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Original Article

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Serum Tumor Markers for Preoperative Discrimination of Benign and Malignant Adnexal Masses

Besim Haluk Bacanakgil[a], Fehmi Unal[a], Sevinj Aliyeva[a, b], Isa Shukru Oz[a], Roya Karimova[a]

Abstract

Background: We aimed to determine the diagnostic values of individual tumor marker or combined in preoperative discrimination between benign and malignant ovarian tumors.

Methods: Medical data of 322 patients operated because of adnexal masses during 2009 - 2014 in Istanbul Research and Traning Hospital (a tertiary center) were retrospectively analyzed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (ACC) were determined for each individual tumor marker or markers combined.

Results: Median age of patients was 43 years. Of all patients, 68.3% were premenopausal and 31.7% were postmenopausal. CA125 levels in 29.8% patients, CA19-9 in 16.3% and CA15-3 in 6.1% were found higher than the cutoff value. The postmenopausal group had significantly higher levels of CA 125 and CA15-3 ($P = 0.021$ and $P = 0.002$, respectively) compared with the premenopausal group. In malignant cases, CA125 and CA15-3 were significantly higher ($P < 0.001$). Sensitivity, specificity, PPV, NPV and ACC of CA125 were 70.5%, 76.6%, 32.3%, 94.2% and 75.8%, respectively. Sensitivity, specificity, PPV, NPV and ACC of CA15-3 were 34.1%, 98.2%, 73.7%, 90.8% and 89.8%, respectively. There was no significant difference in CA19-9 levels between the benign and malignant groups. The ACC of combined CA125 + CA15-3 was 90.7%.

Conclusion: The elevated levels of CA125 or CA15-3 individually have a high diagnostic value for preoperative discrimination of benign/malignant adnexal masses. Combination of CA125 and CA15-3 does not present addtive effect. CA19-9 is not an appropriate marker for discrimination of benign/malignant adnexal masses.

Keywords: Tumor markers; Adnexal mass; Ovarian cancer; Diagnostic accuracy

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[a]Istanbul Education and Research Hospital, Gynecology and Obstetrics Clinic, Turkey
[b]Corresponding Author: Sevinj Aliyeva, Istanbul Education and Research Hospital, Gynecology and Obstetrics Clinic, Turkey. Email: gynsevinc@gmail.com

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Introduction

According to the 2015 Guidelines of Centers For Disease Control and Prevention and National Cancer Institute, about 20,000 new cases of ovarian cancer are diagnosed in the United States each year [1]. The ovarian cancer is the eighth most common malignant tumor and the fifth most common cause of cancer death in females in the United States. It is the most fatal cancer of the female reproductive system. Over 14,000 women died of ovarian cancer in the Unites States in 2012 and the 5-year survival rate is a dismal 45% [1].

Preoperative differential diagnosis of ovarian cancers is very important, which facilitates the optimal treatment and helps prognosis prediction. As the ovarian cancers do not have spesific diagnostic symptoms, 65% cases when diagnosed are at stages 3 and 4 [2]. Blood cancer antigen 125 (CA125) is the most used tumor marker for ovarian cancer diagnosis. Using the cutoff value of 35 U/mL, CA125 has 80% sensitivity and 75% specificity for ovarian tumor diagnosis [3].

Preoperative benign/malignant distinction of the adnexal masses is important for the management of patients, and hgh levels of CA125 can be detected in several benign cases that include endometriosis, pelvic inflammatory disease, pregnancy, menstrual cycle, etc., resulting in false positive reports [2, 4]. In this study, we aimed to use preoperative serum CA125, CA19-9 and CA15-3 levels individually or combined to discriminate malignant and benign adnexal masses.

Methods

Medical data of 322 patients operated because of adnexal masses between 2009 and 2014 were retrospectively analyzed. Cutoff values of blood CA125, CA19-9 and CA15-3 were set at 35, 35 and 31 U/mL, respectively. Tumor markers were evaluated individually and combined.

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics were expressed as average, standard deviation and median for quantitive variables. The comparison of the independent groups was performed via Mann-Whitney U analysis. In the independent groups, rate comparison was made using Chi-square analysis. The relationship between the quantitive variables was analized via Spearman Correlation test when parametric test conditions did not fit. Statistically, alpha significant rate was accepted as $P < 0.05$.

