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# Comparison of benign, borderline, and malignant mucinous ovarian tumors

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**Summary**

*Objective*: The aim of this study was to evaluate the preoperative tumor marker levels and imaging findings of patients diagnosed with mucinous ovarian tumors and to determine the utility of these parameters as predictors of malignant cases. *Materials and Methods*: This was a retrospective study involving 20 women with mucinous cystadenocarcinoma and 27 women with mucinous borderline tumor of intestinal type registered between November 1, 2006, and April 30, 2016, and of 47 women with mucinous cystadenoma registered between September 1, 2011, and April 30, 2016. The mucinous ovarian tumors were divided into three groups: benign group, borderline group, and malignant group. Preoperative tumor markers and imaging findings were compared among the three study groups. *Results*: In patients with definitive diagnoses of benign tumors and malignant tumors, the area under the curve (AUC) of CA125 was the highest, and the AUC of number of septa was second. In patients with definitive diagnoses of mucinous borderline tumors and mucinous carcinomas, the AUC of CA125 was the highest, and the AUC of CA72-4 was second. *Conclusion*: In mucinous tumors, measurements of CA125 and CA72-4 levels were helpful to distinguish malignant from benign tumors. The number of septa was a significant predictor of malignancy.

*Key words:* Mucinous ovarian tumor; CA125; CA72-4; Number of septa; Borderline tumor; Malignancy.

## Introduction

Primary mucinous tumors account for 12-15% of all ovarian tumors [1, 2]. Such tumors are generally large but in an early stage at diagnosis. The vast majority are benign (75%), 10% are borderline, and 15% are carcinomas [3]. As opposed to invasive ovarian carcinomas, borderline ovarian tumors (BOT) have a much better prognosis [4, 5]. Surgical treatment of BOT is generally tailored for each patient according to menopausal status and fertility desire. Therefore, it is important to distinguish BOT from ovarian carcinoma. Thus, intraoperative frozen section examination plays a critical role [6]. Although the sensitivity of frozen section analysis approaches about 90% for benign and malignant ovarian tumors, the sensitivities for detection of BOT (all histologies) and mucinous BOT decrease to about 50-85% and 29-48%, respectively [7-15].

Borderline tumors represent approximately 10-15% of all epithelial ovarian carcinomas, and the patients are younger and more often show early stage disease compared to those with invasive carcinoma, resulting in an excellent prognosis. Although there have been many reports describing the clinical features and prognosis of borderline tumors, there have been few comparative studies analyzing mucinous borderline tumor and carcinoma.

The most commonly used clinical tools for evaluation of adnexal masses are imaging modalities and tumor markers [16, 17]. The aim of this study was to evaluate preoperative tumor marker levels and imaging findings in patients diagnosed with mucinous ovarian tumor and to determine the utility of these parameters as predictors of malignant cases.

## Materials and Methods

This was a retrospective study of clinical data obtained from 20 women with mucinous cystadenocarcinoma and 27 women with mucinous borderline tumor of intestinal type between November 1, 2006, and April 30, and 47 women with mucinous cystadenoma between September 1, 2011 and April 30, 2016, registered and scheduled for laparotomy and laparoscopy at the Department of Obstetrics and Gynecology of Kochi Health Sciences Center. Data including patient age, tumor marker levels, and menopausal status were evaluated. All patients were required to have a pelvic ultrasound, computed tomography, magnetic resonance imaging, or any combination of imaging modalities for documentation of an ovarian tumor or pelvic mass. Active infection, gastrointestinal malignancy, pregnancy, and use of anticoagulants were used as exclusion criteria.

Preoperative tumor markers were compared among the study groups (malignant, borderline, and benign) using ANOVA. The upper reference limits for CA125, CA19-9, CA72-4, and carcinoembryonic antigen (CEA) were taken as 35 IU/ml, 37 IU/ml, 8 IU/ml, and 5 IU/ml, respectively.

Statistical analysis was performed using BellCurve software. *P* values less than 0.05 were considered significant. For parameters that were found to be significant on univariate analyses, receiver operating curve (ROC) analyses were performed. Area under the curve (AUC), sensitivity, and specificity were calculated.

