 (55%)	
Mean CA19-9 (U/ml)	42.4 ± 39.9	38.7 ± 43.3	48.1 ± 34.3	NS *
CA19-9 - High	18 (36%)	8 (26.7%)	10 (50%)	
Normal	32 (64%)	22 (73.3%)	10 (50%)	NS **
CA125+CA 19-9				
High	11 (22%)	4 (13.3%)	7 (35%)	NS **
Normal	39 (78%)	26 (86.7%)	13 (65%)	

* Mann-Whitney U test; ** Chi-square test.

Table 2. — *Correlations between tumor markers and clinical features according to histotypes.*

Menopause status	Premenopause (n = 22)	Menopause (n = 8)	*p*	Premenopause (n = 14)	Menopause (n = 6)	*p*
CA125	14 (63.6%)	4 (50%)	NS	5 (37%)	4 (66.6%)	NS
CA125+CA19-9	3 (13.6%)	1 (12.5%)	NS	4 (28.5%)	3 (50%)	NS
CA19-9	6 (27.2%)	2 (25%)	NS	6 (42.8%)	4 (66.6%)	NS
Age	*< 40 age (n: 15)*	*> 40 age (n: 15)*		*< 40 age (n: 7)*	*> 40 age (n: 13)*	
CA125	9 (60%)	9 (60%)	NS	4 (57.1%)	5 (38.4%)	NS
CA125+CA19-9	3 (20%)	1 (6.6%)	NS	3 (42.8%)	4 (30.7%)	NS
CA19-9	6 (40%)	3 (13.3%)	NS	4 (57.1%)	6 (46.1%)	NS
Parity	*Nulliparous (n: 12)*	*Multiparous (n: 18)*		*Nulliparous (n: 10)*	*Multiparous (n: 10)*	
CA125	9 (75%)	9 (50%)	NS	3 (30%)	6 (60%)	NS
CA125+CA19-9	2 (16.6%)	2 (11.1%)	NS	3 (30%)	4 (40%)	NS
CA19-9	2 (16.6%)	6 (33.3%)	NS	5 (50%)	5 (50%)	NS
Stage	*Stage I (n: 25)*	*Stage II-III (n: 5)*		*Stage I (n: 19)*	*StageII-III (n: 1)*	
CA125	15 (60%)	3 (60%)	NS	9 (47.3%)	–	NS
CA125+CA19-9	2 (8%)	–	< 0.05	7 (36.8%)	–	NS
CA19-9	5 (20%)	1 (20%)	NS	10 (52.6%)	–	NS
Tumor size	*Tumor size 5-10 cm (n: 21)*	*Tumor size > 10 cm (n: 9)*		*Tumor size 5-10 cm (n: 11)*	*Tumor size > 10 cm (n: 9)*	
CA125	12 (57.1%)	6 (66.6%)	NS	4 (36.3%)	5 (55.5%)	NS
CA125+CA19-9	2 (9.52%)	2 (22%)	NS	4 (36.3%)	3 (33.3%)	NS
CA19-9	4 (19.04%)	4 (44%)	NS	5 (45.4%)	5 (55.5%)	NS
Tumor features	*Cystic (n: 26)*	*Solid content (n: 4)*		*Cystic (n: 15)*	*Solid content (n: 5)*	
CA125	17 (65.3%)	1 (25%)	NS	6 (40%)	3 (60%)	NS
CA125+CA19-9	4 (15.3%)	–	NS	5 (33.3%)	2 (40%)	NS
CA19-9	7 (26.9%)	1 (25%)	NS	7 (46.6%)	3 (60%)	NS
Papilla	*Papilla negative (n: 16)*	*Papilla positive (n: 14)*		*Papilla negative (n: 8)*	*Papilla positive (n: 12)*	
CA125	8 (50%)	10 (71.4%)	NS	1 (12.5%)	8 (66.6%)	< 0.05
CA125+CA19-9	2 (12.5%)	2 (14.2%)	NS	–	7 (58.3%)	< 0.05
CA19-9	6 (37.5%)	2 (14.2%)	NS	2 (25%)	8 (66.6%)	NS
Septa	*Septa negative (n: 19)*	*Septa positive (n: 11)*		*Septa negative (n: 14)*	*Septa positive (n: 6)*	
CA125	11 (57.8%)	7 (63.6%)	NS	6 (42.8%)	3 (50%)	NS
CA125+CA19-9	1 (5.2%)	3 (27.2%)	NS	5 (35.7%)	2 (33.3%)	NS
CA19-9	4(21.05%)	4 (36.3%)	NS	8 (57.1%)	2 (33.3%)	NS
Tumor bilateralism	*Unilateral (n: 18)*	*Bilateral (n: 12)*		*Unilateral (n: 15)*	*Unilateral (n: 5)*	
CA125	12 (66.6%)	6 (50%)	NS	6 (40%)	3 (60%)	NS
CA125+CA19-9	3 (16.6%)	1 (8.3%)	NS	4 (26.6%)	3 (60%)	NS
CA19-9	4 (22.2%)	4 (33.3%)	NS	7 (46.6%)	3 (60%)	NS
Lymph node metastases	*Lymph node negative (n: 23)*	*Lymph node positive (n: 1)*		*Lymph node negative (n: 15)*	*Lymph node positive (n: 0)*	
CA125	13 (56.5%)	1 (100%)	NS	7 (46.6%)	–	NS
CA125+CA19-9	3 (23%)	1 (100%)	< 0.05	9 (60%)	–	NS
CA19-9	7 (30%)	1 (100%)	NS	10 (66.6%)	–	NS
Cytology	*Cytology negative (n: 25)*	*Cytology positive (n: 5)*		*Cytology negative (n: 16)*	*Cytology positive (n: 4)*	
CA125	15 (60%)	3 (60%)	NS	6 (37.5%)	3 (75%)	NS
CA125+CA19-9	2 (8%)	2 (40%)	NS	4 (25%)	3 (75%)	NS
CA19-9	4 (16%)	4 (80%)	< 0.05	6 (37.5%)	2 (100%)	< 0.05
Implant	*Implant negative (n: 25)*	*Implant positive (n: 5)*		*Implant negative (n: 19)*	*Implant positive (n: 1)*	
CA125	15 (60%)	3 (60%)	NS	9 (47.3%)	–	NS
CA125+CA19-9	2 (8%)	2 (40%)	NS	7 (36.8%)	–	NS
CA19-9	5 (20%)	3 (60%)	NS	10 (52.4%)	–	NS
Adjuvant chemotherapy	*Adjuvant chemotherapy negative (n: 27)*	*Adjuvan chemotherapy positive (n: 3)*		*Adjuvan chemotherapy negative (n: 19)*	*Adjuvan chemotherapy positive (n: 1)*	
CA125	15 (55.5%)	3 (100%)	NS	9 (47.3%)	–	NS
CA125+CA19-9	2 (7.4%)	2 (66.6%)	< 0.05	7 (36.8%)	–	NS
CA19-9	6 (22.2%)	2 (66.6%)	NS	10 (52.2%)	–	NS
Recurrence	*Recurrence negative (n: 27)*	*Recurrence positive (n: 3)*		*Recurrence negative (n: 19)*	*Recurrence positive (n: 1)*	
CA125	16 (59.2%)	2 (66.6%)	NS	8 (42.1%)	1 (100%)	NS
CA125+CA19-9	2 (7.4%)	2 (66.6%)	< 0.05	6 (31.5%)	1 (100%)	NS
CA19-9	5 (18.5%)	3 (100%)	< 0.05	9 (47.3%)	1 (100%)	NS

