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Cancer antigens 19.9 and 125 as tumor markers in patients with mucinous ovarian tumors

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Summary

Purpose of investigation: To determine the accuracy of carcinoembryonic antigen (CEA), cancer antigen (CA) 15.3, CA 19.9, and CA 125 for diagnosis of mucinous ovarian cancer (MOC). *Materials and Methods:* Samples were collected preoperatively from patients with mucinous ovarian tumor. The following variables were analysed: CEA, CA 15.3, CA 19.9, and CA 125. After surgery, histology and stage were determined according to FIGO-classification. Patients were classified into two groups according to the diagnosis of ovarian biopsy: NOT MOC and MOC. *Results:* The authors studied 94 patients with ages between 15 and 80 years (median = 43). Eighty-two patients were NOT MOC (68 mucinous ovarian cystadenomas and 14 mucinous borderline ovarian tumors) and 12 were MOC. All MOC patients were in FIGO Stages I or II. No statistically significant differences were found between MOC and NOT MOC patients according to CEA and CA 15.3 ($p > 0.05$). All MOC patients had abnormal serum CA 19.9 and/or CA 125 levels. Using CA 19.9 and CA 125, we performed a linear regression formula CA 19.9+125 = 0.00102 x CA 19.9 + 0.00057 x CA 125. AUCs values were 0.862 ($p = 0.0002$), 0.829 ($p = 0.0021$), and 0.911 ($p = 0.0001$) for CA 19.9, CA 125, and CA 19.9+125, respectively. CA 19.9+125 exhibited 95.1 % specificity and 66.7% sensitivity, increased by 16.7% sensitivity compared with using only CA 19.9 or CA 125. *Conclusions:* Preoperative CA 19.9 and CA 125 levels showed high diagnosis efficacy to predict whether a mucinous ovarian tumour is benign or malignant. Using both markers simultaneously increases the sensitivity for diagnosis of MOC.

Key words: CEA; CA 15.3; CA 19.9; CA 125; Tumor markers; Mucinous ovarian cancer.

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancy [1]. Epithelial ovarian cancer is a heterogeneous disease with a heterogeneous distribution pattern [2]. Epithelial ovarian cancer set by the World Health Organization recognizes eight histological tumor subtypes: serous, mucinous, endometrioid, clear cell, transitional cell, squamous cell, mixed epithelial, and undifferentiated [3]. Serous tumors are the most common form of ovarian carcinoma and make up 30-70% of all diagnoses. Mucinous ovarian cancer (MOC) is an epithelial ovarian cancer that contains cysts and glands lined by mucin-rich cells and constitute 5-20% of ovarian carcinomas [4]. MOC should be considered separate from the other epithelial ovarian cancers. Metastatic primary disease and recurrent mucinous cancers have a substantially worse prognosis than other epithelial ovarian cancers [5]. Tumor markers are biochemical substances found in the blood which may be measured for diagnosis of cancer. The major challenge of developing a screening test is that it must be highly specific, because of the low prevalence of ovarian cancer and to avoid detection of numerous false positives [6]. The aim of this study was to determine the accuracy of carcinoembryonic antigen (CEA), cancer antigen 15.3 (CA 15.3), CA 19.9, and CA 125 for diagnosis of MOC in patients with mucinous ovarian tumors.

Materials and Methods

The authors studied women with mucinous ovarian tumor from 2004 to 2012. Patients with other tumors that could elevate the tumor markers were excluded. Prior to biopsy and after obtaining an informed consent, blood specimens were drawn by venipuncture in gel separator serum tubes and centrifuged at 4,000 rpm for four minutes. The following variables were analysed: CEA, CA 15.3, CA 19.9, and CA 125. The authors measured the serum concentrations of the tumor markers by electrochemiluminescence immunoassay (ECLIA) in MODULAR E-170. The reference ranges are: CEA (0-3.4 ng/ml), CA 15.3 (0-30 U/m), CA 19.9 (0-37 U/ml), and CA 125 (0-35 U/ml). After surgery, histology and stage were determined according to FIGO-classification. Patients were classified into two groups according to the diagnosis of ovarian biopsy: NOT MOC (mucinous ovarian cystadenomas and mucinous ovarian borderline tumor) and MOC. All variables were included in a multivariate regression analysis to identify variables independently associated with MOC. For all statistical comparisons a value of $p < 0.05$ was considered significant. Those variables with $p < 0.05$ by multivariate analysis were used to develop a

