

# Expression and clinical significance of tumor markers in ovarian mature cystic teratoma

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## Summary

**Background:** CA19-9, CA125, AFP, CEA, and CA153 are common cancer biomarkers. This study aimed to detect the expression and assess clinical significance of these biomarkers in ovarian mature cystic teratomas (OMCT). **Materials and Methods:** The clinical data of 312 resected patients with ovarian mature cystic teratoma referred to the third Hospital of Suzhou University from January 2008 to February 2014 were analyzed retrospectively. Levels of serum CA19-9, CA125, CA153, AFP, and CEA were detected. **Results:** Levels of serum CA19-9, CA125, AFP, and CEA were detected in all patients, but the level of serum CA153 was detected in 36 patients. The positive expression of these biomarkers above is 45.83%, 6.09%, 0.00%, 0.64%, and 2.78%, respectively. Ovarian tumor diameter in CA19-9 and CA 125 elevation is larger than that in negative group. The levels of serum CA19-9 and CA125 in multilocular ovarian tumor patients is higher than that in unilocular ovarian tumor patients. The level of serum CA19-9 in bilateral ovarian tumor patients is higher than that in unilateral patients. The level of CA19-9 in patients three months after operation decreased significantly compared with that before operation. **Conclusions:** The present study suggests that elevated CA 19-9 is probably the most reliable marker among many tumor markers in the OMCT. It is valuable for diagnosis and recurrence of OMCT.

**Key words:** Ovarian mature cystic teratoma; Tumor biomarker; Carbohydrate antigen 199.

## Introduction

Ovarian mature cystic teratoma (OMCT) is the most common benign germ cell tumor of the ovary in reproductive aged women [1]. It accounts for 10-25% of all ovarian neoplasms and 95% of ovarian teratoma [2]. Ovarian teratoma tends to lack specific symptoms and signs. It is found by physical examination and a few patients are diagnosed because of acute abdomen torsion for rupture tumor. Ultrasonography is the main diagnostic tool [3]. However, the diagnosis may be confusing as the cyst contains various tissue elements, and so far, there is no definite tumor biomarker for OMCT.

Carbohydrate antigen 19-9 (also called as cancer antigen 19-9) is mainly increased in gastrointestinal system tumors [4]. However, it can be detected in other malignancies and in some benign conditions as well. Histologically, MCT is an admixture of one or more of the three primary tissue layers: ectodermal, endodermal, and mesodermal tissue derivatives [3]. Therefore, various tumor markers, including CA125 and CA19-9, often elevated in ovarian MCT. To the best of the authors' knowledge, the present study reports the serum level of CA 19-9 in association with dermoid cyst, indicating the potential marker in diagnosing OMCT [5]. They aimed to identify clinical characteristics of ovarian MCT in association with serum common tumor marker elevation, especially CA19-9, and

to determine if CA19-9 is a useful marker in discrimination of MCT from OC.

## Materials and Methods

The authors retrospectively reviewed clinical features of 312 patients with pathologically-confirmed MCTs at the Department of Gynaecology of the Third Hospital affiliated to Suzhou University from January 2008 to February 2014, especially concerning tumor markers. Of all, five cases were recurrent cases. The patients with hepatitis, endometriosis, uterine adenomyosis, hysteromyoma, pelvic inflammatory disease, pregnancy, gastrointestinal disease, or other malignant tumor which diseases can cause elevated tumor markers were excluded. The mean age of patients with OMCT was 32.6 years (range 13–68). Thirty-two cases were unmarried, menopause women were 15 cases, and 36 cases were with bilateral ovarian teratomas. The levels of serum CA19-9, CA125, AFP, and CEA were detected in all patients, but serum CA153 was detected in 36 patients.

All the blood samples used for checking tumor markers were obtained preoperatively and postoperatively for three months. The serum level of CA 19-9, CA125, AFP, CEA, and CA153 were determined by radioimmunoassay on a modular analytics E170 module. The cut-off values for CA19-9, CA 125, AFP, CEA, and CA153 were 37, 35, 8, 5, 32 U/ml, respectively.

