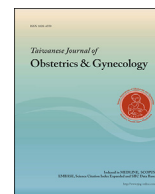Contents lists available at ScienceDirect

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Original Article

The role of preoperative serum cancer antigen 125 in malignant ovarian germ cell tumors

Ju-Hyun Kim, Jeong-Yeol Park[*], Jong-Hyeok Kim, Yong-Man Kim, Young-Tak Kim, Joo-Hyun Nam

Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

A B S T R A C T

Objective: To determine the role of preoperative serum cancer antigen 125 (CA 125) in malignant ovarian germ cell tumors (MOGCTs).
Materials and methods: Using information from medical databases of Asan Medical Center (Seoul, Korea), we investigated 161 patients with histologically diagnosed MOGCTs and whose preoperative serum CA 125 had been checked. We determined the optimal cutoff value of CA 125 as > 249.5 U/mL in MOGCTs using a receiver operating characteristic curve.
Results: The median patient age was 24 years (range, 6–52 years). The most common histologic type was immature teratoma. Most patients had stage I disease. Thirty-two patients (19.9%) had elevated preoperative serum CA 125 levels over 249.5 U/mL. On univariate analysis, tumor size, advanced stage, the presence of ascites, ovarian surface involvement, and tumor rupture were significantly associated with elevated preoperative serum CA 125 levels (>249.5 U/mL). In the median follow-up time of 87 months (range, 9–271 months), 14 patients had a recurrence, and 5 died of the disease. Patients with an elevated serum preoperative CA 125 level (>249.5 U/mL) had poorer disease-free survival, but this was not statistically significant. However, elevated preoperative CA 125 (>249.5 U/mL) was significantly associated with poorer overall survival.
Conclusions: Elevated preoperative serum CA 125 may have prognostic value in patients with MOGCTs.

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare tumors, comprising <5% of all ovarian malignancies [1]. MOGCTs are usually diagnosed in young women, with a peak incidence in women under 20 years of age, although they can also be diagnosed in patients in their sixties and seventies [2–5]. Therefore, in contrast to patients with epithelial ovarian cancer (EOC), the preservation of fertility and ovarian function is important in patients with MOGCTs.

According to a modified version of the third World Health Organization classification (2003 version) of germ cell tumors of the ovary [6], such tumors are categorized as primitive germ cell tumors, biphasic or triphasic teratomas, or monodermal teratomas [6–8]. The group of primitive germ cell tumors is composed of dysgerminomas, yolk sac tumors, embryonal carcinomas, polyembryomas, nongestational choriocarcinomas, and mixed germ cell tumors. Biphasic or triphasic teratomas consist of immature teratomas and mature teratomas [6–8]. The most common MOGCTs include dysgerminomas, immature teratomas, and yolk sac tumors, which comprise 90% of MOGCTs [9]. The remaining 5–10% of MOGCTs include choriocarcinomas, embryonal carcinomas, and polyembryonal carcinomas [10].

The main serum tumor markers of MOGCTs are alphafetoprotein, beta-human chorionic gonadotropin, lactic dehydrogenase, and placental alkaline phosphatase. These may play a fundamental role in the diagnosis and management of MOGCTs and evaluation of response to chemotherapy or recurrence [11].

Serum cancer antigen 125 (CA 125) is generally used as a tumor marker for monitoring EOC or for the differential diagnosis of other pelvic masses [12,13]. In EOC patients, many studies have evaluated serum CA 125 levels checked before any treatment as a prognostic factor [14]. However, the initial serum level of CA 125 in relation to the survival index in EOC is controversial because of several variables like stage and histology [15].

* Corresponding author. Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, South Korea, 05505. Fax: +82 2 476 7331.
E-mail address: catgut1-0@hanmail.net (J.-Y. Park).

In MOGCTs, few studies have investigated the value of preoperative CA 125 as a prognostic factor. Moreover, there are no studies on the correlation between CA 125 and other factors in MOGCTs. In our center, multiple tumor markers including CA 125 are usually evaluated in patients with pelvic mass even though MOGCT is suspected. Using our center's data, we analyzed which factors were associated with preoperative serum CA 125 and were affecting overall survival (OS) and disease-free survival (DFS) in MOGCTs, to determine the role of preoperative serum CA 125 in MOGCTs.

