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ORIGINAL ARTICLE

The relationship between serum CA-125 level and recurrence in surgical stage I endometrial cancer patients

Hua-Hsi Wu[a,b,c], Hung-Tse Chou[a,b,c], Jen-Yu Tseng[a,b,c], I-San Chan[a,b], Yi-Jen Chen[a,b,c,*]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Department of Obstetrics and Gynecology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC

Abstract

Background: The majority of patients diagnosed with early stage endometrial cancer have a favorable prognosis; however, approximately 10% to 15% experience a recurrence. Therefore, the aim of the present study was to evaluate whether postoperative carbohydrate antigen 125 (CA-125) levels could be used to predict recurrence and recurrence-free survival (RFS) in patients with surgical stage I endometrial cancer.

Methods: We enrolled a total of 518 patients with stage I endometrial cancer who underwent surgical treatment between January 2010 and March 2019. Serum CA-125 levels were measured prior to surgery, as well as 6 to 12 months after surgery. Subsequently, the correlations between the CA-125 levels, cancer recurrence, and RFS were analyzed.

Results: Although the preoperative CA-125 level was not associated with the risk of cancer recurrence, the postoperative CA-125 level was found to be the only independent predictor of recurrence in both univariate and multivariate analyses. Additionally, we found that a postoperative CA-125 cutoff value of 13.75 U/mL yielded the best sensitivity and specificity for predicting cancer recurrence. Patients with a postoperative CA-125 level ≥13.75 U/mL, and those with a level <13.75 U/mL, had a median time to recurrence and a 5-year RFS rate of 35.5 vs 50.5 months and 84.7 vs 94.4%, respectively. Additionally, postoperative CA-125 levels were not found to be correlated with preoperative levels.

Conclusion: In patients with stage I endometrial cancer, a postoperative CA-125 level ≥13.75 U/mL was found to be significantly correlated with a higher recurrence rate, as well as a shorter RFS. Therefore, obtaining a follow-up CA-125 level within 6 to 12 months after staging surgery may be a promising noninvasive biomarker for predicting recurrence.

Keywords: Endometrial cancer; Recurrence; Serum CA-125

1. INTRODUCTION

The global prevalence of endometrial cancer, which has become one of the leading gynecological malignancies, has steadily increased over the last 2 decades, with the age-standardized incidence rate increasing significantly, by 0.69% per year. This trend has been observed in most countries and territories worldwide, regardless of sociodemographic status,[1] with >75% of endometrial cancers diagnosed at an early stage. The primary treatment for endometrial cancer is a combined staging surgery, which is comprised of a total hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy. Adjuvant treatment decisions are based on several clinical and pathologic prognostic parameters, such as tumor grade, histologic type, age, depth of myometrial invasion, and lymphovascular space involvement (LVSI).[2–4] Although the majority of women diagnosed with early stage endometrial cancer have a favorable prognosis, approximately 10% to 15% will experience a recurrence.[5] In patients who experience a cancer recurrence, particularly as distant metastasis or peritoneal carcinomatosis, the outcome is typically abysmal, with a median survival of under a year.[6]

Carbohydrate antigen 125 (CA-125) is a tandem repeating epitope of mucin-16 (MUC16), which is overexpressed in multiple malignancies and is associated with tumorigenesis, cell proliferation, and metastasis.[7–9] Abnormal serum CA-125 levels are found in a variety of malignancies[10]; therefore, CA-125 is widely used as a biomarker for numerous clinical manifestations, such as the following: (1) as a diagnostic factor to distinguish between benign and malignant tumors; (2) to predict disease severity before treatment; (3) as a prognostic factor of disease outcome; and (4) for monitoring patient response to treatment.

Unlike ovarian cancer, the potential applications of serum CA-125 in endometrial cancer have not been well studied. Most of the available studies included all stages of endometrial cancer, with inconclusive results. Preoperative serum CA-125 levels in patients with endometrial cancer are associated with disease severity, with

*Address correspondence. Dr Yi-Jen Chen, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, and Institute of Clinical Medicine, National Yang Ming Chiao Tung University, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: chenyj@vghtpe.gov.tw; chenyj@nycu.edu.tw (Y.-J. Chen).