Variables were compared by using the chi-square test.

preoperative computed tomography (CT) scan, first-line laparoscopy and conservative treatment [13].

However abnormal serum tumor markers and other variables were not evaluated according to histotypes in this study. On the contrary in this study, we did not find any significant relation between abnormal markers and tumor size and bilaterality.

Another detailed study by Ayhan *et al*. compared tumor markers and the clinicopathologic relation [10]. In this study the mean values of CA125 and CA19-9 were significantly increased by increasing tumor size and elevated CA125 and CA19-9 relations between age, lymph node metastasis, micropapillary architecture, tumor bilateralism, surgical staging choice, history of smoking and use of oral contraceptive pills were not significant. But elevated CA125 was found to be significant at FIGO stage, parity and implant [10]. This study did not investigate the correlation of tumor markers and variables with histotypes. In our study, we did not find any stage, parity, or peritoneal implant association with tumor markers.

In another study, when the serum CA125 value was 35 IU/ml, the mean tumor size was 7.7 cm, and when CA 125 value was ≥ 100 IU/ml, the mean tumor size was 14.2 cm [8]. We did not find a significant relation between tumor size and tumor markers in either group. Tumor marker and stage of the tumor is another issue.

Patients with mucinous borderline tumors tended to have lower tumor stages.

In another study 79.4% of patients with serous BOTs were Stage I-II, and 97.8% of the mucinous BOT patients were Stage I. In this study 20.6% of serous tumors were at Stage III, while only 2.2% mucinous were reported at this stage [6]. Therefore, serous and mucinous tumors have different serum markers at different stages.

