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Serum CA125 predicts extrauterine disease and survival in uterine carcinosarcoma

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Abstract

Objective—The purpose of this study was to determine the clinical utility of CA125 measurement in patients with uterine carcinosarcoma (CS).

Methods—Ninety-five consecutive patients treated for CS at a single institution were identified. All 54 patients who underwent preoperative CA125 measurement were included in the study. Data were abstracted from the medical records. Tests of association between preoperative CA125 and previously identified clinicopathologic prognostic factors were performed using Fisher's exact test and Pearson chi-square test. To evaluate relationship of CA125 elevation and survival, a Cox proportional hazard model was used for multivariate analysis, incorporating all of prognostic factors identified by univariate analysis.

Results—Preoperative CA125 was significantly associated with the presence of extrauterine disease ($P<0.001$), deep myometrial invasion ($P<0.001$), and serous histology of the epithelial component ($P=0.005$). Using univariate survival analysis, stage ($HR=1.808$, $P=0.004$), postoperative CA125 level ($HR=9.855$, $P<0.001$), and estrogen receptor positivity ($HR=0.314$, $P=0.029$) were significantly associated with survival. In the multivariate model, only postoperative CA125 level remained significantly associated with poor survival ($HR=5.725$, $P=0.009$).

Conclusion—Preoperative CA125 elevation is a marker of extrauterine disease and deep myometrial invasion in patients with uterine CS. Postoperative CA125 elevation is an independent prognostic factor for poor survival. These findings indicate that CA125 may be a clinically useful serum marker in the management of patients with CS.

Keywords

Carcinosarcoma; CA125; Serum biomarker; Uterine neoplasm

Introduction

Uterine carcinosarcoma (CS), also known as malignant mixed müllerian tumor, is one of the most aggressive types of uterine cancer, with a propensity for extrauterine metastases and a high case fatality rate [1,2]. Although previously classified as a uterine sarcoma, CS is defined by the presence of both malignant epithelial and mesenchymal components. Immunohistochemical and genetic analyses of CS suggest a commonclonal endometrial origin of both elements, supporting the view of CS as a metaplastic carcinoma [3–7].

Given the aggressive nature of this malignancy, several studies have explored the clinical and pathological features associated with poor prognosis. From these studies, age, stage, myometrial invasion, and lymphovascular involvement have been identified as prognostic factors [2,6,8]. In addition, the presence of serous or clear cell carcinoma components is associated with a less favorable outcome [8]. Immunohistochemical and molecular studies demonstrate overexpression of tyrosine kinase receptors (e.g. HER-2, EGFR, KIT) in some cases of CS, suggesting potential targets for therapeutic intervention in subgroups of CS [9–14]. However, serum markers have yet to be identified and evaluated for uterine carcinosarcoma.

Monitoring of serum markers has proven utility in another aggressive gynecologic malignancy, epithelial ovarian cancer [15]. The most studied and validated serum marker in ovarian cancer is CA125. The serum assay utilizes a monoclonal antibody to CA125, the antigenic determinant on a large glycoprotein encoded by the gene MUC16 [16]. Prospective trials involving ovarian cancer patients have validated the use of CA125 for monitoring clinical response to therapy and for the detection of recurrent disease [17]. More recently, the potential utility of CA125 measurement has been evaluated in endometrial cancer patients. Several investigators have found that preoperative CA125 elevation in endometrial cancer patients is associated with pathologic risk factors such as high grade, deep myometrial invasion, lymphovascular involvement, extra-uterine disease, and nodal metastases [18–23]. In addition, preoperative CA125 elevation is associated with reduced actuarial survival in at least one study [24]. Others have proposed that CA125 measurement may be useful for the detection of endometrial cancer recurrence and for monitoring response to chemotherapy, particularly those with high-risk histologies such as serous carcinoma [25–30].

Several case reports and case series have reported elevated serum CA125 in patients with uterine CS [31–33]. In addition, positive tissue staining for CA125 has been reported in an immunohistochemical study of CS [34]. However, none of the studies in the literature included sufficient numbers of CS patients to evaluate CA125 as a serum marker in this patient population. The purpose of this study was to determine the utility of CA125 as a prognostic factor and disease surveillance tool in patients with this aggressive type of uterine cancer.

Materials and methods

Patient selection

The Montefiore Medical Center and Albert Einstein College of Medicine (MMC/AECOM) computerized databases were searched to identify all patients with a diagnosis of uterine carcinosarcoma. The charts of 95 consecutive patients evaluated and treated from 1985 to 2005 were identified. Of these, 54 patients underwent preoperative CA125 measurement, and all of these patients were included in this analysis. Demographic, clinical, pathologic, CA125 levels, treatment, and outcome information was obtained from the patient medical records. Operative and pathology reports were used to confirm FIGO stage. Deaths were identified through patient charts, our hospital-based patient information system, and the Social Security Death Index (<http://ssdi.rootsweb.com/>). Chart information was reviewed to ascertain the cause of death.