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higher CA-125 levels frequently found in patients with advanced stage cancer, higher grading, cervical involvement, lymph node metastasis, or extrauterine spreading.[11,12] Based on the results of a 2-year prospective nonrandomized study, a preoperative CA-125 level >20 U/mL and/or a grade 3 tumor correctly identified 75% to 87% of patients requiring lymphadenectomy.[13] Preoperative CA-125 levels, therefore, have been suggested as an adjunct, to be incorporated into preoperative risk stratification models for treatment planning in women diagnosed with endometrial cancer.[14,15]

The roles of CA-125 levels in predicting cancer recurrence have not yet been elucidated; therefore, the present study explored the roles of serum CA-125 levels on predicting recurrence in patients with stage I endometrial cancer, focusing particularly on postoperative and other clinicopathological factors.

2. METHODS

2.1. Patients

A total of 733 patients with endometrial cancer limited to the uterus underwent staging surgery at our hospital between January 2010 and March 2019, for whom we reviewed the electronic medical records for clinicopathological data. Patients were staged using the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, and disease recurrence was confirmed based on radiological and/or histological findings. Histological grading of the surgical specimens was based on the 2004 World Health Organization pathological classification, which is dependent on the percentage of solid components and nuclear atypia of a given specimen. The preoperative CA-125 level was defined as that obtained closest to the operation, while the postoperative level was defined as that obtained within 6 to 12 months after the surgery. Serum CA-125 levels were determined via enzyme immunoassay, using commercially available kits according to the manufacturer's standard instructions. Body mass index (BMI) was obtained by dividing each patient's weight in kilograms by the square of their height in meters. The Charlson Comorbidity Index (CCI) was calculated for each patient, along with the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) diagnosis codes from our hospital's abstract data and the associated weights for each category.

Adjuvant treatment strategies for endometrial cancer include external beam pelvic irradiation, vaginal vault brachytherapy, chemotherapy, and chemoradiotherapy. Indications for postoperative treatment were based on certain clinical and pathological risk factors, based on the recommendations of the Society of Gynecologic Oncology (SGO) or European Society of Gynaecological Oncology (ESGO)/European SocieTy for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP) guidelines.[16,17]

All patients received periodic follow-up at our institution, as the postoperative monitoring of endometrial cancer includes physical examinations and systemic reviews performed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Additionally, serum CA-125 levels and vaginal cytology were checked every 6 months for 3 years, and annually thereafter. In cases of suspected recurrence, patients underwent imaging via computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET).

2.2. Inclusion criteria

The inclusion criteria for the present study were as follows: (1) patients with pathologically diagnosed stage I endometrial cancer with the presence of endometrioid, serous, clear cell, and/or other cell types, such as squamous, mucinous, and undifferentiated/dedifferentiated cells and 2) patients underwent complete staging surgery, including total hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy at our hospital. Patients with uterine carcinosarcoma were excluded from the present study, due to its poor prognosis and earlier recurrence rate compared with other cell types,[18] as were those with synchronous endometrial and ovarian carcinomas, or other primary malignancies. Based on the inclusion criteria, 215 patients were excluded from the present study due to incomplete staging (n = 133), recurrence or loss of follow-up within 6 months (n = 33), carcinosarcoma histology (n = 27), or a second or synchronous primary malignancy developing within 5 years (n = 22). After applying the exclusion criteria, a total of 518 patients were included in the present study.

The protocol for the present study was approved by our hospital's institutional review board (no. 2022-07-007C).

2.3. Statistical analysis

The prognostic variables analyzed in the present study were as follows: patient age, BMI, CCI, myometrial invasion depth, cell type, histological grading, tumor size, LVSI, preoperative hysteroscopy, peritoneal cytology, adjuvant treatments, surgical method, lymphadenectomy field, and preoperative and postoperative CA-125 levels. Baseline characteristics were compared using the *t*, chi-square, or Fisher exact test, as appropriate, while univariate and multivariate Cox proportional hazards analyses were used to assess the prognostic significance of various characteristics. Variables with a $p < 0.2$ on the chi-square or univariate Cox proportional hazard analysis were selected for further multivariate Cox regression analysis.

