

ORIGINAL ARTICLE

The prognostic role of preoperative serum CA 125 levels in patients with endometrial carcinoma

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Summary

Purpose: Previous studies have shown that elevated preoperative serum CA 125 levels strongly correlate with various clinical and pathological variables and prognosis of patients with endometrial carcinoma (EC). The aim of the present study was to evaluate the clinical significance of preoperative serum CA 125 levels in patients with EC.

Methods: A retrospective study of all EC patients treated at our institution between 1995 and 2010 with available follow-up was conducted. The preoperative serum level of CA 125 was measured in 99 patients and evaluated in relation to various clinical and pathological variables and outcome. We used the cut-off level of 20 U/ml for CA 125 on chi-square test for categorical variables. Survival analysis was performed with the use of Kaplan Meier method, the log rank test and Cox proportional hazards regression analysis.

Results: In the early stages of disease the mean values of CA 125 were 35 U/ml (SD±70) for stages IA-IB and 21 U/ml (SD±29) for stage IC (Mann-Whitney test for continuous variables). In advanced stages of disease (III-IV), the values of preoperative serum CA 125 levels were statistically increased, with mean value 54 U/ml (SD±44), in comparison to stages IA-IB ($p=0.02$) and IC ($p=0.007$). According to the multivariate analysis, elevated preoperative serum CA 125 level ($p=0.043$) and histological tumor type ($p=0.004$) were independent prognostic factors for disease free survival (DFS) and overall survival (OS) of patients with EC.

Conclusion: The current study suggests that measurement of preoperative serum CA 125 is a useful clinical tool in the prognosis of patients with EC.

Key words: CA 125, endometrial carcinoma, prognosis

Introduction

EC is the most common malignancy of the female genital tract in developed countries. In the United States, more than 43,470 new cases of EC were detected in 2010, leading to an estimated 7,950 cancer-related deaths [1]. The incidence rate of EC is rising in the last few years because of the ageing of the population, the use of estrogen unopposed with progesterone hormone replacement therapy and increasing rates of obesity [2]. Most of the risk factors that have been described are related to prolonged unopposed estrogen stimulation of the endometrium [3].

EC constitutes a heterogeneous group of le-

sions with distinct risk factors, clinical presentation, pathological features and molecular characteristics. Two different subtypes of EC according to biological, molecular and clinicopathological features are recognized [4]. Type I, estrogen-sensitive carcinoma, mainly endometrioid carcinoma, arises in a background of endometrial hyperplasia. This is the most common subtype of EC, comprising approximately 80% of EC. On the contrary, type II carcinomas are not related to estrogen, are high grade tumors such as uterine papillary serous carcinoma or clear cell carcinoma and arise in a background of endometrial atrophy. These cancers tend to have aggressive clinical course

and poor prognosis and account approximately for 15-20% of all ECs [5]. In general, most ECs have favorable prognosis, with 5-year OS around 80% because they are diagnosed at an early stage [6].

CA 125, an epithelial surface tumor antigen also found in the blood as a circulating serum glycoprotein, is used as a valuable marker for diagnosis and post-treatment monitoring of patients with epithelial ovarian carcinoma (EOC) [7,8]. Generally, the preoperative serum CA 125 in EC has been studied less than in EOC and its role has, yet, to be clearly defined. Niloff and coworkers first described that in EC patients, preoperative serum CA 125 levels were elevated in recurrent or disseminated disease [9]. A number of studies have since shown that elevated preoperative serum CA 125 levels strongly correlated with various surgical prognostic factors such as advanced stage and grade, deep myometrial invasion, lymph node metastases as well as the presence of extra-uterine disease [10-17]. In addition, elevated preoperative serum CA 125 levels appear to be a significant independent predictor of disease recurrence and prognosis after primary treatment [13, 18-20].

Several authors have suggested a lower preoperative serum cut-off level of CA 125 (20 U/ml) as more appropriate for EC. This novel level, derived from clinical data of EC patients, indicates higher sensitivity and specificity in the prediction of extra-uterine spread of disease and early detection of recurrence after primary treatment [13,17, 21-23].

