Original Article

The Prognostic Significance of Preoperative Cancer Antigen-125 Levels in Uterine Papillary Serous Carcinomas

Uterin Papiller Seröz Karsinomlarda Preoperatif Kanser Antijen-125 Düzeylerinin Prognostik Önemi

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ABSTRACT

Introduction: This study aimed to determine the relationship between preoperative cancer antigen(CA)-125 levels and clinicopathologic prognostic factors as well as appropriate cut-off levels for pure uterine papillary serous carcinoma.

Materials and Methods: Study data were collected from the documents and electronic medical records of patients who were diagnosed with pure uterine papillary serous carcinoma between 2005 and 2020 in our institution. The association between clinicopathological variables and CA-125 were analyzed. The accuracy of the preoperative serum CA-125 value in predicting metastasis sites was evaluated by the receiving operating characteristic curve analysis and the most appropriate cut-off values available were selected.

Results: Seventy-eight patients met the study criteria. Median value of preoperative serum CA-125 level was higher in patients with omental (P<0.001), ovarian (P<0.001), cervical involvement (P=0.017) and deep myometrial invasion (≥50%) (P= 0.001). According to the receiving operating characteristic curve, the optimal cut-off value of preoperative CA-125 level for predicting omental involvement was 35.5 U/mL (sensitivity: 93.8%, specificity: 79.3%), cervical involvement was 15.0 U/mL (sensivity: 86.8%, specificity: 44.7%) and ovarian involvement was 32.5 U/mL (sensivity: 77.3%, specificity: 72.2%).

Discussion: An elevated level of preoperative serum CA-125 is a marker for omental, ovarian, cervical involvement and deep myometrial invasion. The value for cervical involvement may be a guide that radical hysterectomy should be considered in the foreground in patients undergoing surgery. There is a need for future studies to evaluate the role of CA-125 in predicting recurrence and survival in uterine papillary serous carcinoma.

Keywords: Biomarkers, cervix uteri, endometrial cancer, hysterectomy

ÖZET

Giriş: Bu çalışmada, pür uterin papiller seröz karsinomda preoperatif kanser antijeni(CA)-125 düzeylerinin çeşitli klinikopatolojik değişkenlerle ilişkisinin ve metastaz bölgesini öngörmede optimal cut-off değerlerinin belirlenmesi amaçlanmıştır

Gereç ve Yöntemler: Çalışma verileri, kurumumuzda 2005-2020 yılları arasında pür uterin papiller seröz karsinom tanısı alan hastaların belgelerinden ve elektronik tıbbi kayıtlarından toplandı. Klinikopatolojik değişkenler ile CA-125 arasındaki ilişki analiz edildi. Preoperatif serum CA-125 değerinin metastaz bölgelerini tahmin etmedeki doğruluğu, ROC(receiving operating characteristic) eğrisi analizi ile değerlendirildi ve mevcut en uygun cut-off değerleri seçildi.

Bulgular: Yetmiş sekiz hasta çalışma kriterlerini karşıladı. Ameliyat öncesi serum CA-125 düzeyi ortanca değeri omental (P<0,001), over (P<0,001), servikal tutulum (P=0,017) ve derin miyometriyal invazyon (≥%50) (P = 0,001) olan hastalarda daha yüksekti. ROC eğrisine göre, omental tutulumu öngörmek için preoperatif CA-125 seviyesinin optimal cut-off değeri 35.5 U/mL (duyarlılık: %93,8,

First Received: 11.02.2022, Accepted: 04.04.2022 doi: 10.5505/aot.2022.98624

özgüllük: %79,3), servikal tutulum için 15.0 U/mL (duyarlılık: %86,8, özgüllük: %44,7) ve over tutulumu için 32,5 U/mL (duyarlılık: %77,3, özgüllük: %72,2) idi.
Tartışma: Preoperatif serum CA-125'in yüksek seviyesi omental, over, servikal tutulum ve derin myometrial invazyon için bir belirteçtir. Servikal tutulum için cut-off değeri, cerrahi uygulanacak hastalarda radikal histerektominin ön planda düşünülmesi gerektiğine dair bir rehber olabilir. Uterus papiller seröz karsinomunda CA-125'in nüks ve sağkalımı öngörmedeki rolünü değerlendirecek ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Biomarker, endometrial kanser, histerektomi, serviks uteri