Recurrence-free survival (RFS) was defined as the length of time between the primary surgery and the disease recurrence or the final oncological visit. Kaplan-Meier analysis was used to determine RFS, and patient survival was compared among subgroups using the log-rank test.

All statistical analyses were performed using SPSS statistical software v26.0 (IBM, Chicago, IL, USA), with a two-tailed $p < 0.05$ was considered to be statistically significant.

3. RESULTS

3.1. Patient characteristics

A total of 518 patients who met the inclusion criteria were included in the present study, with a mean patient age of 57 years (22–87 years) and a mean BMI of 25.5 kg/m^2 (14.4–47.5 kg/m^2). The median preoperative CA-125 level was 18.5 U/mL (5–4239 U/mL), while the median postoperative CA-125 level was 9.3 U/mL (2–143 U/mL). Based on the 2009 FIGO stage classification, 423 (81.7%) patients were diagnosed with stage IA disease, while 95 (18.3%) were diagnosed with stage IB disease. No adjuvant treatment was necessary in 301 (60%) patients, and of the remaining 217 patients, 147 (28.4%) received radiotherapy, 25 (4.8%) received chemotherapy, and 45 (6.8%) received combined chemoradiotherapy. The median follow-up duration was 49 months (7–136 months), during which time 41 (7.9%) patients experienced recurrence. The detailed numbers and frequencies (percentages) of patients with each clinicopathological characteristic are shown in Table 1.

3.2. Relationship between clinicopathological factors and recurrence

In the present study, we explored whether the following factors were associated with tumor recurrence: age (<65 vs ≥65 years), BMI (<27 vs ≥27), CCI (<5 vs ≥5), endometrioid cell grade (1+2 vs 3), cell type (endometrioid vs nonendometrioid), myometrial invasion (<50 vs ≥50%), tumor size (<2 vs ≥2 cm), LVSI (no vs yes), peritoneal cytology (negative vs positive), preoperative hysteroscopy (no vs yes), surgical method (laparotomy vs laparoscopy), lymphadenectomy field (pelvis only vs pelvis + para-aortic), adjuvant treatment (none vs radiotherapy vs chemotherapy vs

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Table 1

Patient characteristics

Characteristics	Patient number (n)	Percentage (%)
Age group		
20-40	40	7.7
41-50	100	19.3
51-60	208	40.4
60-70	129	24.9
>70	41	7.9
Body mass index		
<27	319	61.6
≥27	199	38.4
Charlson Comorbidity Index		
<5	435	84.0
≥5	83	16.0
Histologic group		
Endometrioid	465	89.8
Serous	9	1.7
Clear cell	4	0.8
Others	40	7.7
Endometrioid cell grading		
1	81	15.6
2	358	69.1
3	68	13.1
Myometrial invasion, %		
<50	423	81.7
≥50	95	18.3
Lymphovascular invasion		
Negative	453	87.5
Positive	65	12.5
Peritoneal cytology		
Negative	479	96.0
Positive	17	3.4
Tumor size, cm		
<2	231	44.6
≥2	287	55.4
Preoperative hysteroscopy		
No	405	78.2
Yes	11	21.8
Surgical approach method		
Laparotomy	359	69.3
Microinvasive	159	30.7
Lymphadenectomy field		
Pelvic	243	46.9
Pelvic + para-aortic	275	53.1
Adjuvant therapy		
No adjuvant therapy	311	60.0
IVRT only	113	21.8
EBRT only	29	5.6
IVRT + EBRT	5	1.0
Chemotherapy only	25	4.8
Chemoradiotherapy	45	6.8
Preoperative CA-125, U/mL		
<35	393	75.9
≥35	107	20.7
Postoperative CA-125, U/mL		
<35	481	92.9
≥35	10	1.9
<13.75	393	75.8
≥13.75	98	18.9
Recurrence		
No	477	92.1
Yes	41	7.9

CA-125 = carbohydrate antigen 125; EBRT = external beam radiotherapy; IVRT = intravaginal radiotherapy.

chemoradiotherapy), preoperative CA-125 level (<35 vs ≥35 U/mL), and postoperative CA-125 levels at different cutoff values (<35 vs ≥35 U/mL and <13.75 vs ≥13.75 U/mL). None of the aforementioned factors was significantly associated with recurrence of stage I endometrial cancer based on the chi-square analysis, except for postoperative CA-125 levels (Table 2).

