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Original Article

Significance of serum CA125 level in surgically resected cervical adenocarcinoma with adverse features

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ABSTRACT

Objective: Unlike cervical squamous cell carcinoma, there are no consensus criteria for serum tumor markers in cervical adenocarcinoma. This study aimed to identify the prognostic value of preoperative carbohydrate antigen 125 (CA125) levels in cervical adenocarcinoma patients with adverse pathologic features.
Methods: A total of 105 patients who underwent radical hysterectomy followed by adjuvant radiotherapy (RT) or concurrent chemoradiation therapy were included. Locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) were evaluated using the Cox proportional hazard regression model.
Results: Using a cutoff value of 50 U/mL, 83 and 22 patients had low- and high-CA125, respectively. Patients with high-CA125 had a larger tumor size, more frequent parametrial extension, and more frequent lymph node metastasis than those with low-CA125. During a median follow-up of 59.3 (interquartile range, 32.7–97.8) months, patients with high-CA125 showed inferior 5-year LRFS, DMFS, and OS rates compared to those with low-CA125 (38.5% vs. 70.0%; 37.0% vs. 69.4%; 43.6% vs. 78.1%, respectively, all $p<0.05$). In multivariable analysis, the high-CA125 remained significant prognostic factor for LRFS, DMFS, and OS (all $p<0.05$). Furthermore, 12 patients with high-CA125 at recurrence exhibited lower 5-year OS rates than 21 patients with low-CA125 at recurrence (0.0% vs. 51.3%, $p=0.003$).
Conclusion: In this retrospective analysis, the serum CA125 level at diagnosis and recurrence was related to the extent of disease and prognosis of cervical adenocarcinoma with adverse pathologic features. A CA125 level of ≥50 U/mL may be a prognostic surrogate marker for cervical adenocarcinoma in patients with the presence of adverse factors.

Keywords: Cervical Cancer; Adenocarcinoma; Carbohydrate Antigen 125; Radiotherapy; Prognosis

INTRODUCTION

Although the incidence of cervical squamous cell carcinoma (SCC) has decreased, the incidence of cervical adenocarcinoma (ADC) has increased recently, accounting for 20%–25% of all cases of cervical cancer [1,2]. Although there are conflicting results regarding

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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the impact of histology on outcomes, several previous studies have suggested ADC is more aggressive and has poorer outcomes than SCC [3-6].

Despite the absence of consensus criteria for squamous cell carcinoma antigen (SCC-Ag), the prognostic value of SCC-Ag has been well known for cervical SCC [7]. A recent systematic review of 61 studies illustrated the significance of both pre-treatment SCC-Ag (range of cutoff level, 1.1–40.0 ng/mL) and post-treatment SCC-Ag (range of cutoff level, 1.5–2.0 ng/mL) for predictive survival outcomes [7]. In addition, a cohort study reported that the SCC-Ag level helped clinical decision making regarding the administration of post-operative radiotherapy (RT) in patients with SCC [8].

Regarding cervical ADC, limited reports are available for serum tumor markers, including carbohydrate antigen-125 (CA125), CA 19-9, and carcinoembryonic antigen [9-12]. Among aforementioned markers, CA125 has been established as an important marker in the diagnosis and monitoring of other gynecologic tumors, such as ovarian and endometrial cancer [12-15]. Although several reports have noted its significance in cervical cancer, the reports included heterogeneous groups of patients, including those with both ADC and adenosquamous cell carcinoma, and patients treated with either definitive RT or adjuvant RT.

Herein, we have investigated the role of CA125 in patients with cervical ADC treated with radical hysterectomy followed by adjuvant RT.