The purpose of this retrospective study was to evaluate the clinical utility of preoperative measurement of serum CA 125 level as a prognostic factor and disease surveillance tool in EC patients.

Methods

We retrospectively analyzed all endometrial carcinoma patients treated at our institution between 1995 and 2010 with available follow-up. The preoperative serum CA 125 levels were measured in 99 patients. All patients had undergone surgical treatment with total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection. None of the patients had received neoadjuvant chemotherapy or radiotherapy. The operative procedures were performed either by a general gynecologist or by a gynecologic oncologist and further treatment options were discussed by the institutional gynecologic oncology board. All the surgical specimens were examined at the Department of Pathology of our institution.

Surgical staging was based on the 1988 criteria of the International Federation of Gynecology and Obstetrics (FIGO) system [24]. The histological classification

was performed using the criteria of the World Health Organization (WHO) [25]. Adjuvant treatment in the form of radiation therapy and/or chemotherapy was administered to patients with high-risk factors for recurrence, such as advanced-stage disease, high tumor grade, positive lymph nodes, increased depth of myometrial invasion (>50% of the myometrial thickness) or unfavorable histology.

All patients were evaluated regularly for disease recurrence by clinical examination and diagnostic imaging methods. Measurement of tumor markers was also performed every 3 months in the first 2 years after primary therapy.

We correlated the preoperative serum CA 125 levels with various clinical and pathological parameters such as patient age, FIGO stage, myometrial invasion, presence of extra-uterine disease, recurrence and prognosis. A series of cut-off values of CA 125 were tested. These included previously used cut-off points, as well as the mean and median values in our study. The serum CA 125 cut-off value of 20 U/ml giving the best p-values regarding survival was selected for preoperative evaluation of all patients. This retrospective study was approved by the ethical committee of the hospital.

Statistics

Correlation between groups was performed using the non parametric Mann-Whitney test for continuous variables. For categorical variables, the chi-square test was used. Survival analysis was performed with the use of Kaplan-Meier method, the log rank test (univariate analysis) and the Cox proportional hazards regression model (multivariate analysis). A p-value < 0.05 was considered as statistically significant. All analyses were performed with SPSS 17.0 (SPSS Inc. Chicago, IL, USA).

Results

Among the 99 patients studied, 90 (90.9%) had histological type I and 9 (9.09%) type II EC. The mean age of the patients was 64.2 years (range 37 - 84). According to FIGO criteria 11 (11.1%) patients had stage IA, 31 (31.3%) IB, 34 (34.3%) IC, 12 (12.1%) II and 11(11.1%) III-IV. Tumor grades 1,2 and 3 were seen in 37(37.4%), 40 (40.4%) and 22 (22.2%) patients, respectively.

The mean preoperative serum CA 125 level for the entire study group was 35.8 U/ml (range 2-426). The mean preoperative CA 125 level in premenopausal patients was higher (mean 65.1 U/ml) than in postmenopausal patients (mean 28.9 U/ml) and this difference was statistically significant ($p=0.025$).

Thirty-nine patients (39.3%) had elevated preoperative serum CA 125 levels, above the cut-off level of 20 U/ml. Thirteen of these patients

Table 1. Preoperative serum CA 125 levels in relation to disease stage

Stage	No. of EC patients with CA 125 \leq 20 U/ml N (%)	No. of EC patients with CA 125 $>$ 20 U/ml N (%)
IA-IB	29 (29.9)	13 (13.1)
IC	22 (22.2)	12 (12.1)
II	6 (6.06)	6 (6.06)
III-IV	3 (3.03)	8 (8.08)
Total (%)	60 (60.6)	39 (39.3)

p=0.066. EC: endometrial cancer

Table 2. Preoperative serum CA 125 levels in relation to myometrial invasion

Myometrial invasion	No. of EC patients N (%)	Preoperative mean CA 125 levels \pm SD (U/ml)
MI $<$ 1/2	44 (44.4)	34.3 \pm 69.4
MI $>$ 1/2	55 (55.5)	37.0 \pm 59.6

p=0.833. EC: endometrial cancer, MI: myometrial invasion

Table 3. Preoperative serum CA 125 levels in relation to presence of extra-uterine disease