Material and methods

After obtaining the approval of the Institutional Review Board of Asan Medical Center (AMC, Seoul, Korea), we investigated patients with histologically diagnosed MOGCTs who were treated and had been checked for preoperative CA 125 at AMC between 1992 and 2015. We obtained the patients' demographic and clinicopathologic data from their medical records, including age, history of surgery, tumor size, histologic type, International Federation of Gynecology and Obstetrics (FIGO) stage of tumor, preoperative level of CA 125, surgical procedures, adjuvant treatment, presence of lymph node metastasis, ascites, surface involvement, cytology, residual tumor, number of deliveries, recurrence, and survival. We classified the histologic type of MOGCTs according to the modified version of the third World Health Organization classification (2003 version) of germ cell tumors of the ovary [6–8], and the stage was determined according to the FIGO staging system [16,17]. We defined fertility-sparing surgery as the conservation of the uterus and at least one adnexa. Staging surgery included exploration of the peritoneum, cytology of ascites, omental biopsy, and lymph node evaluation.

OS time was defined as the time interval in months between the date of diagnosis and the date of death from the disease, or the last follow-up. DFS was defined as the time interval in months from the date of diagnosis to the date of recurrence or censoring as described in our previous study [18].

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). To determine the association between clinicopathologic factors and preoperative serum CA 125 levels, the chi-square test was used. When we calculated the OS and DFS, we chose the optimal cutoff value of CA 125 using a receiver operating characteristic curve (ROC). OS and DFS curves were obtained using the Kaplan–Meier survival method. To compare the differences in survival rates, we used a log-rank test. A p value of <0.05 in a two-sided test was regarded as statistically significant.

Results

During our study period, 199 patients were diagnosed with MOGCTs by surgery at Asan Medical Center. Among them, 161 patients whose preoperative serum CA 125 had been checked were eligible for our study. The demographic and clinicopathologic characteristics of the patients are summarized in Table 1. The median age was 24 years (range, 6–52 years), and more than half (53.4%) were aged <24 years. Most patients (82.6%) had no history of delivery. The most frequent histologic type was immature teratoma (32.9%), followed by dysgerminoma (31.7%), mixed MOGCTs (18.6%), and yolk sac tumors (14.9%). There were one case of non-gestational choriocarcinoma and two cases of embryonal carcinoma. Stage I disease was the most common (71.4%), followed by stage III (15.5%). The median preoperative serum CA 125 level was 78.3 U/mL. Forty-eight patients (29.8%) had a normal range of preoperative serum CA 125 (<35 U/mL). Thirty-two patients (19.9%) had elevated preoperative CA 125 levels over 249.5 U/mL. The median size of the tumors was 15 cm.

Table 1
Demographic and clinicopathologic characteristics of patients (n = 161).

Characteristics	Values	Percentage (%)
Age (years)		
Median (range)	24 (6–52)	
≤24	86	53.4
>24	75	46.6
Parity (n)		
0	135	83.9
1	10	6.2
2	15	9.3
3	1	0.6
Histology (n)		
Dysgerminoma	51	31.7
Immature teratoma	53	32.9
Yolk sac tumor	24	14.9
Choriocarcinoma	1	0.6
Embryonal carcinoma	2	1.2
Mixed	30	18.6
FIGO stage (n)		
I	115	71.4
II	19	11.8
III	25	15.5
IV	2	1.2
Preoperative CA 125 (U/mL)		
Median (range)	78.3 (3–2390)	
≤249.5	129	80.1
>249.5	32	19.9
Ascites (n)		
Yes	94	58.4
No	67	41.6
Size (cm)		
Median (range)	15.00 (1–29)	
<15	77	47.8
≥15	84	52.2
Tumor rupture (n)		
Yes	51	31.7
No	110	68.3
Peritoneal cytology (n)		
Negative	132	82.0
Positive	14	8.7
Not done	15	9.3
Ovarian surface invasion (n)		
Not involved	100	62.1
Involved	61	37.9
Lymph node Metastasis (n)		
Yes	12	7.5
No	149	92.5
Residual tumor (n)		
Yes	6	3.7
No	155	96.3
Treatment (n)		
Surgery only	29	18.0
Adjuvant chemotherapy	131	81.4
Transfer to other hospital	1	0.6