Table 1. Features of Patients

Age (years), average ± SD/median/IQR	43.6 ± 14.2/43/34 - 52
Menopause, n (%)	
Premenopausal	220 (68.3)
Postmenopausal	102 (31.7)
Preop CA125 (U/mL), average ± SD/median/IQR	116.8 ± 543.2/16.4/9.1 - 43.8
≤ 35, n (%)	226 (70.2)
> 35, n (%)	96 (29.8)
Preop CA19-9 (U/mL), average ± SD/median/IQR	35.9 ± 103.9/12.4/6.4 - 26
≤ 35, n (%)	268 (83.8)
> 35, n (%)	52 (16.3)
Preop CA15-3 (U/mL), average ± SD/median/IQR	22.9 ± 80.3/13.8/8.6 - 18.7
≤ 31, n (%)	294 (93.9)
> 31, n (%)	19 (6.1)
Tumor size (cm), average ± SD/median/IQR	6.7 ± 4.3/5.5/4 - 8
Tumor form, n (%)	
Solid	16 (5.0)
Cystic	191 (59.3)
Mix	115 (35.7)
Tumor type, n (%)	
Benign	278 (86.3)
Malignant	44 (13.7)

SD: standard deviation; IQR: interquartile range.

Results

The average age of patients was 43.6 years, 68.3% of patients were premenopausal and 31.7% were postmenopausal. Of all patients, 29.8% had a higher than cutoff CA125 level, 16.3% had a higher than cutoff CA19-9 level and 6.1% had a higher than cutoff CA15-3 level. Average tumor size was 6.7 cm, 59.3% of tumoral masses were cystic, 86.3% were benign and 13.7% malignant (Table 1).

According to the histopathological analysis, in the benign group the most common ovarian tumor found in our series was serous cystadenoma (21.7%), and in the malignant group serous adenocarsinoma was the most common one (5.9%) (Table 2).

CA125 and CA15-3 levels were significantlly higher in postmenopausal patients than in premenopausal patients ($P = 0.021$ and $P = 0.002$, respectively). There was no significant difference in CA19-9 levels between these 2 groups (Table 3). The malignancy rate was 7.3% in premenopausal group, and 27.4% in postmenopausal group. This difference was statistically significant ($P < 0.001$) (Table 3).

CA125 and CA15-3 levels were significantly higher in malignant group than in benign group ($P < 0.001$) (Table 4). There was no significant difference in CA 19-9 levels between malignant and benign groups.

According to tumor markers' cutoff values, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (ACC) were determined (Table 5). The highest sensitivity and NPV values were seen for CA125 (70.5% and 94.2%, respectively), the highest specificity and PPV values were detected for CA15-3 (98.2% and 73.7%, respectively). CA15-3 reached the highest diagnostic accuracy rate (89.8%). When these markers were combined and calculated, the most significant combination was CA125 + CA15-3. Via this combination, specificity and diagnostic accuracy became 99.3% and 90.7%, respectively but sensitivity was compromised (Table 5).

Discussion

For preoperative benign/malignancy differentation of adnexal masses, an optimal tumor marker must have a high specificity. CA125 is the most commonly used surface epithelial sourced tumor marker. Blood CA 125 is detected to be elevated in 90% of advanced stage and 50% of early stage epithelial ovarian tumors [6, 7]. Medeiros et al have reported 80% sensitivity and 75% specificity for CA125 in the diagnosis of ovarian tumors [3]. Other investigations show similar results [8]. In our study, we identified 70.5% sensitivity and 76.6% specificity, and the diagnostic accuracy of 75.8% for CA125 in the discrimination of benign/malignant adnexal masses.

Diagnostic value of CA15-3 for benign/malignant adnexal masses is variable with sensitivity reported ranging 26-62%,

Table 2. Histopathological Results

	n	%
Serous cystadenoma	70	21.7
Endometrioma	62	19.3
Mature cystic teratoma	45	14.0
Serous adenocarcinoma	19	5.9
Serous cystadenofibroma	19	5.9
Corpus luteal cyst	18	5.6
Mucinous cystadenoma	16	5.0
Paraovarian cyst	13	4.0
Fibrotecoma	10	3.1
Granulosa cell tumor	8	2.5
Clear cell carcinoma	7	2.2
Follicular cyst	7	2.2
Seromucinous cystadenom	5	1.6
Basic serous cyst	4	1.2
Fibroma	4	1.2
Carcinosarcoma	4	1.2
Mucinous adenocarsinoma	4	1.2
Tuboovarian abscess	3	0.9
Brenner tumor	1	0.3
Endometrioid type adenocarsinoma	1	0.3
Germ cell tumor	1	0.3
Cystadenofibroma	1	0.3

specificity 84-96%, PPV 66-80%, and NPV 46-81% [9-12]. In our study, specificity was 34.1%, however sensitivity was 98.2%. The specificity and negative predictive values we found were some higher than those previously reported. In our patients, diagnostic accurracy rate of CA15-3 was 89.9%.