Table 2

The relationship between clinicopathological factors and recurrence

Clinicopathological factors	Recurrence (n = 41)	No recurrence (n = 477)	*p*[a]
Age			
<65	30	389	0.190
≥65	11	88	
BMI			
BMI < 27	29	290	0.209
BMI ≥ 27	12	187	
Charlson Comorbidity Index			
Score < 5	30	405	
Score ≥ 5	11	72	0.050
Endometrioid cell grade			
Low (1 + 2)	32	411	
High (3)	9	59	0.090
Cell type			
Endometrioid	38	427	0.520
Nonendometrioid	3	50	
Myometrial invasion, %			
<50	30	393	0.143
≥50	11	84	
Tumor size, cm			
<2	18	213	0.920
≥2	23	264	
Lymphovascular space involvement			
No	34	419	0.360
Yes	7	58	
Peritoneal cytology			
Negative	36	442	0.127
Positive	3	17	
Preoperative hysteroscopy			
No	33	372	0.710
Yes	8	105	
Surgical method			
Laparotomic	32	372	0.206
Laparoscopic	9	150	
Lymphadenectomy field			
Pelvis only	21	222	0.339
Pelvis + para-aortic	20	255	
Adjuvant treatments			
No	20	291	0.543
Radiotherapy only	14	128	
Chemotherapy only	2	23	
Chemoradiotherapy	4	31	
Preoperative CA-125, U/mL			
<35	30	369	0.560
≥35	10	97	
Postoperative CA-125, U/mL			
<35	33	449	0.002b
≥35	5	4	
<13.75	22	371	0.002b
≥13.75	15	83	

BMI = body mass index; CA-125 = carbohydrate antigen 125.

[a]*p* value was calculated by chi-square method.

[b]$p < 0.05$ means statistically significant.

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3.3. Univariate and multivariate analysis of clinicopathological factors as predictors of recurrence in stage I endometrial cancer

Based on prior results, the following factors were evaluated via Cox hazard regression analysis to determine which factors are predictors of tumor recurrence: age, endometrioid cell grade, CCI, myometrial invasion depth, peritoneal cytology, preoperative CA-125 level, and postoperative CA-125 level. As shown in Table 3, the postoperative CA-125 level was the only statistically significant predictor of recurrence in stage I endometrial cancer, based on the univariate Cox regression analysis. Furthermore, we analyzed factors with a $p < 0.2$ via multivariate Cox regression analysis, including endometrial cell grade, CCI, myometrial invasion depth, peritoneal cytology, and postoperative CA-125 levels, and found that postoperative CA-125 levels were independently associated with cancer recurrence.

3.4. Relationship of postoperative CA-125 to RFS

In the present study, the median RFS of patients with postoperative CA-125 levels <35 and ≥35 U/mL was 48.0 months (1–136 months) and 13.0 months (8–66 months), respectively. Based on the log-rank test, a higher postoperative CA-125 level (cutoff value, 35 U/mL) was significantly associated with worse RFS (Fig. 1A); however, using 35 U/mL as the cutoff value, the sensitivity and specificity were 13.2% and 99.1%, respectively. We therefore used the receiver operating characteristic (ROC) curve to determine the optimal postoperative CA-125 cutoff value for predicting the recurrence of stage I endometrial cancer. Using the Youden index, if the cutoff value was set at 13.75 U/mL, the sensitivity and specificity were 50.5% and 81.7%, respectively. The number of patients with postoperative CA-125 levels >13.75 U/mL were as follows: 14 of 35 (40%) in the recurrent subgroup vs 83 of 454 (18.2%) in the nonrecurrent subgroup. The recurrent hazard ratio for stage I endometrial cancer patients with a CA-125 level ≥13.75 U/mL to those <13.75 U/mL was 3.04 (95% CI, 1.51-6.12; $p = 0.002$), based on the univariate Cox regression. Based on the multivariate Cox regression analysis results, a recurrence hazard ratio of 2.339 showed statistical significance (95% CI, 1.09-5.00; $p = 0.038$).