CA 125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

All patients underwent surgical management. Ninety-four patients (58.4%) had ascites at surgery. Intraoperative or preoperative spillage of the tumor was observed in 51 patients (31.7%). Cytology was performed in 146 patients (90.7%), and 14 (8.7%) had positive cytology. Twelve patients (7.5%) had lymph node metastasis. Moreover, 61 patients (37.9%) had surface involvement of tumors. Six patients (3.7%) had residual tumors.

The surgical procedures are summarized in Table 2. A total of 144 patients (89.4%) underwent surgery via laparotomy, and 17 patients (10.6%) via laparoscopy. Radical surgery was performed in 23 patients (14.3%), and fertility-sparing surgery in 138 patients (85.7%). Meanwhile, 118 patients underwent staging surgery (73.3%).

We identified the reference level of CA 125 (>249.5 U/mL) using a ROC (Fig. 1). On univariate analysis, tumor size, advanced stage,

Table 2
Surgical management of MOGCTs (n = 161).

Surgical procedure	Number	Percentage (%)
Laparoscopic surgery	17	10.6
Laparotomy	144	89.4
Adnexa surgery		
BSO	22	13.7
USO, UO	95	59.0
USO, UO + UOC	36	22.4
UOC	4	2.5
BOC	4	2.5
Radical surgery	23	14.3
Fertility-sparing surgery	138	85.7
Staging surgery	118	73.3

BOC, bilateral ovarian cystectomy; BSO, bilateral salpingo-oophorectomy; MOGCTs, malignant ovarian germ cell tumors; UO, unilateral oophorectomy; UOC, unilateral ovarian cystectomy; USO, unilateral salpingo-oophorectomy.

the presence of ascites, ovarian surface involvement, and tumor rupture were positively correlated with elevated preoperative serum CA 125 level (>249.5 U/mL) (Table 3).

The median follow-up time was 87 months (range, 6–271 months). Four patients died of the disease, and 14 had a recurrence. The 5-year OS rate was 97%, and the 5-year DFS rate was 90.6%. Elevated serum preoperative CA 125 level (>249.5 U/mL) was associated with poorer DFS, but this was not statistically significant (Fig. 2). However, elevated preoperative CA 125 (>249.5 U/mL) was significantly associated with poorer OS (Fig. 2).

Discussion

The prognostic and predictive role of CA 125 in EOC has been well investigated in several clinical situations, including preoperative CA 125 level, the actual value of CA 125 at different times

Table 3
Univariate analysis of risk factors associated with elevated cancer antigen 125 (CA 125).

Factors	CA 125 ≤ 249.5 U/mL	CA 125 > 249.5 U/mL	p value
LN meta, (n)			
Negative	120	29	0.644
Positive	9	3	
Peritoneal cytology (n)			
Negative	107	25	0.262
Positive	9	5	
Ascites (n)			
No	61	6	0.003
Yes	68	26	
Ovarian surface invasion (n)			
No invasion	90	10	<0.001
Invasion	39	22	
Tumor rupture (n)			
No	99	11	<0.001
Yes	30	21	
Age (n)			
≤24 years	68	18	0.720
>24 years	61	14	
Size (n)			
<15 cm	69	8	0.004
≥15 cm	60	24	
Stage (n)			
I	102	13	<0.001
II	12	7	
III	5	11	
IV	1	1	

LN meta, lymph node metastasis.