In this study, we found CA19-9 had 30.2% sensitivity and 85.9% specificity for the discrimination of benign/malignant adnexal masses. CA19-9 levels were not significantly different

Table 3. Preoperative Tumor Marker Levels and Menopausal Situations

	Premenopause, average ± SD/min. -max./median	Postmenopause, average ± SD/min. -max./median	P
CA125, U/mL	6.2 ± 157.3/0.6 - 1632.8/19.3	249.5 ± 931.1/1.8 - 7,170/11.1	0.021
CA19-9, U/mL	37.0 ± 114.9/0 - 1,174.7/12.6	33.6 ± 75.4/0 - 580.7/11.3	0.737
CA15-3, U/mL	14.1 ± 13.4/0 - 173.3/12.6	41.6 ± 139.4/1.5 - 1,306/15.6	0.002
Pathology, n (%)			
Benign	204 (92.7)	74 (72.6)	< 0.001
Malignant	16 (7.3)	28 (27.4)	

Table 4. Preoperative Tumor Marker Levels

	Pathology		P
	Benign, average ± SD/min. -max./median	Malignant, average ± SD/min. -max./median	
CA125, U/mL	36.4 ± 78.4/0.6 - 1,053/15	624.7 ± 1,362.8/3.3 - 7,170/59.8	< 0.001
CA19-9, U/mL	68.0 ± 146.4/0 - 705.9/14.5	68.0 ± 146.4/0 - 705.9/14.5	0.5
CA15-3, U/mL	14.6 ± 16.2/0 - 193.2/12.9	78.5 ± 211.9/3.3 - 1,306/21.2	< 0.001

Table 5. Preoperative Tumor Marker Diagnostic Values

	Sensitivity	Specificity	PPV	NPV	ACC
CA125	70.5%	76.6%	32.3%	94.2%	75.80%
CA19-9	30.2%	85.90%	25.0%	88.8%	78.40%
CA15-3	34.1%	98.20%	73.7%	90.8%	89.80%
CA125 + CA15-3	34.1%	99.3%	87.5%	90.9	90.7%

between premenopausal and postmenopausal, also between benign and malignant patient groups. Therefore we felt CA19-9 was not a sensitive marker for preoperative discrimination of adnexal masses between benign and malignant tumors. Similar results were revealed by Bozkurt et al [12].

High CA125 levels in differentiation of benign and malignant masses are more important in postmenopausal patients [13-15]. Malkasian et al have reported high CA125 levels have diagnostic sensitivity of 60% and 80%, and specificity of 73% and 91% in premenopausal and postmenopausal patients, respectively [13]. Preoperative CA125 and CA15-3 levels were significantly higher in our postmenopausal patients compared with premenopausal individulas and the rate of malignancy in postmenopausal group was 26.7%. In postmenopausal patients, elevated CA125 and CA15-3 levels have been shown to be suggestive of possible malignant pathology [13, 16]. Our findings also support this consideration.

Although several studies have used combination of tumor markers for preoperative detection of benign/malignant tumors, the conclusion remains elusive. Therefore, no combination has been recommended yet. However, it is suggested some combinations might be beneficial [2-6, 9, 11]. In our study, combination of CA125 and CA15-3 minimally improved the diagnostic accuracy in discrimination of benign and malignant ovarian tumors. Similarly, Bozkurt et al. applied different combinations of CA125, CA19-9, CA15-3 and CEA, and concluded that these combinations didn't improve diagnostic accuracy significantly.

Conclusion

Elevated levels of CA125 have high sensitivity and specificity for discrimination of benign and malignant adnexal masses, however combination of CA125 and CA15-3 does not show additive effect on diagnostic accuracy. CA19-9 is not a suitable marker in this regard. Specific attention and careful analysis should be given if postmenopausal patients have high CA125 and CA15-3 levels.

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