A Kaplan-Meier survival curve was constructed to demonstrate the time to recurrence. By adopting a cutoff value of 13.75 U/mL, the time to recurrence in patients with stage I endometrial cancer patients with a postoperative CA-125 level ≥13.75 U/mL was significantly shorter than those with CA-125 levels <13.75 U/mL (median [range], 35.5 months [4–109 months] vs 50.5 months [4–136 months]), with a $p = 0.001$, according to the log-rank test (Fig. 1B). By using 13.75 U/mL as the cutoff value, the 5-year RFS in patients with elevated CA-125 levels was 84.7%, compared with that in patients with lower CA-125 levels, which was 95.4%.

Furthermore, we used the Pearson method to evaluate the correlation between the preoperative and postoperative CA-125 levels. The results of this analysis indicated that these two values were not linearly related. The Pearson correlation coefficient was 0.062, with a two-tailed $p = 0.18$.

4. DISCUSSION

From the Surveillance, Epidemiology, and End Results (SEER) database of people diagnosed with endometrial cancer between 2011 and 2017, the 5-year relative survival rates of localized, regional, and distant endometrial cancers were 96, 71, and 20%, respectively. According to the European Society for Medical Oncology- European Society of Gynaecological Oncology-European Society for Radiotherapy & Oncology (ESMO-ESGO-ESTRO) classification, the recurrence rates in low-, intermediate-, and high-risk endometrial cancers were 6% to 9%, 9% to 16%, and 21% to 35%, respectively.[19,20] The results of the present study indicated a similar recurrence rate in patients with stage I endometrial cancer, at 7.9%.

In the present study, the common prognostic factors for early-stage endometrial cancers, such as tumor grade, histologic type, LVSI, and myometrial invasion depth, were not found to predict cancer recurrence. There are two possible reasons for this—first, the patients in the present study received adequate adjuvant treatment based on known risk factors; and second, the power of the sample size was not sufficiently large enough to achieve statistical significance.

Whether preoperative CA-125 levels can serve as a useful prognostic factor for patients with stage I endometrial cancer remains uncertain, although the results of the present study showed that preoperative CA-125 levels were not useful predictive markers for recurrence. This may be because the patients in the present study did not have extrauterine metastases, and received adjuvant treatment based on their clinicopathological risk factors. This result is similar to that of a retrospective Korean multicenter study, in which they reported that preoperative serum CA-125 levels may not be useful for predicting most prognostic factors, and may not contribute to the preoperative selection of patients with intermediate- or high-risk disease who need adjuvant radiotherapy in early-stage endometrial cancer.[21] Conversely, Jiang et al,[14] in an analysis of 995 patients with endometrial cancer, found that elevated CA-125 was an independent prognostic factor; however, their study included stage I to IV patients, and almost 20% of the patients with endometrial cancer were excluded due to a lack of preoperative

Table 3

Univariable and multivariable analysis of clinicopathological factors as predictors of recurrence in stage 1 endometrial cancer

	Univariate analysis		Multivariate analysis	
Clinicopathological factors	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age (≥65 vs <65)	0.473 (0.139-1.604)	0.229		
Endometrioid cell grade (grade 3 vs grade 1 + 2)	1.959 (0.891-4.309)	0.094	1.673 (0.703-3.98)	0.245
Charlson Comorbidity Index (≥5 vs <5)	2.026 (0.98-4.30)	0.054	1.939 (0.859-4.378)	0.111
Myometrial invasion (≥50 vs <50)	1.993 (0.993-4.069)	0.058	1.60 (0.715-3.60)	0.252
Peritoneal cytology (positive vs negative)	2.67 (0.724-9.60)	0.141	2.5.5 (0.606-10.43)	0.204
Preoperative CA-125, U/mL (≥35 vs <35)	1.247 (0.589-2.641)	0.563		
Postoperative CA-125, U/mL (≥35 vs <35)	10.88 (2.79-42.4)	0.001a	2.339 (1.094-5.00)	0.038a
Postoperative CA-125, U/mL (≥13.75 vs <13.75)	3.04 (1.51-6.12)	0.002a		

CA-125 = carbohydrate antigen 125; HR = hazard ratio.