Extra-uterine disease	No. of EC patients N (%)	Preoperative mean CA 125 levels \pm SD (U/ml)
Yes	5 (5.05)	58.2 \pm 28.9
No	94 (94.9)	34.6 \pm 65.0

p=0.428. EC: endometrial cancer

Table 4. Preoperative serum CA 125 levels in relation to recurrence of disease

Recurrence of disease	No. of EC patients N (%)	Preoperative mean CA 125 levels \pm SD (U/ml)
No	66 (82.5)	29.5 \pm 60.4
Yes	14 (17.5)	39.3 \pm 39.3

p=0.242. EC: endometrial cancer

(13.1%) had early-stage disease (IA-IB), 12 patients (12.1%) had stage IC disease, 6 patients (6%) had stage II disease and 8 patients (8%) had advanced-stage (III-IV) disease (Table 1).

Preoperative serum CA 125 levels were significantly higher in advanced stages (III-IV), with mean level of 54 U/ml, in comparison to early-stage disease (IA-IB) with mean level of 35 U/ml (p=0.02) and stage IC with mean level of 21 U/ml (p=0.007) according the Mann-Whitney test. In addition, elevated preoperative serum CA 125 levels (mean 31.5 U/ml) in postmenopausal women were significantly correlated with the presence of lympho-vascular space involvement (LVSI) (p=0.01).

The mean preoperative serum CA 125 level

was higher in patients with $>$ 50% myometrial invasion (37 U/ml, range 2-386) compared to patients with $<$ 50% myometrial invasion (34.3 U/mL, range 3-426), but this difference was not statistically significant (p=0.833) (Table 2). Similarly, the mean preoperative serum CA 125 level was higher with the presence of extra-uterine disease than in early-stage disease, (58.2 U/ml and 34.6 U/ml, respectively), but this difference was also not statistically significant (p=0.424) (Table 3). Only 14 patients developed disease recurrence in our study population. These patients had higher preoperative serum CA 125 levels (mean 49.4 U/ml) in comparison to patients free of recurrence (mean 29.5 U/ml) but the difference did not reach statistical significance (p=0.242) (Table 4).

During the follow-up period (mean 52 months, range 1-180) 11 (11.1%) patients died of disease, 4 (4.04%) were alive with disease and 61 (61.6%) were alive with no evidence of disease. According to multivariate analysis, histological type (p=0.004) and preoperative serum CA 125 levels (p=0.043) were independent prognostic factors for DFS and OS (Figures 1, 2).

Discussion

Preoperative evaluation of patients diagnosed with EC is very important in deciding treatment modalities and in the counseling of patients. The necessity to perform extensive surgical staging procedures in EC is based on preoperative clinical and pathological parameters which are associated with the prognosis of patients [26]. Preoperative CA 125 levels have been proposed as a useful tool in the decision making of EC patients [16].

The optimal cut-off level of preoperative serum CA 125 in patients with EC has been the subject of multiple studies [13,17,21-23], setting the cut-off for CA 125 in EC at 20 U/ml. Our results support the use of this novel cut-off level, as it was best correlated with clinical stage and patient prognosis in our series.

Previous studies also reported that elevated preoperative serum CA 125 levels were strongly correlated with advanced-stage disease, higher grade, deep myometrial invasion, lymph node metastases, presence of extra-uterine spread of the tumor and poor prognosis [10-14,17,19-20,27,28]. These findings revealed that preoperative assessment of serum CA 125 levels can be used as a guide to perform aggressive surgical staging with regards to initial treatment modalities as well as to predict prognosis [16,27,29]. The results of our study are partly in accordance with the above reports.