during chemotherapy, and the CA 125 half-life [19]. Cooper et al. concluded that preoperative CA 125 is a prognostic factor for death in EOC [20]. A French multicenter retrospective study has revealed that the serum CA 125 half-life and nadir concentration have prognostic value in EOC [21]. Moreover, the potential value of the
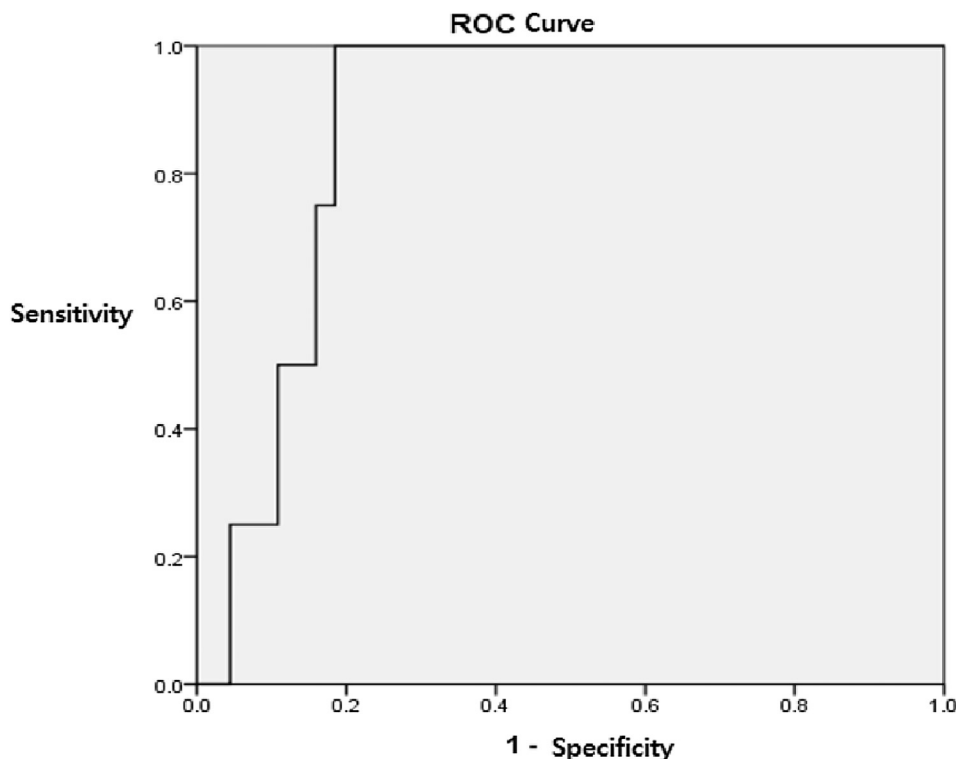
Fig. 1. Receiver operating characteristic (ROC) curve analysis for cancer antigen 125 (CA 125) levels. Best cutoff point of CA 125 was 249.5 U/mL. Area under the curve (AUC) = 0.876; 95% confidence interval, 0.806–0.946; p = 0.010.
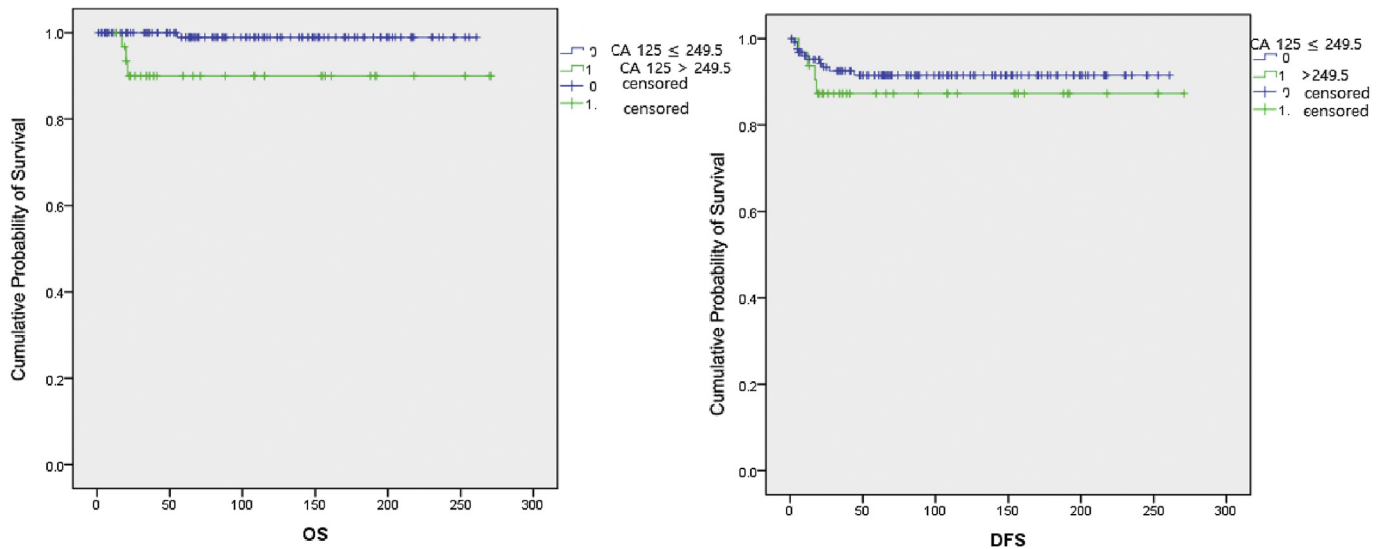
Fig. 2. Overall survival (left) and disease-free survival (right) in patients (n = 161) stratified by preoperative serum cancer antigen 125 (CA 125) level (>249.5 U/mL). $p = 0.005$ (left), $p = 0.404$ (right).