[a]$p < 0.05$ means statistically significant.

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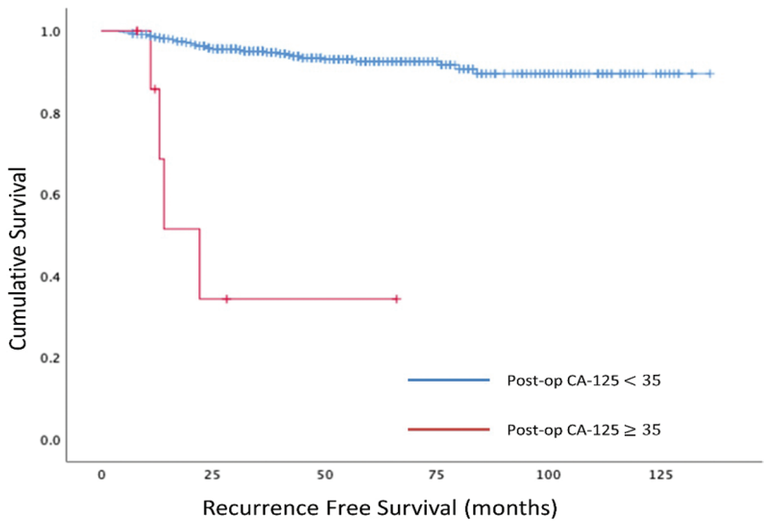
A **Cut-off value of 35 U/ml**

	<35	≧ 35
Recurrence/patients	33/481	4/10
Median, months	48.0	13.0
Hazard ratio (95%CI)	10.88 (2.79-42.4)	
p-value	<0.001*	

**p*-value was calculated by Log rank test and less than 0.05 means statistically significant.



B **Cut-off value of 13.75 U/ml**

	<13.75	≧ 13.75
Recurrence/patients	83/454	14/35
Median, months	50.5	35.5
Hazard ratio (95%CI)	3.04 (1.51-6.12)	
p- value	0.001*	

**p*-value was calculated by Log rank test and less than 0.05 means statistically significant.

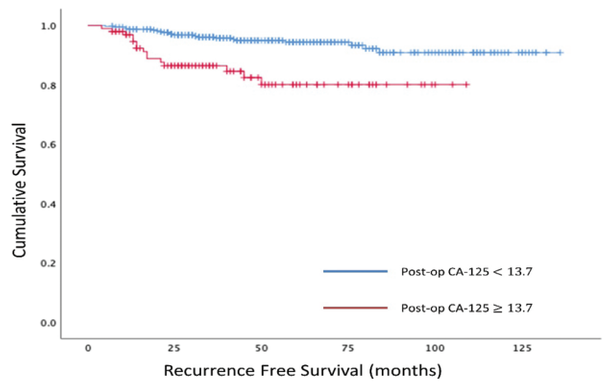


Fig. 1 Recurrence-free survival stratified by different postoperative CA-125 cutoff values in surgical stage I endometrial cancer. A, Cutoff value of 35 U/mL. B, Cutoff value of 13.75 U/mL. CA-125 = carbohydrate antigen 125.

serum CA-125 levels. Recently, a prospective multicenter cohort PIpelle Prospective ENDOmetrial carcinoma (PIPENDO) study, which included women with endometrial cancer, demonstrated that elevated preoperative CA-125 levels were correlated with poor prognosis and independently associated with survival, particularly in low-grade subgroups. Unlike the present study, most women with low-grade endometrial cancer in the aforementioned study did not undergo lymphadenectomy or lymph node sampling, which could have resulted in an inability to detect occult nodal metastasis and were, therefore, understaged.