## Statistical analysis

Statistical analysis was performed using SPSS (version 13.0). Statistical evaluation of the data was performed by Chi-square test in comparing among the sample mean. For all statistical tests, a *p*-value less than 0.05 was considered significant.

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Table 1. — *Tumor markers levels in serum of ovarian mature cystic teratoma (OMCT).*

Tumor marker	Serum level	Normal level	Range	Elevation No.	Elevation rate (%)
CA199 (U/ml)	89.32 ± 102.89	0-37	0-1650	143/312	45.83
CA125 (U/ml)	19.86 ± 16.72	0-35	0-125.32	19/312	6.09
AFP (ng/ml)	2.26 ± 1.69	0-8	0-7.09	0/312	0
CEA (ng/ml)	1.47 ± 1.05	0-5	0-5.87	2/312	0.64
CA153 (U/ml)	12.32 ± 11.78	0-32	0-51.62	1/36	2.78

Table 2. — *Relationship between CA19-9 elevation and clinical characteristics of ovarian mature cystic teratoma (OMCT).*

Characteristics	CA19-9 elevation	CA19-9 normal	<i>p</i>
Age (yr)	33.23 ± 11.02	32.06 ± 12.01	> 0.05
BMI (kg/m <sup>2</sup> )	23.51 ± 2.29	24.02 ± 2.78	> 0.05
Tumor mean diameter (cm)	8.91 ± 3.15	6.17 ± 1.37	< 0.01
CA125 (U/ml)	27.26 ± 12.08	13.60 ± 8.37	< 0.05
CA19-9 (U/ml)	167.56 ± 92.87	23.12 ± 18.96	< 0.01
Bilateral teratoma [No. of pts (%)]	28 (19.58)	8 (4.73)	< 0.05
Multilocular teratoma [No. of pts (%)]	45 (31.47)	13 (7.69)	< 0.05

## Results

### *The levels of tumor markers in the serum of patients with OMCT*

The levels of serum CA19-9, CA125, AFP, and CEA were detected in all patients (100%), but serum CA153 was detected in 36 patients (11.54%). The mean values of serum CA199, CA125, AFP, CEA, and CA153 were 89.32 ± 172.89 U/ml, 19.86 ± 16.72 U/ml, 2.26 ± 1.69 ng/ml, 1.47 ± 1.05 ng/ml, and 12.32 ± 11.78 U/ml, respectively. Abnormal elevation of CA19-9 was observed in 45.83% of OMCT. The highest level (1,650 U/ml) was observed in OMCT. Of CA19-9 elevation patients, the CA19-9 level of five patients with ovarian teratoma recurrence was higher than normal value (57.89–98.16 U/ml). Abnormal increases in the mean value of CA19-9 were observed, but this elevation of other markers could not be observed. Abnormal elevation of CA125 was observed in 6.09% of OMCT, and the highest level was 125.32 U/ml. Abnormal increases of CEA were observed in only 0.64% (2 / 312) of all patients. Normal AFP level were detected in all pa-

tients. Only one case had CA153 elevation in 36 cases (2.78%) (Table 1).