combination of other biomarkers and CA 125 in EOC was evaluated in some studies such as that by Stephen et al. [22]. However, the role of CA 125 in MOGCTs is virtually unknown.

According to our previous study of patients with MOGCTs who underwent fertility-sparing surgery, preoperative CA 125 level over the reference range of 35 U/mL in EOC was not significantly associated with OS and DFS [23]. We supposed there might be a different reference level for CA 125. Therefore, we determined the optical cutoff value of CA 125 (>249.5 U/mL) using a ROC.

CA 125 is a glycoprotein expressed in the epithelium lining of body cavities [24]. Our study revealed the elevated preoperative serum CA 125 was correlated with advanced stage, ascites, ovarian surface involvement, and tumor rupture in MOGCTs. It may help predict advanced disease and extra-ovarian disease in MOGCTs before surgery.

We found out that an elevated preoperative serum CA 125 level over 249.5 U/mL was significantly associated with poorer survival in patients with MOGCTs diagnosed in our center. As far as we know, only one previous study specifically evaluated the prognostic role of CA 125 in MOGCTs [25]. According to this study by Salonen et al., which included 16 women with MOGCTs, increased preoperative serum CA 125 levels indicated poor prognosis for MOGCTs. On the other hand, serum alpha-fetoprotein or beta-human chorionic gonadotropin levels were not valuable predictors [25]. Disease-specific survival among patients with elevated preoperative CA 125 levels was lower compared with that of patients with normal CA 125 levels [25]. According to the Kaplan—Meier analysis, patients older than 30 years had a poorer outcome. In contrast, histology, treatment, and the presence/absence of ascites were not associated with prognosis [25]. To the best of our knowledge, this is the first study that identified the association between preoperative CA 125 levels and survival outcome.

The strength of this study is its large sample size. We analyzed 161 patients, making this study one of the largest for this patient group. We thoroughly investigated the pathologic reports of the 161 patients and reviewed their preoperative CA 125 levels. This study is the second study about the role of preoperative CA 125 in MOGCTs.

This study, however, has several limitations. First, this was a retrospective study. The rarity of MOGCTs has made it difficult to carry out prospective studies. Second, we did not check the

postoperative CA 125 level because we had not expected its association with OS. Thus, further study in this regard, including a decline in CA 125 level during chemotherapy, could improve the understanding of the role of CA 125 in MOGCTs.

Moreover, due to the rarity of MOGCTs, we did not validate the cutoff of 249.5 U/mL. The cutoff should be tested in an independent cohort to conclude its value more reliably. Because a ROC curve describes test performance in one population, application to other populations requires careful consideration.

In conclusion, the elevation of preoperative serum CA 125 levels may be a prognostic factor of MOGCTs. Prospective data and international collaboration of different populations should be needed to make sure its value.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgments

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