Statistical analysis

Preoperative CA125 levels less than 30 units/mL were considered normal, while CA125 levels greater than or equal to 30 units/mL were considered elevated. Tests of association between preoperative CA125 levels and previously identified clinical and pathologic prognostic factors were performed using Fisher's exact test and Pearson chi-square test as appropriate. In the evaluation of postoperative CA125 levels, serum measurements taken at least 1 month after staging surgery were included for analysis.

Length of survival was calculated from the date of initial surgery to the date of death; surviving patients were censored at the date of last contact. A Cox proportional hazard model was used for multivariate analysis to investigate which prognostic factors identified using univariate analysis were significantly associated with length of survival. All statistical analyses were performed using STATA version 9 (StataCorp LP, College Station, TX). A *P*-value of <0.05 was considered significant.

Results

Patient characteristics

The distribution of demographic, clinical, and pathologic variables is shown in Table 1. Most of the patients were post-menopausal women, with a mean age at diagnosis of 65 years old. In addition, most patients were multiparous and overweight or obese. Approximately half of the patients died of disease during their follow-up. One-quarter of patients died of other causes, while one-quarter remain alive and free of disease at last contact.

Comparing the study population characteristics to the characteristics of all carcinosarcoma patients treated during this period at our institution, there was no statistically significant difference in the age or race distribution. There was a marginally significant difference in stage ($P=0.05$) between those who did and did not have CA125 assessment. Some patients with omental involvement at presentation had a preoperative diagnosis of ovarian cancer prompting CA125 assessment, and this may have contributed to the higher percentage (35%) of Stage 4 patients in the study population.

Preoperative CA125

The range of preoperative CA125 levels was 5.7 to 3220 units/mL. The median value was 22.9 units/mL, and the mean value was 214 units/mL. The mean CA125 for the lowest quartile was 7.9 units/mL, whereas the mean CA125 for the highest quartile was 802.7 units/mL. An elevated preoperative CA125 was significantly associated with the presence of extrauterine disease ($P<0.001$) and deep myometrial invasion ($P<0.001$), as shown in Table 2. In addition, the histological type of the epithelial component was significantly associated with preoperative CA125 ($P=0.005$), with CA125 elevation occurring in 75% of patients with serous histology versus fewer than 10% of patients with endometrioid or clear cell histology. Lymphovascular involvement, parity, and estrogen receptor status did not correlate with preoperative CA125 levels.

Survival analysis

By univariate survival analysis using Cox proportional hazard modeling, three variables were significantly associated with survival: stage ($P=0.004$), postoperative CA125 ($P<0.001$), and estrogen receptor status ($P=0.029$). The hazard ratio for each variable is shown in Table 3. Age, parity, BMI, histology, preoperative CA125, and adjuvant therapy (radiation, chemotherapy) did not significantly affect survival. Using multivariate analysis, postoperative CA125 elevation was the only variable significantly associated with survival ($P=0.009$). Adjusting for covariates, patients with an elevated postoperative CA125 had a 5.7 times greater

risk of death compared with patients who had normal postoperative CA125 levels, Table 4. The corresponding survival plot is shown in Fig. 1. Postoperative CA125 remained a significant prognostic variable on univariate and multivariate analysis when patients dying of other causes were excluded.

Exploratory analysis was performed to evaluate the potential interaction of the extent of disease (i.e. stage) and postoperative CA125. When stratifying patients by extent of disease, postoperative CA125 remained an independent poor prognostic factor for patients with disease confined to the uterus (stage 1 and 2) and for patients with extrauterine disease (stage 3 and 4). Patients that had disease confined to the uterus with elevated postoperative CA125 levels were at a greater risk for death (HR=18.1, $P=0.013$) compared with patients that had extra uterine disease with elevated postoperative CA125 levels (HR=6.8, $P=0.006$).

Conclusions

This study is the first to demonstrate the prognostic clinical significance of CA125 elevation in patients with uterine carcinosarcoma. We found that preoperative CA125 elevation in these patients correlates with deep myometrial invasion, extrauterine disease, and serous histology of the epithelial component. In addition, postoperative CA125 elevation is a significant independent poor prognostic factor, conferring a 5.7 times increased risk of death compared with patients with normal follow-up CA125 levels.

Assessment of preoperative CA125 may be a useful test during the initial evaluation of a patient with suspected uterine carcinosarcoma. We demonstrated a strong association of CA125 elevation with extrauterine disease. Although the usual management of CS, regardless of CA125 status, includes surgical staging, an elevated CA125 may prompt imaging studies to detect sites of metastatic disease that may not be clinically apparent. Moreover, the preoperative CA125 establishes a baseline value that may be useful when interpreting the patient's subsequent CA125 levels. Among patients presenting with high-grade endometrial biopsy, CS and serous carcinoma are the most common histological diagnoses on final pathology [35]. Therefore, preoperative CA125 assessment should be considered in all patients with suspected CS or who present with a high-grade endometrial biopsy.

