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# Comparison of Tumor Markers and Risk of Malignancy Index in Borderline Ovarian Tumors

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## ABSTRACT

**Objective:** Borderline ovarian tumors (BOTs) are non-invasive tumors with low malignancy potential frequently observed in patients of reproductive age. Therefore, pre-operative differential diagnosis is important in these patients. Our aim was to differentiate benign and BOTs preoperatively using risk of malignancy index (RMI) and tumor markers.

**Materials and Methods:** In our study, we retrospectively compared tumor markers and RMI of 85 patients aged between 17 and 84 years with post-operative benign (n=52) and borderline (n=33) ovarian cysts.

**Results:** In our study, the mean age of the benign group was significantly higher than the borderline group (p=0.001). Ca 125 and RMI values were significantly higher in the borderline group compared to the benign group (p=0.001 and p=0.018). In addition, mucinous tumors had significantly larger tumor diameter than serous tumors in the borderline group (p=0.022).

**Conclusion:** As a result of our study, since BOTs are seen in young patients of reproductive age, it may be suggested to use Ca125 and RMI for the differential diagnosis of benign and borderline cysts preoperatively.

**Keywords:** Borderline, Ca125, Menopause, Ovarian cysts, Ovarian neoplasms, Risk of malignancy index.

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## INTRODUCTION

Borderline ovarian tumors (BOTs) were firstly described by Taylor in 1929[1] and later on categorized as epitelial ovarian tumor by International Federation of Gynecology and Obstetrics (FIGO) in 1971[2] and the World Health Organization in 2020.[3] BOTS are different type of tumors rather than benign or malignant ovarian tumors. They are also called "ovarian low malignant potential tumors"[4] but they are accepted as non-invasive, low malignant and atypically proliferated tumors and consist 15–20% of all primary ovarian neoplasms.[5,6] Due to presence BOTs in young ages, fertility preserving treatments are the major treatment offers for patients.[7]

These young patients need to precise pre-operative diagnosis for their ovarian masses. Ultrasonographic scanning and tumor markers are the major diagnostic tools for the prediction of ovarian masses. For the differential diagnosis between benign and malignant adnexial masses, a combination of various markers is often used, such as the risk of malignancy

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index (RMI). RMI is an easy, simple, and advicable method to differentiate malignant and benign adnexial masses.[8] RMI is a numeric value which is calculated with the combination of serum Ca125 level, menopausal state, and ultrasonographic findings, and modified to four different versions.[9-12]

In our study, we tried to find out whether the RMI 1 and serum biomarkers differences between benign and BOTs to facilitate pre-operative evaluation and differentiation of ovarian masses.

## MATERIALS AND METHODS

Totally 85 patients aged between of 17 and 84 who were selectively operated for suspected adnexal mass in our clinic between 2016 and 2020 and resulted in BOT and benign ovarian tumor as pathologies were retrospectively included in our study. We divided to patients to benign (*n*=52) and borderline (*n*=33) groups. The study was approved by the İstanbul Medeniyet University ethics committee (date: 02.09.2020, decision no: 2020/0571) and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Pre-operative ultrasonographic examinations were performed in all patients participating in the study. Age, parity, menopausal status, alpha-fetoprotein (AFP) (ng/mL), Ca125 (U/mL), Ca15-3 (U/mL), Ca19-9 (U/mL), Carcinoembryonic antigen (CEA) (ng/mL) values, ultrasonography findings (multiloculation, solid field or papillary protrusion, bilaterality, mass diameter), pre-operative neutrophil/lymphocyte ratios (NLR), frozen pathology and final pathology results were recorded. The patient's ultrasonographic findings, Ca-125 serum level, and menopausal status were scored, and RMI values were calculated numerically (as RMI 1=Ultrasonography score [U score] × Menopause score [M score] × CA-125 level [mIU/mL]). The patients whose records were incomplete or whose RMI calculation could not be performed had been excluded from the study. After RMI was calculated, the results were compared with histopathological results.

### Statistical Analysis

Analyses the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) was evaluated in 22 package programs. In the study, descriptive data were shown with n. % values in categorical data, mean ± standard deviation, and median interquartile range (25–75 percentile values) values in continuous data. Chi-square analysis (Pearson Chi-square) was applied to compare categorical variables between groups. The conformity of continuous variables to normal distribution was evaluated by the Kolmogorov-Smirnov test. The Mann–Whitney U-test was used to compare the pairwise groups. The Spearman correlation test was used to examine the relationship between continuous variables. In the analyzes, the statistical significance level was accepted as $p<0.05$.

## RESULTS

The age of the patients who were in benign group was significantly higher than the patients who were in borderline group ($p=0.001$). Furthermore, Ca 125 ($p=0.001$) and RMI score ($p=0.018$) were found to be significantly lower than borderline patients. While 69.4% of menopausal women had benign masses, 55.1% of premenopausal women had benign final pathology, and there was no significant difference between them (p=0.180). There was no significant difference between the last pathology in terms of other parameters (p>0.05) (Table 1).