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In the present study, postoperative CA-125 levels were obtained between 6 and 12 months after the completion of primary staging surgery and adjuvant therapy to avoid transient elevation of serum CA-125 levels. Serum CA-125 levels are often falsely elevated in patients with disease-free endometrial cancer, and decrease to normal levels 3 months after treatment. Some possible mechanisms for this elevation include peritoneal irritation, mediators of inflammation that induce CA-125 production in the mesothelium, tumor cell shedding from tumor tissues during surgery, or cardiopulmonary function changes after treatment.[22,23]

Among patients with stage I endometrial cancer, postoperative CA-125 levels were found to be significantly higher in cases of recurrence, and were shown to be independent predictors of recurrence via a multivariate analysis. Patients with increased serum CA-125 levels had higher recurrence rates and shorter RFS periods than those with lower serum CA-125 levels, regardless of the cutoff value selected. The results of the present study also showed that postoperative CA-125 levels had no correlation with preoperative CA-125 levels. Similarly, Patsner et al[24] reported that preoperative serum CA-125 levels were normal in 123 of 125 (98.4%) patients with early clinical and surgical stage endometrial adenocarcinoma, and remained normal in all patients, without evidence of either isolated vaginal recurrence or postoperative radiation enteritis. Marked elevations in CA-125 levels were noted in patients with pelvic, abdominal, or pulmonary metastases; therefore, they suggested that serum CA-125 levels may be beneficial in the posttreatment monitoring of patients with early-stage endometrial carcinoma.[24] In contrast to the present study, postoperative CA-125 levels were obtained more frequently in the aforementioned study (every 3–4 months postoperatively), with a shorter follow-up time (median, 18 months) and a smaller study population. Furthermore, we reported that obtaining the postoperative CA-125 level within 6 to 12 months after surgery is not only an indicator, but is also a predictor of, recurrence in patients with stage I endometrial cancer.

Compared with epithelial ovarian cancer, the role of CA-125 in the surveillance of endometrial cancer is inconclusive, as the CA-125 blood test is not routinely performed as part of treatment follow-up in some countries. The monitoring of serum CA-125 is suggested in select patients, for example, those with advanced disease, serous cell type, or elevated preoperative CA-125 levels.[25,26] Based on the findings of the present study, and the fact that the CA-125 assay is inexpensive, reproducible, and objective, obtaining CA-125 levels within 6 to 12 months after staging surgery may play a role in stage I endometrial cancer follow-up. If the patient has postoperative CA-125 levels >13.75 U/mL, a minimal follow-up schedule may not be recommended. More studies, therefore, are needed to validate an optimal cutoff value of postoperative CA-125 in predicting cancer recurrence.

To the best of the authors' knowledge, the present study was the largest retrospective study conducted at a single institution to explore the relationship between CA-125 levels and recurrence risk in patients with stage I endometrial cancer. This study, however, has some limitations. The primary limitation of the present study was its retrospective, single-center design. Second, the area under curve (AUC) of the selected postoperative CA-125 cutoff value (13.75 U/mL) in the present study was only 0.606. Nevertheless, this cutoff value could significantly distinguish between RFS and outcomes. Nowadays, increasing literature has revealed that molecular classification is closely associated with time to first recurrence, pattern of recurrence, and survival after recurrence in patients with endometrial cancer.[27] Furthermore, increased serum CA-125 levels have proven to coincide with the expression of a metastasis-associated gene signature and with alterations in "driver" gene expression involved in cancer metastasis.[28] Due to the retrospective nature of the present study, however, it was difficult to elucidate the relationship of molecular classification, gene signatures with CA-125 levels. The strength of the present study lies in the fact that all patients underwent comprehensive surgical staging of the disease as well as a similar treatment strategy involving adjuvant treatments.

In conclusion, the results of the present study indicated that in surgical stage I endometrial cancer, preoperative serum CA-125 levels were not a predictor of recurrence, while postoperative CA-125 levels were significantly associated with tumor recurrence. A postoperative CA-125 cutoff value of 13.75 U/mL yields the best sensitivity and specificity for predicting recurrence, as patients with postoperative CA-125 levels >13.75 U/mL had shorter RFS. Postoperative CA-125 level obtained within 6 to 12 months after staging surgery may, therefore, be a promising noninvasive biomarker for monitoring stage I endometrial cancer recurrence. If the patient had postoperative CA-125 levels >13.75 U/mL, a minimal follow-up schedule may not be appropriate. Further research to define a more optimal cutoff value of postoperative CA-125 values for the prediction of recurrence is therefore needed.

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