### *The relationships between CA 19-9 elevation, CA125 elevation, and clinical characteristics of OMCT*

The median tumor diameter of OMCT was 7.58 cm (range 1.0–19.8 cm, mean 7.43 ± 4.17 cm). In CA19-9 elevation group, the median diameter was 8.61 cm (mean 8.91 ± 3.15 cm). In CA125 elevation group, the median diameter was 8.76 cm (mean 9.21 ± 3.25 cm). The mean diameter of OMCT with CA 19-9 elevation was significantly greater than those without CA19-9 elevation (8.91 ± 3.15 cm vs. 6.17 ± 1.37 cm, *p* = 0.002). The mean diameter of tumor with CA125 elevation was greater than that without CA125 elevation (9.21 ± 3.25 cm vs. 7.31 ± 2.48 cm, *p* = 0.003). Likewise, the presence of multilocular or bilateral tumor was more frequently observed in OMCT with CA 19-9 elevation (31.47% vs. 7.69%, *p* < 0.001; 19.58% vs. 4.73%, *p* < 0.001). There were no significant differences in terms of body mass index (BMI) and age in CA 19-9 elevation (Table 2). Similarly, CA125 elevation was more frequently observed in OMCT with multilocular tumor (18.42 ± 11.12 cm vs. 26.15 ± 12.57 cm, *p* = 0.035). However, there was no significant differences in CA125 level between bilateral and unilateral tumors (20.31 ± 12.01 vs. 17.75 ± 9.15, *p* = 0.186). CA125 elevation was more frequently observed in CA19-9 elevation patients (CA19-9 positive) than patients without CA19-9 elevation (CA19-9 negative). Moreover, CA19-9 and CA125 elevation was more frequently observed in torsion tumor cases (10.49% vs. 2.37%, *p* < 0.001). CA19-9 elevation was detected in 143 preoperative patients, and CA19-9 level decreased significantly after operation for three months (*p* < 0.001). However, CA125 level was not observed the similar results (*p* = 0.147) (Table 3).

Table 3. — *Relationship between CA19-9/CA125 elevation and clinical characteristics of ovarian mature cystic teratoma.*

Characteristics	No. of pts.	CA19-9 (U/ml)	<i>p</i>	CA125 (U/ml)	<i>p</i>
Unilocular teratoma	254	69.48 ± 53.27	< 0.001	17.75 ± 9.15	0.035
Bilocular teratoma	58	176.21 ± 121.65		20.31 ± 12.01	
Unilateral teratoma	276	75.89 ± 66.31	< 0.001	17.75 ± 9.15	0.186
Bilateral teratoma	36	192.25 ± 178.21		20.31 ± 12.01	
Torsion	13	272.28 ± 173.26	< 0.001	41.07 ± 15.22	< 0.001
Without Torsion	299	81.37 ± 71.28		18.94 ± 10.21	

## Discussion

Despite the characteristic ultrasonographic appearance of OMCTs, including fat component and calcification by pelvic imaging studies, assessing the preoperative likelihood of malignancy in patients with an adnexal mass may be difficult [6]. According to a report by Mais *et al.*, nearly 30% of OMCT may not be apparent in sonography, due to the presence of associated pelvic abnormalities (e.g., endometriomas, large fibromas, or large contralateral ovarian masses) or intrinsic sonographic characteristics of OMCTs [7]. Actually, 80% of cystic teratomas were reported to have an echo pattern that should suggest malignancy [8]. In addition, other features of OMCT, such as a very large tumor size and significantly elevated tumor markers could make the diagnosis more difficult. Because the surgical procedure performed is quite different for benign and malignant tumors, differential diagnosis is very important for women with an ovarian mass.

As a tool to assist in the diagnosis of OMCT, the importance of serum CA19-9 level has been proposed in many studies, and CA19-9 elevation rate is 39.6%–86% [4–6]. CA19-9 is a sialylated Lewis A antigen, which is associated with mucins in gastrointestinal adenocarcinomas [3]. It is not surprising that CA19-9 is commonly elevated in patients with OMCT, considering the histological feature of OMCT, which contains various kinds of tissue.

According to the present results, five tumor markers were assessed in OMCT patients. CA153, CEA, and AFP were elevated in 2.78%, 0.64%, and 0% of patients, respectively. Nevertheless, CA19-9 was elevated in 45.83% of patients with OMCTs. CA19-9 was more frequently elevated than CA 125 (6.09%). Thus CA19-9 could be a more useful marker in OMCT. The rate of CA19-9 elevation in MCT has been reported to be from 39.6% to 86% [4–6]. Although CA19-9 testing alone is not sufficient for the diagnosis of OMCT, it might be a potent tool assisting OMCT diagnosis. There have been only a few reports elucidating the relationship between serum CA19-9 level and characteristics of OMCT. In a retrospective study evaluating 163 patients with ovarian MCT, the authors concluded that CA 19-9 elevation appears to correlate with a larger tumor diameter and higher rate of ovarian torsion [6]. Likewise, another retrospective study evaluating 215 patients with ovarian MCT concluded that serum CA19-9 level was correlated with larger tumor size, although they failed to show a positive relationship between bilaterality and CA19-9 elevation [9]. However, to the best of the present authors' knowledge, this study showed significant correlation between CA19-9 elevation and large tumor diameter, bilateral tumor, and multilocular tumor in OMCT. The elevated CA19-9 level of five patients with ovarian teratoma recurrence was observed in the present study, but the sample size was limited to assess the value of CA19-9 for cancer recurrence, which need further study to be evaluated.