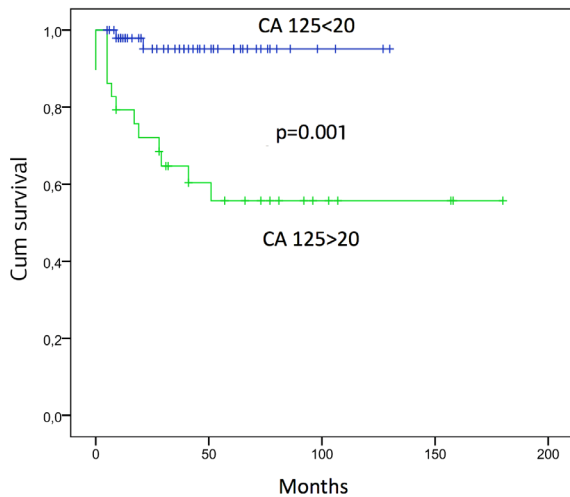


Figure 1. Kaplan-Meier curve for disease free survival in relation with preoperative CA 125 levels in endometrial carcinoma.

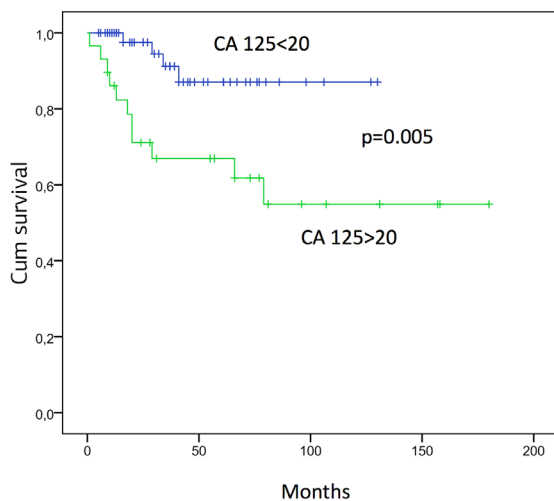


Figure 2. Kaplan-Meier curve for overall survival in relation with preoperative CA 125 levels in endometrial carcinoma.

Similarly to previous reports [10-18,20,22-23,27], we found a strong association between preoperatively elevated CA 125 levels and advanced stage of disease. Therefore, preoperative serum CA 125 assessment should be considered in all patients with suspected advanced disease stage or presence of unfavorable histology in endometrial biopsy as an adjunct to the prediction of the stage of disease and subsequent patient management.

The depth of myometrial invasion in EC is strongly associated to lymph node metastasis, risk of recurrence and patient prognosis [30]. Traditionally, intra-operative evaluation of myometrial invasion can be performed by gross visual examination of the cut surface of the hysterectomy specimen [31]. In addition, imaging studies, mainly ultrasound and magnetic resonance imaging, are used preoperatively alone or in combination with other clinical and pathological variables

to predict the depth of myometrial invasion or the presence of extrauterine disease with varying degrees of success [32]. Elevated CA 125 levels have been associated with deep myometrial invasion [12-15,20,22,27]. In this study, the mean preoperative serum CA 125 level was higher in patients with deep myometrial invasion than in those with superficially invading tumors, but this difference was not statistically significant, nor significant association was observed with extrauterine spread of the carcinoma.

In agreement with a previous report [23], our data showed that the mean preoperative serum CA 125 level in premenopausal patients was significantly higher in comparison to postmenopausal ones. According to a recent study, this finding has implications to the management of many premenopausal patients with early-stage disease wishing to maintain their endocrine function, without worsening the prognosis [28]. However, in the present study the number of premenopausal patients was small (19 cases) and did not allow for further subgroup analysis.

Many previous studies [12,14,27], have shown that elevated preoperative serum CA 125 levels correlates strongly with the presence of LVSI in endometrial carcinoma. Our data also support the association of elevated preoperative serum CA 125 levels with positive LVSI in postmenopausal patients.

In previous reports the preoperative serum CA 125 level was found to be an independent predictor for DFS and OS after initial treatment in patients with EC [12,14], and elevated CA 125 levels have been significantly associated with shorter DFS and OS [20,27,29]. In agreement with the above studies, our findings also demonstrated that CA 125 levels together with histological type were independent prognostic factors for both DFS and OS.

Conclusions

Although large prospective studies are needed to firmly establish the prognostic role of preoperative serum CA 125 in EC, the present study suggests that preoperative assessment of CA 125 should be incorporated into the initial preoperative evaluation of EC patients. Preoperative serum CA 125 level is a clinically valuable tool for individualizing patient management and for the prediction of prognosis in EC patients since it is correlated with clinical stage and is an independent predictor of survival.

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