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Table 1. — *Descriptive statistics of tumor markers.*

	MOC	n	Lowest value	Highest value	Median (95% CI)	Interquartile range
CEA (ng/ml)	0	82	0.2	6.7	1.4 (1.0−1.9)	1.6
	1	12	0.5	4.0	2.7 (1.7−3.8)	3.4
CA 15.3 (U/ml)	0	82	5.4	38.7	12.8 (7.1−18.1)	8.4
	1	12	10.9	35.3	16.0 (7.2−26.8)	9.2
CA 19.9 (U/ml)	0	82	0.6	428.4	8.3 (5.0−19.0)	22.3
	1	12	8.5	655.9	230.4 (30.5−450.3)	471.6
CA 125 (U/ml)	0	82	6.4	313.7	20.4 (16.0−34.5)	25.99
	1	12	25.1	1537.0	139.66 (28.6−307.5)	237.4

CI: Confidence interval

Table 2. — *The frequency of abnormal serum levels CA 19.9 and CA 125 in MOC and NOT MOC patients.*

	MOC	NOT MOC
CA 19.9 (+) and CA125 (-)	4 (33.33 %)	6 (07.32 %)
CA19.9 (+) and CA 125 (+)	6 (50.00 %)	10 (12.19 %)
CA19.9 (-) and CA 125 (-)	0 (00.00 %)	50 (60.98 %)
CA 19.9 (-) and CA 125 (+)	2 (16.67 %)	16 (19.51 %)
TOTAL	12 (100.0 %)	82 (100.0 %)

CA 19.9 (+): >37 U/ml; CA 125 (+): >35 U/ml.

model to predict patients with MOC. The accuracy of serum tumor markers and the resulting model for the diagnosis of MOC was determined using receiver operating characteristic (ROC) techniques by analysing the area under the ROC curve (AUC). The optimal cut-off value was considered with higher 95% specificity. Statistical analysis was performed using the software MEDCALC.

Results

The authors studied 94 patients with ages between 15 and 80 years (median = 43). Eighty-two patients (87.2 %) were NOT MOC (68 mucinous ovarian cystadenomas and 14 mucinous ovarian borderline tumors) and 12 patients (12.8%) were MOC. Thirty-two patients were postmenopausal and 62 patients were premenopausal. All MOC patients were in FIGO Stages I or II. Descriptive statistics of serum tumor markers in MOC and NOT MOC patients are showed in Table 1. No statistically significant differences were found between MOC and NOT MOC patients according to CEA and CEA 15.3 ($p > 0.05$). The frequency of abnormal serum levels CA 19.9 and CA125 in MOC and NOT MOC patients are shown in Table 2.

In the present authors' model building process, statistically significant difference was observed only for CA 19.9 in the logistic regression analysis; however, using linear regression analysis CA 19.9 and CA 125 were statistically significant. The authors performed a linear regression of a combined use of CA 19.9 and CA 125 values to distinguish between MOC and NOT MOC patients. The coefficients of independent variables were 0.00102 ($p = 0.0003$) and 0.00057 ($p = 0.0018$) for CA 19.9 and CA 125, respectively. The regression formula was: CA 19.9+125 = 0.00102 x CA 19.9 + 0.00057 x CA 125. AUC, optimal cut-off value, sensitivity, and specificity of ROC curves for diagnosis of MOC using CA 19.9, CA 125, and CA 19.9+125 are displayed in Table 3.

No statistically significant differences were found between premenopausal and postmenopausal women according to CEA, CA 15.3, CA 19.9, CA 125, and CA 19.9+125. Also, these tumor markers were not statistically significant for the diagnosis of mucinous borderline ovarian tumors ($p > 0.05$).

Discussion

CEA has been noted to be elevated in almost one-third of all ovarian carcinomas. CEA is much more likely to be elevated in mucinous ovarian carcinomas than in non-mucinous ovarian carcinomas [5, 7-9]. CA 15.3 has found elevated levels in patients with advanced epithelial ovarian cancer [9, 10]. In this study, CEA and CA 15.3 were not useful to differentiate benign from malignant mucinous ovarian tumors.