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Table 1. — *Patient characteristics by group.*

| Variables | Benign n=47 | Borderline n=27 | Malignant n=20 | P value |
|---|---|---|---|---|
| Age (years) Mean (SD) | 51.6 (13.7) | 57.3 (8.2) | 54.7(16.2) | NS |
| BMI Mean (SD) | 22.9 (3.8) | 23.9(3.6) | 22.02(4.2) | NS |
| Menopausal status | | | | |
| Premenopausal | 25 (53.2%) | 13 (48.1%) | 12 (60.0%) | NS |
| Postmenopausal | 22 (46.8%) | 14 (51.9%) | 8 (40.0%) | |
| Parity (number of full-term pregnancies) | | | | |
| 0 | 9 (65.5%) | 11 (65.5%) | 8 (60.7%) | |
| 1 | 13(10.9%) | 4 (10.9%) | 4 (17.9%) | NS |
| ≧2 | 25 (23.6%) | 12 (23.6%) | 8 (21.4%) | |
| Current or previous smoking history | 10 (22.2%) | 8(34.8%) | 4(22.2%) | NS |
| missing | 2 | 4 | 2 | |

Table 2. — *Tumor markers parameters characteristics by group.*

| Variables | | Mean (SD) | ANOVA P value | Comparison group | P value |
|---|---|---|---|---|---|
| CA125 (U/ml) | Benign | 21.2 (26.7) | | 1 vs 2 | NS |
| | Borderline | 26.7 (17.8) | < 0.0001 | 1 vs 3 | < 0.01 |
| | Malignant | 128.0 (184.1) | | 2 vs 3 | < 0.01 |
| CA19-9 (U/ml) | Benign | 24.9 (29.1) | | 1 vs 2 | NS |
| | Borderline | 34.3 (45.5) | < 0.001 | 1 vs 3 | < 0.01 |
| | Malignant | 522.0 (949.2) | | 2 vs 3 | < 0.01 |
| CA72-4 (U/ml) | Benign | 3.3 (3.3) | | 1 vs 2 | NS |
| | Borderline | 2.9 (2.0) | 0.0031 | 1 vs 3 | < 0.01 |
| | Malignant | 254.2 (535.8) | | 2 vs 3 | < 0.05 |
| CEA (U/ml) | Benign | 2.03 (1.56) | | 1 vs 2 | NS |
| | Borderline | 2.95 (2.83) | 0.035 | 1 vs 3 | < 0.05 |
| | Malignant | 9.67 (21.81) | | 2 vs 3 | NS |

Table 3. — *Tumor characteristics by group.*

| Variables | Benign n=47 | Borderline n=27 | Malignant n=20 | P value |
|---|---|---|---|---|
| Tumor size (cm) Mean (SD) | 11.5 (5.3) | 15.4 (6.7) | 14.4 (5.0) | 0.012 |
| Bilateral tumors | 4 (8.5%) | 3 (11.1%) | 2 (10.0%) | NS |
| Type of tumor | | | | |
| Unilocular | 13 (27.7%) | 2 (7.4%) | 0 | |
| Unilocular-solid | 1 (2.1%) | 0 | 3 (15.0%) | < 0.0001 |
| Multilocular | 26 (55.3%) | 10 (37.0%) | 4 (20.0%) | |
| Multilocular-solid | 7 (14.9%) | 15 (55.6%) | 13 (65.0%) | |
| Number of septa | | | | |
| ≤4 | 35 (74.5%) | 9 (33.3%) | 4 (20.0%) | |
| 5-9 | 4 (8.5%) | 5 (18.5%) | 3 (15.0%) | < 0.0001 |
| 10-14 | 1 (2.1%) | 5 (18.5%) | 1 (5.0%) | |
| ≥15 | 7 (14.9%) | 8 (29.6%) | 12 (60.0%) | |
| Ascites | 2 (4.3%) | 3 (11.1%) | 10 (50.0%) | < 0.0001 |

Table 4. — *The diagnostic values of parameters to distinguish BOT and carcinoma from benign tumor.*

4. The diagnostic values of parameters to distinguish BOT and carcinoma from benign tu

| Parameter | Cut-off | AUC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| CA125 (U/ml) | 34.6 | 0.775 | 46.7 | 91.5 | 84.6 | 63.1 |
| CA19-9 (U/ml) | 50.1 | 0.591 | 35.6 | 90.9 | 79.5 | 58.5 |
| CA72-4 (U/ml) | 8.0 | 0.646 | 34.2 | 91.4 | 76.7 | 58.2 |
| CEA (U/ml) | 5.0 | 0.620 | 26.8 | 97.5 | 91.3 | 57.1 |
| Tumor size (cm) | 13.3 | 0.670 | 55.3 | 74.5 | 68.4 | 62.5 |
| Number of septa | 7.0 | 0.753 | 70.2 | 80.9 | 78.6 | 73.1 |

AUC: Area Under Curve.
PPV: Positive Predictive Value
NPV: Negative Predictive Value