In our multivariate analysis, an elevated postoperative CA125 level was a significant independent predictor of decreased survival, conferring a 5.7 times greater risk of death compared with patients with normal CA125 levels. Exploratory analysis suggested that the poor prognostic impact of an elevated postoperative CA125 level was even more pronounced in patients with early stage compared with advanced stage disease. These findings indicate that CA125 may be a useful tool for prognostic purposes and disease assessment in the postoperative and surveillance period. If prospective studies confirm that CA125 levels accurately reflect disease activity, CA125 measurement could be very helpful in evaluating the therapeutic efficacy of new treatments for CS, particularly in patients with non-measurable lesions.

The potential benefit of serial monitoring of CA125 during follow-up of CS is influenced by whether or not early detection of recurrent disease is advantageous. In a GOG study comparing ifosfamide with a combination of ifosfamide/cisplatin for the treatment of patients with advanced or recurrent uterine CS, the overall survival was similarly poor for both treatment groups, with a median survival of 8 and 9 months, respectively [36]. As more effective treatment regimens are identified, the early detection of asymptomatic recurrence will have greater potential clinical benefit.

In summary, we have demonstrated that CA125 has potential clinical application as a serum biomarker in the management of uterine CS. Preoperative CA125 elevation is predictive of

deep myometrial invasion and extrauterine disease. Moreover, postoperative CA125 elevation is a significant independent risk factor for death. Assessment of CA125 should be incorporated into prospective studies of patients with uterine carcinosarcoma in order to further validate these findings.

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Fig. 1. Kaplan-Meier survival plot for uterine carcinosarcoma patients with normal postoperative CA125 levels versus those with elevated postoperative CA125 levels ($P=0.009$).

Table 1

Patient population characteristics

Variables	N	%
<i>Age at diagnosis</i>		
< 50	1/54	1.9
50–59	10/54	18.5
60–69	24/54	44.4
> 70	19/54	35.2
<i>Ethnicity</i>		
Non-Hispanic White	24/54	44.4
Non-Hispanic Black	25/54	46.3
Hispanic	5/54	9.3
<i>Parity</i>		
≤1	9/52	17.3
> 1	43/52	82.7
<i>Menopause</i>		
Premenopausal	1/54	0.0
Postmenopausal	53/54	100.0
<i>BMI</i>		
< 18.5 (underweight)	1/51	2.0
18.5–24.9 (normal)	13/51	25.5
25–29.9 (overweight)	15/51	29.4
> 30 (obese)	22/51	43.1
<i>FIGO stage</i>		
I	15/54	27.8
II	5/54	9.2
III	15/54	27.8
IV	19/54	35.2
<i>Histological type of the epithelial component</i>		
Endometroid	10/53	18.9
Serous	16/53	30.2
Clear cell	2/53	3.8
Not specified	22/53	41.5
Mixed	3/53	5.6
<i>Status</i>		
Dead of disease	25/54	46.3
Dead of other causes	13/54	24.1
Alive with disease	2/54	3.7
No evidence of disease	14/54	25.9

Table 2
Clinicopathological variables and preoperative CA125

	CA125 < 30, N (%)	CA125 ≥ 30, N (%)	P-value
FIGO stage			< 0.001
I or II	19/20 (95%)	1/20 (5%)	
III or IV	13/34 (38%)	21/34 (62%)	
Parity			0.083
≤1	3/9 (33%)	6/9 (67%)	
>1	28/43 (65%)	15/43 (35%)	
Histological type of the epithelial component			0.005
Endometrioid	9/10 (90%)	1/10 (10%)	
Serous	4/16 (25%)	12/16 (75%)	
Clear cell	2/2 (100%)	0/2 (0)	
Not specified	14/22 (64%)	8/22 (36%)	
Mixed	2/3 (67%)	1/3 (33%)	
Myometrial invasion			< 0.001
<50%	20/23 (87%)	3/23 (13%)	
≥50%	12/31 (39%)	19/31 (61%)	
LVI			0.845
No	11/18 (61%)	7/18 (39%)	
Yes	21/36 (58%)	15/36 (42%)	
ER positivity			0.676
Negative	11/19 (58%)	8/19 (42%)	
Positive	11/17 (65%)	6/17 (35%)	

Table 3

Univariate survival analysis

Variable	Hazard ratio	95% confidence interval	P-value
Age at diagnosis	1.006	0.962–1.051	0.806
FIGO stage	1.808	1.212–2.696	0.004
Histological type	1.088	0.807–1.469	0.577
Preoperative CA125	1.946	0.855–4.429	0.112
Postoperative CA125	9.855	3.340–29.078	< 0.001
BMI	0.996	0.949–1.045	0.862
Adjuvant radiation therapy	0.712	0.456–1.113	0.136
Adjuvant chemotherapy	1.204	0.911–1.592	0.192
ER positivity	0.314	0.111–0.890	0.029
Parity	0.591	0.197–1.769	0.347

Table 4

Multivariate survival analysis

Variables	Hazard ratio	95% confidence interval	P-value
FIGO stage	1.496	0.846–2.644	0.166
Postoperative CA125	5.725	1.555–21.070	0.009
ER positivity	0.599	0.131–2.740	0.509