MATERIALS AND METHODS

1. Patient population

After receiving Institutional Review Board approval of Samsung Medical Center (SMC 2020-10-052), we retrospectively reviewed data on patients with ADC treated with surgery and adjuvant RT between January 2001 and April 2018. Patients were excluded if an adenosquamous carcinoma component was discovered in the pathological specimen (n=31), if simple extrafascial hysterectomy or trachelectomy was performed (n=14), if the CA125 level at diagnosis or surgical pathology data were not available (n=11), if synchronous endometrial and cervical cancer was diagnosed (n=3), or if follow-up details were missing (n=2). Finally, 105 patients were included in the analysis (**Fig. S1**). The requirement for informed consent was waived due to the retrospective nature of the study.

2. Treatment

All patients were evaluated using diagnostic image modalities such as magnetic resonance imaging (n=105), or computed tomography (n=93), or 18F-Fludeoxyglucose positron emission tomography (n=57) before curative surgery. All patients underwent radical hysterectomy with pelvic lymph node (LN) dissection, and 36 (34.3%) patients underwent paraaortic LN dissection. The median number of dissected nodes was 19 (interquartile range [IQR]=13–26). Patients with two or more risk factors (intermediate-risk group), such as among tumor size ≥4 cm, depth of invasion ≥1/2 of the stroma, and positive lymphovascular invasion (LVI), received adjuvant RT. In addition, patients with positive parametrial extension, positive resection margins, or positive LNs were treated with concurrent chemoradiation therapy (CCRT; high-risk group). In total, 43 and 62 patients received adjuvant RT and CCRT, respectively. Except five patients who received intensity-modulated RT, standard four-field three-dimensional conformal RT with a median total dose of 50.4 Gy

in 28 fractions was performed in 100 patients. Ninety-eight patients received whole pelvic RT; seven patients were treated with extended-field RT covering up to T12/L1. Regarding vaginal cuff brachytherapy, a total dose of 18 Gy in 3 fractions was administered in eight patients with positive resection margins. For 62 patients who underwent CCRT, either weekly cisplatin 40 mg/m^2 (n=50) or cisplatin 60 mg/m^2 (day 1) and 5-fluorouracil 1,000 mg/m^2/day (days 1–5) every 3 weeks (n=12) was administered.

3. Follow-up and toxicity assessment

After treatment, follow-up examinations, including pelvic magnetic resonance imaging, computed tomography, and serum tumor marker measurement, were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Local failure was defined as a recurrent tumor at the vaginal cuff that was histologically confirmed. Regional and distant failures were defined as regional LN or pelvic wall recurrence within the pelvic region and other recurrent disease outside the pelvis, respectively.

4. Statistical analysis

The R package "MaxStat," which iteratively tests all possible cutoff points to find the one achieving the maximum rank statistic, was used to dichotomize the pre-operative CA125 level (**Fig. S2**) [16]. Patients were then categorized into the high-CA125 (CA 125 levels ≥50 U/mL, 22 patients) and low-CA125 (CA 125 levels <50 U/mL, 83 patients) groups. The baseline characteristics of patients in the high-and low-CA125 groups were compared using the Pearson chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) were calculated from the date of initial diagnosis to the date of each event or death from any cause, whichever occurred first. Overall survival (OS) was calculated from the date of initial diagnosis to death from any cause or the last follow-up. The Kaplan-Meier method was performed to estimate the LRFS, DMFS, and OS rates using the log-rank test to assess prognostic significance. A Cox regression model was used for multivariable analysis of factors affecting LRFS, DMFS, and OS; only factors with statistical significance in univariable analysis were included. In all analyses, a two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Baseline characteristics

The patient and tumor characteristics according to a preoperative CA125 level of 50 U/mL are summarized in **Table 1**. Using a median pre-operative CA125 level of 17.2 (IQR, 9.1–38.6) U/mL, the median CA125 levels in the high-CA125 and low-CA125 group were 91.0 (IQR, 77.7–174.3) U/mL and 12.2 (IQR, 7.8–21.8) U/mL, respectively. Patients with high-CA125 more frequently had FIGO stage III disease than those with low-CA125 at diagnosis (p<0.001). Pathological results revealed that patients in the high-CA125 group presented with larger tumors than those in the low-CA125 group (median, 5.0 cm vs. 4.0 cm, p=0.016); 45.5% and 12.0% patients in the high-CA125 and low-CA125 groups, respectively, had tumors measuring ≥6 cm (p=0.004). Regarding high-risk features, patients in the high-CA125 group more frequent had pathologically positive LNs than those in the low-CA125 group (median, 3 vs. 0, p<0.001). The rates of ≥1/2 stromal invasion, LVI, and parametrial extension were comparable between the high-CA125 and low-CA125 groups.