Introduction

Endometrial cancer is the most common gynecologic malignancy in women[1]. The prognosis of endometrioid type tumors is excellent, but there are high grade tumors such as uterine papillary serous carcinoma (UPSC) [2,3]. UPSC has a poorer prognosis even if diagnosed at an early stage[2]. Although UPSC accounts for 10% of endometrial cancer cases, it is responsible for about half of deaths and recurrences[2–4]. UPSC has a higher propensity for deep myometrial invasion, cervical involvement and metastasis to omentum, ovaries and lymph nodes[3–5]. At the time of diagnosis approximately 55% to 85% of women with UPSC will have extrauterine spread [2,3,6].

Sensitivity of preoperative radiological imaging for detecting extrauterine spread is limited[7,8]. Due to the high frequency of extrauterine spread, patients with UPSC require a more extensive surgical procedure [3,9]. This surgical procedure should include hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection and omentectomy. However, this surgical procedure is associated with higher complication rates[10]. For these reasons, a preoperative test or tumor marker that can predict extrauterine spread in the early period can contribute to determining the clinical approach and treatment plan.

Today, the use of preoperative measurement of cancer antigen (CA) 125 level for the diagnosis of endometrial cancer and post-treatment follow-up is increasing. Many studies have demonstrated the role of CA-125 level in endometrial cancer and its relationship with deep myometrial invasion, extrauterine spread, positive peritoneal cytology, lymph node metastasis, recurrence, advanced stages, and reduced survival [11–14]. The studies have included different histological types of tumors and suitable cut-off levels of CA-125 as a predictor and also have shown its relationship with various prognostic factors[15–17].

This study aimed to determine the relationship between preoperative CA-125 levels and clinicopathologic prognostic factors as well as appropriate cut-off levels for pure UPSC.

Material and Methods

Study data were collected from the documents and electronic medical records of patients who underwent surgery for endometrial cancer between 2005 and 2020 at a tertiary cancer center. The study was approved by the institutional ethics committee. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients were operated by gynecologic oncologists and all surgical specimens were evaluated by gynecological pathologists.

The inclusion criteria were histopathological confirmation of pure UPSC and patients who had CA-125 levels measured (chemiluminescence microparticle immunoassay 91 technique-Architect i2000 SR Immunoassay

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Analyzers/ Abbott Laboratory, 92 Diagnostics Division, Abbott Park, IL, USA) at most 10 days prior to operation.

The exclusion criteria were patients who received primary radiotherapy and neo-adjuvant chemotherapy, had mixed histology, had synchronous cancers of the ovary, fallopian tube, or peritoneum, who did not have preoperative CA-125 levels, and in-complete medical records and follow-ups. Thus, the study included a total of 78 patients who met the inclusion criteria.

Treatment

In the preoperative period, UPSC was diagnosed by pipelle biopsy or fractional dilation and curettage. All patients were evaluated by computed tomography or magnetic resonance imaging. Comprehensive surgery was attempted to perform in all patients according to National Comprehensive Cancer Network (NCCN) guidelines. A vertical midline incision was preferred in all patients for ease of access during abdominal exploration and organ resection. After entering the peritoneal cavity, a peritoneal wash was obtained for cytology. Exploration of the abdominal cavity included a systematic examination of the peritoneal surfaces, omentum, colon and small intestine, and para-colic, pelvic, mesenteric and para-aortic sites, as well as palpation to locate suspicious lesions. Optimal surgery (cytoreduction) included hysterectomy, bilateral salpingo-oophorectomy(BSO), pelvic and para-aortic lymph node dissection, omentectomy and excision of lesions suspected to be a metastasis, if any. Suboptimal surgery included at least hysterectomy, BSO and/or pelvic lymph node sampling and/or omentum biopsy. Lymphadenectomy was defined as simultaneous pelvic and para-aortic lymph node dissection. Pelvic lymphadenectomy was defined as the removal of lymphatic tissue in the external, internal, and common iliac and obturator regions. Para-aortic lymph-adenectomy was defined as removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the level of the aortic bifurcation and up to the left renal vessels. Radical hysterectomy was performed on patients suspected of having cervical involvement on preoperative imaging. Stage was defined as according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria for uterine cancer[18]. Patients who were diagnosed before 2009 revised according to the 2009 FIGO criteria. Adjuvant therapy decisions were made by multidisciplinary tumor boards according to NCCN guidelines.