**Table 1.** Comparison of tumor markers, tumor sizes, N/L ratio, and RMI score by final pathology

| | Benign (*n*=52) Median (IQR) | Borderline (*n*=33) Median (IQR) | *p*[a] |
|---|---|---|---|
| Age | 49 (42–59.5) | 36 (30–49) | **0.001*** |
| Ca 125 (U/mL) | 17.55 (10.90–30.00) | 34.70 (16.30–86.00) | **0.001*** |
| AFP (ng/mL) | 2.90 (2.07–4.45) | 2.15 (1.54–4.49) | 0.203 |
| Ca 15.3 (U/mL) | 14.65 (9.80–19.40) | 14.30 (10.30–19.10) | 0.801 |
| Ca 19.9 | 12.06 (7.05–22.52) | 15.03 (8.43–24.30) | 0.415 |
| CEA (ng/mL) | 1.50 (1.04–2.03) | 1.48 (1.09–2.29) | 0.399 |
| RMI score | 43.10 (0.00–72.90) | 72.90 (16.00–717.00) | **0.018*** |
| Diameter | 8.00 (6.00–11.25) | 8.50 (8.00–13.00) | 0.130 |
| NLR | 2.34 (1.67–3.22) | 2.20 (1.86–2.87) | 0.853 |
| | ***n* (%)** | ***n* (%)** | |
| Menopausal status | | | |
| Menopause | 25 (69.4) | 11 (30.6) | 0.180[b] |
| Premenopause | 27 (55.1) | 22 (44.9) | |

[a]Mann–Whitney U test; [b]Chi-square analysis was applied; *$p<0.05$. N/L: Neutrophil/lymphocyte, RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

**Table 2.** Comparison of tumor markers, tumor sizes, N/L ratio and RMI score by tumor type

| | Mucinous (*n*=11) Median (IQR) | Serous (*n*=17) Median (IQR) | *p*[a] |
|---|---|---|---|
| Ca 125 (U/mL) | 25.95 (16.00–40.10) | 80.30 (21.55–324.85) | 0.135 |
| AFP (ng/mL) | 1.98 (1.55–3.14) | 2.02 (1.46–4.28) | 0.879 |
| Ca 15-3 (U/mL) | 11.05 (8.50–16.20) | 15.05 (13.80–19.50) | 0.109 |
| Ca 19.9 | 16.69 (1.10–21.82) | 15.09 (8.43–24.30) | 0.892 |
| CEA (ng/mL) | 1.35 (1.04–2.38) | 1.67 (1.09–2.29) | 0.841 |
| RMI score | 37.45 (10.40–248.40) | 175.20 (39.85–989.50) | 0.087 |
| Diameter | 20.00 (8.00–20.00) | 8.00 (7.50–9.00) | **0.022*** |
| NLR | 2.10 (1.80–3.40) | 2.25 (1.97–2.98) | 0.578 |

[a]Mann–Whitney U test was applied; *$p<0.05$. N/L: Neutrophil/lymphocyte; RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen, AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

The tumor diameter of mucinous tumors was found to be significantly higher than in serous patients (p=0.022). There was no significant difference between tumor types in terms of other parameters ($p>0.05$) (Table 2).

In the correlation analysis performed in the borderline group, a significant positive correlation was observed between the RMI score and Ca 125. There is a significant positive correlation between Ca 125 and Ca 15.3. A significant positive correlation was found between age and parity (Table 3).

## DISCUSSION

Adnexial masses are the most common reason for gynecologic oncology referral. Because ovarian carcinoma, which is the most mortal cancer of female reproductive system, should be ruled out.[13] Due to the fact that the discrimination of the masses, benign or malignant, is really important. BOT is a tumor between benign and malignant tumors[14] and staged according to FIGO staging system for epithelial ovarian carcinoma.[15] In our study, we compared borderline tumors with benign adnexial masses and found out that borderline group is younger than benign group. Due to the presence of BOT in reproductive-aged patients, fertility-conserving treatment of the BOT should dominantly considered, but the recurrence rates are higher and mostly benign in early stage BOT's patients.[14,16]

For the differentiation of the BOT from benign masses, ultrasonographic findings and serum tumor markers are used frequently. In our study, Ca125 levels, age, and RMI values in the BOT group are higher than benign group. Ca 125 is a precious marker for predicting benign or borderline tumors, but not alone.[17] RMI combines ultrasonographic findings, menopausal status, and Ca 125 levels and considers malignancy risk of the masses.[9] Moreover, there are 4 different types for RMI (1–4) which are considering different numeric status for each counting parameters. In the comparison of RMI1-4 for differentiation on of BOT's from benign ovarian tumors, RMI 1 was the best method when compared with the other RMI methods.[18] Hence, in our study, we also calculated RMI1 for comparing the groups. For the menopausal status we could not find any difference between our study groups. However, a significant difference was found between the two groups in terms of age. In literature, almost 30% of BOTs occur in women of reproductive age under 40 years of age, as in our study.[19]