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Table 1. Patient and tumor characteristics according the elevation of preoperative CA125 levels

Variables	Total (n=105)	CA125 <50 U/mL (n=83)	CA125 ≥50 U/mL (n=22)	p-value
Age (yr)	48 [41–56]	49 [42–56]	44 [38–54]	0.262
Tumor markers at diagnosis				
CA125, U/mL	17.2 [9.1–38.6]	12.2 [7.8–21.8]	91.0 [77.7–174.3]	<0.001
Pathologic FIGO stage*				0.001
I–II	55 (52.4)	51 (61.4)	4 (18.2)	
III	50 (47.6)	32 (38.6)	18 (81.8)	
Differentiation				0.475
WD	18 (17.1)	14 (16.9)	4 (18.2)	
MD	23 (21.9)	20 (24.1)	3 (13.6)	
PD	11 (10.5)	7 (8.4)	4 (18.2)	
NA	53 (50.5)	42 (50.6)	11 (50.0)	
Tumor size (cm)	4.0 [3.0–5.2]	4.0 [3.0–5.0]	5.0 [3.5–7.5]	0.016
<4 cm	46 (43.8)	39 (47.0)	7 (31.8)	0.004
≥4 cm and <6 cm	39 (37.1)	34 (41.0)	5 (22.7)	
≥6 cm	20 (19.0)	10 (12.0)	10 (45.5)	
Depth of invasion (mm)	13.0 [9.0–19.0]	13.0 [9.0–17.0]	15.0 [10.0–20.0]	0.195
≥1/2 stromal invasion	81 (77.1)	66 (79.5)	15 (68.2)	0.401
Lymphovascular invasion	57 (54.3)	45 (54.2)	12 (54.5)	1.000
Parametrial extension	30 (28.6)	23 (27.7)	7 (31.8)	0.909
Positive resection margin	7 (6.7)	7 (8.4)	0 (0.0)	0.340
Number of positive LN	0 [0–2]	0 [0–1]	3 [1–5]	<0.001
Any LN involvement	50 (47.6)	32 (38.6)	18 (81.8)	0.001
Pelvic LN involvement	49 (46.7)	37 (44.6)	12 (54.5)	0.405
Paraaortic LN involvement	4 (3.8)	2 (2.4)	2 (9.1)	0.146
Risk group				0.002
Intermediate risk†	45 (42.9)	42 (50.6)	3 (13.6)	
High risk‡	60 (57.1)	41 (49.4)	19 (86.4)	
Adjuvant treatment				0.028
RT	43 (41.0)	39 (47.0)	4 (18.2)	
CCRT	62 (59.0)	44 (53.0)	18 (81.8)	

Values are presented as the number of patients (%) or median (interquartile range).
CA125, carbohydrate antigen 125; CCRT, concurrent chemoradiation therapy; FIGO, Federation of Gynecology and Obstetrics; MD, moderately differentiated; NA, not available; PD, poorly differentiated; RT, radiation therapy; WD, well-differentiated.
*FIGO stage refers to the revised 2018 FIGO staging system; †Intermediate-risk group refers to two or more of the following factors: lymphovascular invasion, ≥1/2 stromal invasion, or size ≥4 cm; ‡High-risk group refers to one or more of the following factors: parametrial extension, positive resection margin, or positive lymph node.