Follow-up

The follow-up intervals of the patients were every 3 months for the first 2 years, every 6 months up to 5 years and annually after 5 years. Follow-up visits consisted of clinical examination, ultrasonography of pelvis and abdomen, CA-125 testing in the case of high preoperative levels. Computed tomography or magnetic resonance imaging was used for the suspected presence of metastases. A biopsy procedure was performed in the case of accessible suspicious metastases. Recurrence was confirmed by gynecological pathologists or experienced radiologists in the multi-disciplinary tumor board.

Statistical Analysis

Clinicopathological and demographic data including age, parity, FIGO stage, type of surgery, recurrence, presence of extrauterine disease, the involvement of ovary, lymph node, cervix and omentum, lymphovascular space invasion (LVSI), deep myometrial invasion were collected. Their association with preoperative CA-125 levels was evaluated. The level of preoperative CA-125 was considered elevated if they were equal to or greater than 35 U/mL. A statistically significant logistic regression model (enter) was created using age, tumor size, preoperative serum CA-125 value, myomet-

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Table 1. Characteristics of the study group

Variables	Mean±SD	Median (min-max)
Age (years) (n=78)	64.9±8.4	65.0 (45.0-82.0)
Parity (n=78)	2.9±1.2	3.0 (0.0-7.0)
		n (%)
FIGO stage (n=78)		
1A		11 (14.1)
1B		8 (10.3)
2		11 (14.1)
3A		9 (11.5)
3B		2 (2.5)
3C1		6 (7.7)
3C2		13 (16.7)
4		18 (23.1)
Extrauterine involvement (n=78)		
No		30 (38.5)
Yes		48 (61.5)
Cytoreduction *(n=78)*		
Optimal		59 (75.6)
Suboptimal		19 (24.4)
Lymph node involvement (n=60)		
Negative		33 (55.0)
Positive		27 (45.0)
Depth of myometrial invasion (n=78)		
<50%		25 (32.1)
≥50%		53 (67.9)
Cervical involvement (n=78)		
Negative		38 (48.7)
Positive		40 (51.3)
Omental involvement (n=76)		
Negative		59 (77.6)
Positive		17 (22.4)
LVSI (n=78)		
Negative		25 (32.1)
Positive		53 (67.9)
Preoperative serum CA-125 (U/mL) (n=76)		
<35		46 (60.5)
≥35		30 (39.5)
Recurrence (n=77)		
No		56 (72.7)
Yes		21 (27.3)

CA-125: Cancer antigen-125, FIGO: International federation of gynecologists and obstetrics, LVSI: Lymphovascular space invasion, SD: Standard deviation.

rial invasion, lymphovascular space invasion status as independent variables and extrauterine involvement as dependent variable. The association of extrauterine disease with preoperative CA-125 level, age, tumor diameter, myometrial invasion, and LVSI were investigated and an appropriate cut-off value was determined.

Study data were analyzed using the SPSS (statistical software package) version 20.0 (IBM Corp., Armonk, NY, USA). Number, percentage, mean, standard deviation, median, minimum and maximum values were used to present the data. The t-test was used as a parametric test, while the Mann-Whitney U test was used as nonparametric test according

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to results of conformity to normal distribution test. The chi-square test was used in the analysis of categorical data. The Hosmer-Lemeshow statistical fit test was used to examine the suitability of the logistic regression analysis (Enter method). The accuracy of the preoperative serum CA-125 value in predicting metastasis sites was evaluated by the receiving operating characteristic (ROC) curve analysis and the most appropriate cuttoff values available were selected. A p-value <0.05 was considered statistically significant.