Leinhard *et al*. reported a relation of tumor stage with increased CA125 [19]. Rice *et al*. reported that in serous BOTs, patients with advanced stage had higher CA125 levels than Stage I patients [20]. In the literature, elevated CA125 rates for serous were 35-66.7% at Stage I, while 71.4-100% of Stage II-IV patients had elevated CA125 [10, 11]. CA125 elevation in mucinous tumors at Stage I was found to be 37%, while this rate was 67% for Stage II-IV tumors in a review of 325 patients [8, 10, 11]. Reports on elevated CA19-9 and stage comparison for both serous and mucinous tumors are few in the literature. In one study, elevated CA19-9 rates for serous Stage I and III BOTs were found to be less than mucinous tumors at the same stage [10]. However, we did not find elevated CA125 and CA19-9 levels according to the stages of serous and mucinous tumors. The other issue is tumor marker and cytology. The rate of high preoperative CA125 level increases in cases of positive peritoneal cytology results was shown. This significant increase was not observed for the positivity of serum CA19-9 [10]. However, we found that cytology was positively associated with elevated CA125+CA19-9 and CA19-9, but was not related to CA125 in the serous group, contrary to this study. Also, we found an elevated CA19-9 association with positive cytology in the mucinous group. But, this and our study were different according to histotypes as the rates of cytology positivity of serous and mucinous tumors were 11 vs 3 and 5 vs 4, respectively, and this study did not compare tumor markers to histotypes as other studies.

The rate of positive peritoneal cytology of serous BOTs is more than mucinous.

In one study, positive peritoneal cytology was found to be 35.7% for serous versus 8.5% for mucinous [6]. However, in our study the rate of positive cytology was similar in both groups, and differences may be due to this finding.

Published reports have shown 38-40% bilaterality for serous tumors and only 8% for mucinous tumors [21]. In another study the bilaterality rate for serous versus mucinous tumors was 27.9% versus 1.1% [6].

Bilateralism and tumor markers were evaluated by Ayhan *et al*. and found to be non significant [10]. In our study we did not find a significant relation between serum tumor markers and bilaterality for either group. As for relations between serum tumor markers and recurrence there are conflicting results in the literature. In a study consisting of 266 cases with a recurrence rate of 23 (8.6%), progression-free survival (PFS) was related to CA125 [12]. In another study (233 cases, 21 recurrences) in five years PFS analyses showed that CA125 > 144 cases with high recurrence rate and PFS were related to CA125 [19]. In another study Leinhard *et al*. showed that CA125 elevated preoperatively had a prognostic value for recurrence, but it was not significant for overall survival [19]. However in another study, recurrence and CA125 were not significantly associated; the elevated CA125 rate was 13.1% for recurrence versus 86.9% for non recurrence [16].

Another study showed abnormal serum tumor marker status was not associated with the risk of recurrence [13], but this study did not evaluate the detailed analyses of the histotypes as we did.

In our study, we found that only in the serous group, elevated CA125 and CA125+CA19-9 were significantly related to recurrence.

An important issue is implants and tumor markers. The rate of implants of serous BOTs was much more than mucinous. In this study the rate of implants was 22.4% for serous versus 3.6% for mucinous [6]. Implant and survival relation has been shown in several studies, but a relation between implant and tumor markers are limited. Ayhan *et al*. showed peritoneal implants were significantly associated with elevated CA125, but not with CA19-9 [10]. Leinhard *et al*. showed elevated CA125 was significantly related to implants [19]. However in our study, we did not find any implant association with tumor markers, contrary to these studies.

Another issue is lymph node involvement in BOTs. Combined data from five studies (161 cases) by Fadare indicated that lymph node involvement ranged from 0%-42% (average 27%) in BOTs and estimation of involvement rate was difficult, because most BOTs were not formally staged [22]. Also, lymph node involvement and

tumor marker relation studies are few. In one study, lymph node involvement rate was 8.33%, which was not related to either to CA125 nor to CA19-9, similar to our results.

The rate of intracystic papilla was reported to be between 48-78% [23-25]. Gotlieb *et al*. showed that mucinous tumors tended to be larger on US than serous tumors; the rate of multilocularity was 50% and contained papillations in 40%. In another study, serous tumors were multilocular in 30% of patients, but presented with solid or papillary patterns in 78% [8].

In another study, 48% of BOTs showed papilla and 24% showed septa, of which 18% were multilocular, and the author indicated that the presence of internal papillae and multiple septa was the most significant sonographic pattern associated with BOT [23]. Another multivariant analysis study indicated that only intracystic papillae were an independent predictor of BOT [24]. However, few studies evaluated tumor markers and papilla. Micropapillary architecture and tumor markers were evaluated by Ayhan *et al*. and they did not find any significant relation. But, only in the mucinous group, we interestingly found elevated CA125 and CA125+CA19-9 and papilla presence, and we did not find any relation with septa formation [10].

Our study group was small and the rate of some features low in both serous and mucinous groups. We compared serum tumor markers with all clinicopathologic features of both serous and mucinous histotypes and all our cases had both elevated CA125 and CA19-9. To the best of our knowledge, there are no similarly designed studies as ours in the literature. There is a need for large series to confirm the knowledge about tumor markers in BOTs, which may reflect differences of serous and mucinous BOTs.

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