2. Patterns of failure

A total of 41 (39.0%) patients experienced disease progression after initial treatment; there were 24 (22.9%) and 35 (33.3%) locoregional failure and distant metastasis events, respectively (**Table 2**). Overall, patients with high-CA125 more frequently experienced disease progression compared to those with low-CA125 (59.1% vs. 33.7%, p=0.045). The rate of locoregional recurrence differed significantly between the groups, favoring the low-CA125 group (low-CA125 vs. high-CA125 groups: 18.1% vs. 40.9%, p=0.047). In addition, the rate of distant metastasis was higher in the high-CA125 group than in the low-CA125 group, but the difference was not statistically significant (50.0% vs. 28.9%, p=0.107). The most frequent distant metastasis site was the lungs (n=17, 16.2%) in both groups.

3. Survival outcomes

During a median follow-up of 59.3 (IQR=32.7–97.8) months, the 5-year LRFS, DMFS, and OS rates for the entire cohort were 63.4%, 62.7%, and 72.4%, respectively (**Fig. S3**). Patients in the high-CA125 group showed inferior 5-year LRFS and DMFS rates than those in the low-CA125 group (38.5% vs. 70.0% and 37.0% vs. 69.4%, respectively, all p<0.001, **Fig. 1A and B**). Multivariable analysis revealed that high pre-operative CA125 ≥50 U/mL (hazard ratio

Table 2. Failure patterns stratified by preoperative CA125 level

Variables	Total (n=105)	CA125 <50 U/mL (n=83)	CA125 ≥50 U/mL (n=22)	p-value
Overall failure	41 (39.0)	28 (33.7)	13 (59.1)	0.045
Locoregional failure	24 (22.9)	15 (18.1)	9 (40.9)	0.047
Vaginal stump	13	8	5	
Intrapelvic region	6	4	2	
Pelvic LN	8	4	4	
Inguinal LN	1	1	0	
Retroperitoneal LN	11	6	5	
Distant metastasis	35 (33.3)	24 (28.9)	11 (50.0)	0.107
Peritoneum	11	8	3	
Lung	17	12	5	
Liver	5	2	3	
Gastrointestinal tract	5	2	3	
Bone	5	4	1	
Extra-regional LN	6	4	2	

Values are presented as number of patients (%).
CA125, carbohydrate antigen 125; LN, lymph node.