Results

The study population consisted of 78 women. The characteristics of the study group are shown in Table 1. In order to achieve optimal cytoreduction, rectosigmoid colon resection was performed on six patients, total colectomy on one patient, segmenter transverse colon resection on one patient, and peritonectomy on five patients (not shown in the table).

Preoperative serum CA-125 values were compared with univariate analyses according to clinicopathological features. There was a statistically significant difference between preoperative serum CA-125 values and omental involvement (P <0.001), ovarian involvement (P <0.001), cervical involvement (P = 0.017), myometrial invasion (P = 0.001). The median value of preoperative serum CA-125 level was higher in patients with omental, ovarian, cervical involvement and myometrial invasion depth equal to or greater than 50%. When preoperative serum CA-125 values were compared according to lymph node involvement, LVSI and recurrence, no statistically significant difference was found(P>0.05) (Table 2).

Percentage of patients with levels of preoperative CA- 125 greater than and less than 35 U/mL, according to clinicopathologic characteristics, are shown in Table 3.

Preoperative CA-125 value (P=0.001) and LVSI (P=0.029) were significantly associated with the presence of extrauterine involvement in univariate analysis. Extrauterine involvement was present in 86.7% of those with preoperative serum CA-125 value of 35 U/mL and above and in 69.8% of those with positive LVSI (Table 4). However in multivariate analysis only serum CA-125 value of 35 U/mL and above was associated with the presence of extrauterine involvement. Logistic regression model revealed that a preoperative serum CA-125 value of 35 U/mL and above increased extrauterine involvement risk 8.255 (95% confidence interval, 2.271-29.999) times(not shown in the table).

ROC curves were determined for the predictive value of preoperative serum CA-125 values for cervical, omental and ovarian involvement (Figure 1). Preoperative serum CA125 value was found to be the best cut-off point of 15.0 U/mL in estimating cervical involvement, 35.5 U/mL in estimating omental involvement, and 32.5 U/mL in estimating ovarian involvement (Table 5).

Discussion

Our study is the one of the largest studies in the literature evaluating preoperative CA-125 levels in patients with pure UPSC. CA-125 elevation is not a common condition in endometrioid type of endometrial cancer, but it is used in diagnosis and follow-up in epithelial serous ovarian cancer cases[19]. Although UPSC is a type of endometrial cancer, it is more similar to serous cancer of the ovary because of its spread into the peritoneal cavity and histological patterns[15]. For this reason, CA-125 elevation is more common in UPSC compared to endometrioid type of endometrial cancer. In our study preoperative CA-125 levels were significantly associated with omental, ovarian, cervical involvement and deep myometrial invasion but not with the recurrence, LVSI, lymph node involvement.

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Table 2. Preoperative CA-125 values of women with UPSC

Variables	Preoperative serum CA125 (U/mL)		*P* value
	Mean±SD	Median (min-max)	
Omental involvement			
Negative	59.4±226.9	19.5 (3.0-1743.0)	**<.001***
Positive	253.5±227.5	205.0 (34.0-862.0)	
Ovarian involvement			
Negative	33.3±33.9	19.5 (3.0-141.0)	**<.001***
Positive	381.7±648.7	79.5 (4.0-2687.0)	
Lymph node involvement			
Negative	53.0±91.5	25.0 (4.0-454.0)	.136
Positive	188.9±514.4	34.0 (3.0-2687.0)	
Cervical involvement			
Negative	179.0±521.9	16.5 (3.0-2687.0)	**.017***
Positive	89.3±123.5	32.5 (7.0-454.0)	
LVSI			
Negative	131.6±375.5	25.0 (3.0-1743.0)	.309
Positive	135.4±385.0	26.0 (4.0-2687.0)	
Depth of myometrial invasion			
<50%	103.3±354.3	14.0 (3.0-1743.0)	**.001***
≥50%	148.4±393.0	34.0 (4.0-2687.0)	
Recurrence			
No	156.6±440.1	26.0 (3.0-2687.0)	.801
Yes	73.2±110.8	24.5 (4.0-400.0)	

P -values were calculated with Mann-Whitney U test. CA-125: Cancer antigen-125,
LVSI: Lymphovascular space invasion, SD: Standard deviation, UPSC: Uterine papillary serous carcinoma.
* *P* -value < .05.