Table 5. — *The diagnostic values of parameters to distinguish carcinoma from BOT.*

| Parameter | Cut-off | AUC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|
| CA125 (U/ml) | 31.1 | 0.823 | 84.2 | 73.1 | 69.7 | 86.0 |
| CA19-9 (U/ml) | 55.2 | 0.625 | 52.6 | 84.6 | 71.4 | 70.6 |
| CA72-4 (U/ml) | 8.0 | 0.783 | 76.5 | 90.5 | 85.5 | 83.8 |
| CEA (U/ml) | 3.2 | 0.632 | 52.6 | 87.3 | 75.5 | 71.3 |
| Tumor size (cm) | 18.0 | 0.532 | 90.0 | 37.0 | 51.4 | 83.3 |
| Number of septa | 16.0 | 0.662 | 60.0 | 74.1 | 63.2 | 71.4 |

AUC: Area Under Curve.
PPV: Positive Predictive Value
NPV: Negative Predictive Value

## Results

Of 94 patients, 41 had benign tumors (group 1), 27 had mucinous BOT (group 2), and 20 had mucinous carcinomas (group 3). These three groups were similar with regards to patient age, body mass index (BMI), menopausal status, parity, and smoking history ($p > 0.05$) (Table 1). CA125, CA19-9, and CA72-4 levels were significantly higher in group 3 than in groups 1 and 2 (Table 2).

The mean tumor size was 11.5 cm for benign tumors, 15.4 cm for mucinous BOT tumors, and 14.4 cm for mucinous carcinomas; malignant tumors (group 2 or 3) were significantly larger. Unilocular-solid and multilocular-solid type tumors were present in 2.1% and 14.9% of group 1, in 0% and 55.6% of group 2, and 15.0% and 65.0% of group 3, respectively. Both groups 2 and 3 had a larger number of septa than group 1 (Table 3).

In patients with definitive diagnoses of benign tumors and malignant tumors (mucinous BOT and mucinous carcinomas), the AUC of CA125 was the highest, and the AUC of the number of septa was second (Table 4). In patients with definitive diagnoses of mucinous BOT and mucinous carcinomas, the AUC of CA125 was the highest, and the AUC of CA72-4 was second (Table 5).

## Discussion

It is very difficult to distinguish malignant from benign mucinous ovarian tumors before surgery. This study analyzed the characteristics of mucinous tumors, including benign, borderline tumor, and carcinoma.

The serum CA 125 levels that were determined for the differential diagnosis of benign and malignant pelvic masses were similar to those reported in other studies. Although this marker is especially useful to detect serous malignant tumors, it may also be elevated preoperatively in mucinous invasive carcinomas [18-20]. However, Tempfer *et al.* suggested that tumor size was the only significant parameter for increasing frozen section accuracy, and that CA125 levels and histology did not have a remarkable effect [11]. In the present study, CA125 was elevated in mucinous carcinomas, and histology was also associated with the CA125 level. Several studies reported that CA19-9 and CA72-4 had higher sensitivities than CA125 in mucinous carcinomas [21, 22], although these markers are less useful to distinguish malignant tumors from other ovarian tumors than CA125. In the present study, CA19-9 and CA72-4 levels were significantly increased, especially in mucinous carcinomas (Table 2). Kikkawa *et al.* suggested that CA72-4 was the most useful tumor marker to distinguish BOT and carcinoma from benign tumors among four clinically available tumor markers (CA125, CA19-9, CA72-4, and CEA) on ROC analysis [23]. In the present study, CA125 was the most useful tumor marker, and CA72-4 was the second most useful tumor marker to distinguish BOT and carcinoma from benign tumors among the four clinically available tumor markers on ROC analysis (Table 4). These findings suggest that measurement of CA72-4 is recommended when multilocular cysts are observed on imaging.

The present study showed that the presence of solid components was an important risk factor for BOT and carcinoma arising from a benign tumor. The mean tumor size with malignancy was 14.4 cm, which was significantly larger than that of cysts without malignancy (Table 3). The number of septa was useful, like CA125, to distinguish BOT and carcinoma from benign tumors (Table 4).

Some limitations of the present study should be acknowledged. In addition to the retrospective design and the relatively small sample size, the present series represented a selected population, because the authors' centers are referral institutions, but the results may, nevertheless, show potential trends. The results of the present study showed that CA125 levels and the number of septa were useful to distinguish BOT and carcinoma from benign tumors. Furthermore, CA125 and CA72-4 levels were useful to distinguish carcinoma from BOT. This distinction may be important for surgical planning, especially in view of the well-known limitations of intraoperative frozen section examination.

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