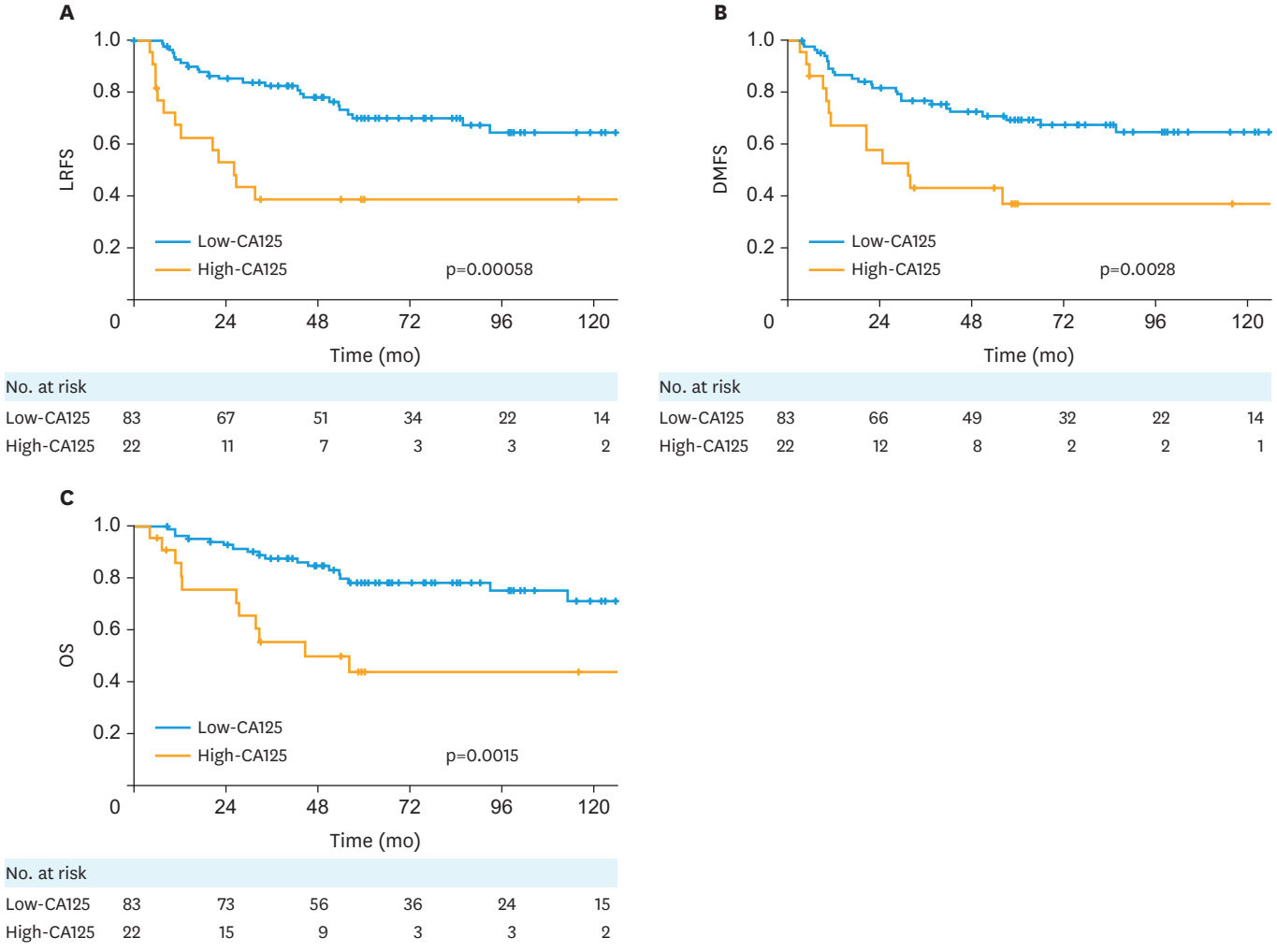

Fig. 1. Survival outcomes according to preoperative CA125 level. Locoregional recurrence-free survival (A), distant metastasis-free survival (B), and overall survival (C).
CA125, carbohydrate antigen 125; DMFS, distant metastasis-free survival; LRFS, locoregional recurrence-free survival; OS, overall survival.

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[HR]=2.31; 95% confidence interval [CI]=1.07–4.97; p=0.033) and presence of LVI (HR=2.32; 95% CI=1.11–4.88; p=0.026) were significant factors related to poor LRFS (**Table 3**). Further, preoperative high-CA125 (HR=2.17; 95% CI=1.02–4.78; p=0.036), pathologically positive LNs (HR=3.41; 95% CI=1.33–8.79; p=0.011), and tumor size contributed to inferior DMFS. Patients with high-CA125 had lower 5-year OS rates than those with low-CA125 (43.6% vs. 78.1%, p<0.001; **Fig. 1C**). In multivariable analysis, the preoperative high-CA125 was the only significant factor affecting OS rates (HR=2.27; 95% CI=1.02–5.31; p=0.042; **Table 4**); parametrial extension (HR=2.19; p=0.061) and pathologically positive LNs (HR=2.66; p=0.066) showed marginal significance.

4. Subgroup analysis according to risk groups

Since there were only three patients with high-CA125 in the intermediate-risk group, further statistical analysis was not performed. Subgroup analysis of patients in the high-risk group revealed that patients with high-CA125 showed inferior outcomes compared to those with low-CA125; the 5-year LRFS, DMFS, and OS rates for patients with high-CA125 and low-CA125 were 36.8% and 46.9% (p=0.012, **Fig. S4**), 35.1% and 47.6% (p=0.030), and 42.6% and 60.1% (p=0.034), respectively.