Table 3. Preoperative CA-125 level according to clinicopathological features

Variables	Preoperative serum CA125 (U/mL)		*P* value
	<35	≥35	
	n (%)	n (%)	
FIGO stage			
1	18 (94.7)	1 (5.3)	**<.001***
2	7 (70.0)	3 (30.0)	
3	20 (66.7)	10 (33.3)	
4	1 (5.9)	16 (94.1)	
Extrauterine involvement			
Negative	25 (86.2)	4 (13.8)	**.001***
Positive	21 (44.7)	26 (55.3)	
Depth of myometrial invasion			
<50%	19 (79.2)	5 (20.8)	**.045***
≥50%	27 (51.9)	25 (48.1)	
Cervical involvement			
Negative	26 (68.4)	12 (31.6)	.241
Positive	20 (52.6)	18 (47.4)	
Omental involvement			
Negative	44 (75.9)	14 (24.1)	**<.001***
Positive	1 (6.2)	15 (93.8)	
Ovarian involvement			
Negative	39 (72.2)	15 (27.8)	**.003***
Positive	7 (31.8)	15 (68.2)	
Lymph node involvement			
Negative	21 (67.7)	10 (32.3)	.335
Positive	14 (51.9)	13 (48.1)	
LVSI			
Negative	17 (68.0)	8 (32.0)	.494
Positive	29 (56.9)	22 (43.1)	
Recurrence			
No	34 (61.8)	21 (38.2)	.886
Yes	12 (60.0)	8 (40.0)	

P -values were calculated with Chi-square test. CA-125: Cancer antigen-125,
FIGO: International federation of gynecologists and obstetrics, LVSI: Lymphovascular space invasion.
* *P* -value < .05.

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Table 4. Factors affecting extrauterine involvement, univariate analysis

Variables	Extrauterine involvement				*P* value
	Negative		Positive		
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (years)	65.0±9.5	64.5 (45.0-82.0)	64.9±7.7	65.5 (45.0-82.0)	.958[a]
	n (%)		n (%)		
Tumor size (cm)					
≤2	7 (50.0)		7 (50.0)		.499
>2	23 (35.9)		41 (64.1)		
Preoperative serum CA-125 (U/mL)					
<35	25 (54.3)		21 (45.7)		**.001***
≥35	4 (13.3)		26 (86.7)		
Depth of myometrial invasion					
<50%	12 (48.0)		13 (52.0)		.347
≥50%	18 (34.0)		35 (66.0)		
LVSI					
Negative	14 (56.0)		11 (44.0)		**.029***
Positive	16 (30.2)		37 (69.8)		

P -values were calculated with Chi-square test. CA-125: Cancer antigen-125,
LVSI: Lymphovascular space invasion, SD: Standard deviation. * *P* -value < .05.
a: *P* value was calculated with t test.

Table 5. AUC values, sensitivity, and specificity of CA-125 for metastasis site

Preoperative serum CA-125 (U/mL), Cutoff Value	***Metastasis site***	***AUC***	***Sensitivity (%)***	***Specificity (%)***
15.0	Serviks	.659	86.8	44.7
35.5	Omentum	.919	93.8	79.3
32.5	Over	.803	77.3	72.2

AUC: area under the curve, CA-125: Cancer antigen-125.
Statistical significance level was found to be <.05 in receiving operating characteristic curve analysis.