Furthermore, we made subdivision for our BOTs according to their histologic typing to serous and mucinous group. In literature, Ca 125 level especially is higher in serous group than mucinous, but Ca 19-9 level is higher in mucinous group than serous.[20,21] However, in our study, we could not find any difference for Ca125 or 19-9 levels between serous and mucinous groups. However, we found significantly larger cysts in mucinous borderline group than serous as in literature.[22,23] And also mucinous BOTs are commonly unilateral and have a higher invasive occurrence rate than serous type.[16,23] Due to the fact that salpingo-oophorectomy is recommended for mucinous subtype of BOTs. Hence, pre-operative decision of the type of adnexial masses is extremely important.

In our study, in the borderline group, RMI and Ca 125 values showed a positive correlation. In the literature, increased values of Ca 125 were observed, especially in serous BOT,[24] but in our study, no significant difference was found between serous and mucinous BOT. In studies, it has been observed that Ca 125 value and Ca 19-9 value were also found to be high in BOTs.[21] In our study, we observed a positive correlation between Ca125 and Ca 15-3 among BOTs. Further studies are needed to see whether there is an increase in Ca 15-3 with an increase in Ca 125 in the BOT group.

**Table 3.** Correlation analysis results (in borderline group)

| | RMI | NLR | AFP | Ca 125 | Ca 15-3 | Ca 19.9 | CEA | Diameter | Age |
|---|---|---|---|---|---|---|---|---|---|
| NLR | | | | | | | | | |
| r | 0.337 | | | | | | | | |
| *p* | 0.064 | | | | | | | | |
| AFP | | | | | | | | | |
| r | –0.252 | 0.150 | | | | | | | |
| *P* | 0.205 | 0.457 | | | | | | | |
| Ca 125 | | | | | | | | | |
| r | **0.668** | 0.332 | –0.126 | | | | | | |
| *p* | **0.000*** | 0.068 | 0.532 | | | | | | |
| Ca 15.3 | | | | | | | | | |
| r | 0.301 | 0.332 | 0.263 | **0.367** | | | | | |
| *p* | 0.100 | 0.068 | 0.184 | **0.042*** | | | | | |
| Ca 19.9 | | | | | | | | | |
| r | –0.109 | 0.341 | –0.225 | 0.067 | 0.174 | | | | |
| *p* | 0.567 | 0.065 | 0.269 | 0.724 | 0.357 | | | | |
| CEA | | | | | | | | | |
| r | –0.258 | –0.192 | 0.069 | –0.028 | 0.059 | –0.058 | | | |
| *p* | 0.176 | 0.319 | 0.731 | 0.885 | 0.760 | 0.768 | | | |
| Diameter | | | | | | | | | |
| r | 0.208 | 0.089 | –0.034 | 0.087 | 0.093 | 0.102 | **–0.468** | | |
| *p* | 0.261 | 0.622 | 0.868 | 0.642 | 0.618 | 0.593 | **0.010** | | |
| Age | | | | | | | | | |
| r | 0.179 | 0.205 | –0.020 | –0.021 | 0.187 | –0.051 | 0.071 | 0.066 | |
| *p* | 0.334 | 0.253 | 0.921 | 0.909 | 0.313 | 0.787 | 0.714 | 0.714 | |
| Parity | | | | | | | | | |
| r | 0.153 | 0.334 | –0.034 | –0.022 | 0.018 | –0.074 | 0.097 | 0.007 | **0.657** |
| *p* | 0.412 | 0.057 | 0.865 | 0.907 | 0.923 | 0.697 | 0.617 | 0.970 | **0.000*** |

**p*<0.05. N/L: Neutrophil/lymphocyte; RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

Furthermore, we tried to find out whether any differences also in CEA, AFP, and NLR values between groups, but there were not any significance. Based on the data in the literature that pelvic inflammatory disease increases the risk of ovarian cancer,[24] we used NLR to investigate whether there is a different inflammatory process in BOTs, but we could not obtain a significant result.

## CONCLUSION

While there are studies showing that even benign ovarian tumors increase the risk of borderline tumor in the long term,[25] it may be helpful to consider Ca 125 and RMI values in order to make a differential diagnosis of benign-BOT while preoperatively evaluating this group of patients in reproductive age. More studies are needed to determine other factors that may be helpful for differential diagnosis.

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**Ethics Committee Approval:** This study was approved by the İstanbul Medeniyet University (Date: 02.09.2020, Decision no: 2020/0571).

**Informed Consent:** It is a retrospective study.

**Conflict of Interest:** None declared.

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