According to these findings, the principal mechanism of the elevation of CA19-9 in OMCT is thought to be leakage from the cystic cavity into the blood stream [10–12]. Therefore, in the more probable conditions of leakage into the blood stream, such as larger or bilateral MCT, serum CA19-9 elevation might be expected. Similarly, the present results indicate that CA19-9 elevation is correlated with larger tumor size and bilateral OMCT. CA125 elevation is also correlated with larger tumor size, but not correlated with bilateral OMCT. Mikuni *et al.* showed that the average tumor size and tumor weight were positively associated with CA19-9 [7]. This evidence documented indirectly that CA19-9 was secreted from mature teratoma itself. Therefore, the present authors observed that CA19-9 decreased significantly after tumor resection in OMCTs. However, the result had not yet been observed in CA125 elevation patients. Otherwise, there were five recurrent patients with teratoma resection in this study, whose serum CA19-9 level were elevated (57.89–98.16 U/ml), indicating that CA19-9 is more sensitive than CA125 in OMCTs, and it may be a auxiliary monitor marker for prognosis and recurrence of OMCTs. Furthermore, unilocular ovarian tumors were observed in OMCTs, and multilocular ovarian tumors accounted for 10%–17% [13–15]. In this study, the smallest tumor diameter of teratoma was 1.0 cm. Therefore, more attention should be paid to intraoperative inspection, if necessary, to detect contralateral ovary to avoid omission of very small tumors [13]. However, some researchers supported that OMCTs were diagnosed in fertile women, and conventionally profiling the contralateral ovary may cause ovarian function damage. Otherwise, the incidence of bilateral OMCTs was relatively low. Therefore, there may be no need to conventional profile for normal appearance of the contralateral ovary. In the present study, bilateral and multilocular OMCTs accounted for 11.54% (36/312) and 18.59% (32/312), respectively. The incidence of CA19-9 elevation in bilateral OMCTs was more than that in unilateral OMCTs, and CA19-9 and CA125 elevation was more frequent in multilocular tumors than that in unilocular tumors. The authors suggested that OMCT patients with serum CA19-9 or CA125 elevation, especially with CA19-9 elevation, it should be noticed that bilateral or multilocular OMCT occurred. Tumor ovary and contralateral ovary should be explored carefully to avoid lesion missing.

In all patients, CA19-9 and CA125 elevation was more frequently observed in torsion tumors, indicating that torsion tumor in OMCTs may increase serum CA19-9 and CA125 levels. Ovarian tumors with torsion are a severe complication of OMCT. The routine therapy is emergency operation which can impact the reproductive endocrine function of patients. Data showed that ovarian tumor with CA19-9 elevation and tumor diameter larger than seven cm tended to cause torsion which needed to be cured earlier [16, 17]. These results were consistent with the present study. However, this study indicated that patients with ab-

dominal pain and vomiting should be alarmed for torsion.

According to the present results, serum CA19-9 has more clinical importance as a tool to assist in the diagnosis of OMCT than serum CA125, AFP, CEA, and CA153, although it is not sufficient as a single tool. Bilateral, multi-locular and torsion OMCTs have serum CA19-9 elevation, which should be noticed in clinically in order to determine timely surgery and to guide whether a closer examination of the lesion and the contralateral ovary is required. Recurrent patients of OMCTs with elevated serum CA19-9, but with an obvious preoperative decline of CA19-9 level suggests that the latter may be an important indicator for diagnosis and recurrence of OMCTs.

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