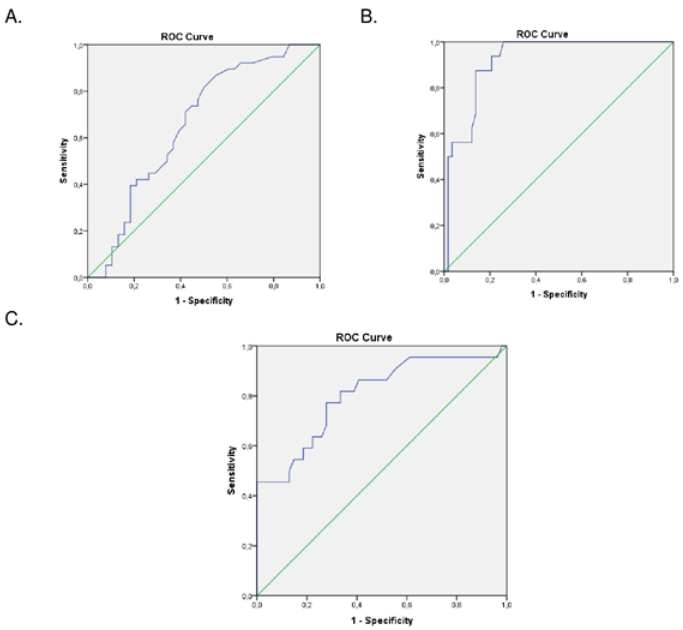


Figure 1. Receiving operating characteristic (ROC) curves for metastasis site in relation with preoperative CA-125 levels in uterin papillary serous carcinoma; A,cervical involvement, area under the curve(AUC)=0.659; B, Omental involvement, AUC=0.919; C, Ovarian involvement, AUC=0.803.

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These results were consistent with the prior studies[15,16,19,20].

Schmidt et al. found that CA-125 level, LVSI, and depth of myometrial invasion were associated with extrauterine involvement in univariate analyses, while the depth of myometrial invasion was insignificant in multivariate analyses[15]. In line with our study, Roelofsen et al. found that CA-125 level and LVSI were associated with extrauterine involvement in univariate analyses, but only CA-125 level remained significant in multivariate analyses[21].

Many previous studies have shown various sensitivity and specificity levels of preoperative serum CA-125 values for extra-uterine metastasis [15,16,19,21]. Never-theless, there was no consensus on the reference cut-off value of preoperative CA-125 level in UPSC. Schmidt et al. found a cut-off value of 57.5U/mL with 68.8% sensitivity and 95.6% specificity for omental involvement, 41.8U/mL with 72.2% sensitivity and 85.7% specificity for ovarian involvement. In our study, we determined cut-off values with higher sensitivity for omental and ovarian involvement. An additional issue not reported in previous studies was what the best cut-off level of CA-125 for predicting cervical involvement. A level of 15.0 U/mL was the best cut-off value for predicting cervical involvement. Although according to the results of ESMO-ESGO-ESTRO 2016 Endometrial cancer consensus conference, radical hysterectomy is not recommended for stage II endometrial cancer, modified (type B) or type A radical hysterectomy should be considered only if required for obtaining free margins[22]. This value may be a guide that radical hysterectomy should be considered in the foreground in patients undergoing surgery.

The fact that CA-125 elevation is associated with ovarian and omental involvement but not with LVSI and lymph node involvement may be an evidence that metastatic cells spread to serous surfaces, just as in serous cancer of the ovary. Moreover only the CA-125 level was significant in the multivariate analyses of the factors affecting extrauterine involvement supports our hypothesis.

The major limitation of our study is its single-center retrospective design. Although the statistical analyses were carried out in a small patient population, our study included one of the largest number of patients in the literature. The strength of the study is that it included pure UPSC patients, all surgeries were performed by the gynecologic oncologists, and the histological diagnosis was confirmed by the gynecological pathologists.

In conclusion, this study contributes to the growing evidence on the use of preoperative serum CA-125 in patients with UPSC. Our data clearly show that an elevated level of preoperative CA-125 is a marker for omental, ovarian, cervical involvement and deep myometrial invasion. Although the relationship between CA-125 elevation and extrauterine involvement has been demonstrated, there is a need for future studies to evaluate the role of CA-125 in predicting recurrence and survival in UPSC.

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Doi: 10.5505/aot.2022.98624

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