The recent paper of the guidelines on the recognition and initial management of ovarian cancer from the National Institute for Health and Clinical Excellence (NICE) stated that general practitioners should measure serum CA 125 in pri-

Table 3. — *AUCs, optimal cut-off value, sensitivity, and specificity of CA 19.9, CA 125, and CA 19.9+125.*

	AUC (95% CI)	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)
CA 19.9	0.862 (0.730−0.945)(p=0.0002)	394.7 U/ml	50.0% (12.4−87.6)	97.6% (87.1−99.6)
CA 125	0.829 (0.691−0.923)(p=0.0021)	109.5 U/ml	50.0% (12.4−87.6)	95.1% (83.4−99.3)
CA 19.9+125	0.911 (0.790−0.974)(p<0.0001)	0.2327	66.7% (22.7−94.7)	95.1% (83.4−99.3)

CI: Confidence interval; CA 19.9+125 = 0.00102 x CA 19.9 + 0.00057 x CA 125.

mary care in women with symptoms that suggest ovarian cancer [11]. Also, a diagnostic approach based on the use of CA 125 in association with ultrasonography has been suggested for the early diagnosis of ovarian cancer [12-14]. The major drawback of using CA 125 as a screening strategy is that up to 20% of ovarian cancers do not express the antigen, and also abnormal serum levels CA 125 may be found in patients with benign ovarian tumors [12-16]. It is therefore necessary to combine CA 125 with other tumor markers that can provide better diagnostic efficiency. Recently, another tumor marker for ovarian cancer has been proposed, serum human epididymis protein 4 (HE4), frequently overexpressed in ovarian cancers, especially in serous and endometrioid histology [6, 13, 14, 16-19]. HE4 improves the utility of CA 125 as a tumor marker in ovarian cancer, and using both markers simultaneously increases the tumor marker sensitivity [6, 16, 19, 20]. Likewise, different studies propose the use of a Risk of Ovarian Malignancy Algorithm (ROMA) to improve the sensitivity and specificity of the combined use of both tumor markers in patients with abdominal masses [6, 16, 21, 22]. The combination of HE4 and CA 125 is the best diagnostic power in comparing benign tumors to epithelial ovarian cancer [9, 23]. However, the HE4 has lowest concentrations in mucinous tumors and has no differences between benign or malignant mucinous ovarian tumors in relation to serum concentrations of this tumor marker [13, 14, 23]. Serum CA 19.9 presents low efficiency for the diagnosis of serous ovarian cancer, but preoperative elevated CA 19.9 levels could be related to a higher probability of MOC [9, 24, 25]. In this paper, CA 125 false positive results (abnormal serum levels) were found in 31.7% of NOT MOC patients and false negative (normal serum levels) in 33.3% of MOC patients. CA 19.9 false positive results were found in 19.5% of NOT MOC group and false negative in 16.6% of MOC group. All MOC patients had abnormal serum CA 19.9 and/or CA 125 levels, and 60.98% NOT MOC patients presented normal CA 19.9 and CA 125 (Table 2). Both tumor markers showed similar sensitivity (50%) in MOC diagnosis and slightly higher specificity with CA 19.9 (97.6%) than with CA 125 (95.1%). Using the proposed CA 19.9+125 improved accuracy in the diagnosis of MOC, compared with CA 19.9 or CA 125 alone. CA 19.9 improved the utility of CA 125 as a tumor marker in MOC, and using both markers simultaneously the authors obtained 66.7% sensitivity and 95.1% specificity, increased by 16.7% sensitivity compared with using only CA 19.9 or CA 125 (Table 3).

In other studies [13, 14], significantly higher serum CA 125 levels were found in premenopausal women than in postmenopausal women; in the present case is was not significant ($p > 0.05$).

In another study, up to 61% of women with borderline ovarian tumors had elevated CA 125 [26]. In mucinous borderline ovarian tumors with papilla formation, other authors found a significant relation between elevated CA 125 and CA 125+CA 19.9 [27]. In the present patients, CA 125, CA 19.9, and CA 19.9+125 were not statistically significantly different ($p > 0.05$) for the diagnosis of mucinous borderline ovarian tumors.

The present authors consider their results to be preliminary and hypothesis-generating. Further studies should be done to confirm the utility and diagnostic value of CA 19.9 and CA 125 in patients with mucinous ovarian tumors.

In conclusion, preoperative CA 19.9 and CA 125 levels showed high diagnosis efficacy to predict whether a mucinous ovarian tumour is benign or malignant. Using both markers simultaneously increases the sensitivity for diagnosis of MOC.

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