Table 3. Prognostic factors of LRFS and DMFS

Variables	(Ref. vs.)*	Univariable analysis			Multivariable analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
LRFS							
Age	(<45 vs. ≥45)	1.45	0.72–2.92	0.303			
Differentiation	(WD/MD vs. PD)	1.63	0.52–5.14	0.406			
Tumor size	(<4 cm vs. 4–6 cm)	1.23	0.58–2.62	0.592	1.49	0.68–3.25	0.315
	(<4 cm vs. ≥6 cm)	2.48	1.11–5.55	0.027	1.90	0.76–4.77	0.170
Depth of invasion	(<1/2 vs.≥1/2 of stroma)	2.82	0.68–11.73	0.153			
LVI	(Negative vs. positive)	2.75	1.34–5.67	0.006	2.32	1.11–4.88	0.026
Resection margin	(Negative vs. positive)	2.01	0.71–5.68	0.189			
Parametrium	(Free vs. involvement)	2.78	1.45–5.33	0.002	1.78	0.81–3.90	0.149
Positive LN	(No vs. yes)	4.05	1.96–8.35	<0.001	2.27	0.92–5.61	0.076
Positive PLN	(No vs. yes)	0.85	0.45–1.62	0.626			
Positive PALN	(No vs. yes)	2.81	0.85–9.31	0.091			
Adjuvant treatment	(RT vs. CCRT)	3.39	1.55–7.41	0.002	1.16	0.44–3.06	0.768
RT field	(WP vs. extended field)	4.39	1.80–10.68	0.001	1.39	0.50–3.88	0.526
Preoperative CA125	(Continuous)	1.01	1.00–1.02	0.020			
Preoperative CA125	(<50 vs. ≥50 U/mL)	3.08	1.57–6.04	0.001	2.31	1.07–4.97	0.033
DMFS							
Age	(<45 vs. ≥45)	1.59	0.79–3.20	0.192			
Differentiation	(WD/MD vs. PD)	0.89	0.25–3.11	0.850			
Tumor size	(<4 cm vs. 4–6 cm)	1.76	0.83–3.73	0.139	2.71	1.20–6.10	0.016
	(<4 cm vs. ≥6 cm)	3.03	1.33–6.88	0.008	3.26	1.30–8.18	0.012
Depth of invasion	(<1/2 vs. ≥1/2 of stroma)	3.18	0.77–13.21	0.111			
LVI	(Negative vs. positive)	2.23	1.13–4.40	0.021	1.75	0.86–3.57	0.125
Resection margin	(Negative vs. positive)	2.94	1.14–7.53	0.025	2.20	0.64–7.59	0.214
Parametrium	(Free vs. involvement)	2.72	1.44–5.15	0.002	1.76	0.80–3.89	0.161
Positive LN	(No vs. yes)	4.25	2.06–8.76	<0.001	3.41	1.33–8.79	0.011
Positive PLN	(No vs. yes)	0.91	0.48–1.71	0.771			
Positive PALN	(No vs. yes)	1.49	0.36–6.21	0.586			
Adjuvant treatment	(RT vs. CCRT)	2.82	1.34–5.96	0.006	0.70	0.25–1.91	0.481
RT field	(WP vs. extended field)	4.61	1.91–11.10	0.001	1.23	0.40–3.81	0.721
Preoperative CA125	(Continuous)	1.02	1.00–1.03	0.006			
Preoperative CA125	(<50 vs. ≥50 U/mL)	2.67	1.37–5.22	0.004	2.17	1.02–4.78	0.036

*The foreparts of parentheses are set as the reference group.
CA125, carbohydrate antigen 125; CCRT, concurrent chemoradiation therapy; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; LN, lymph node; LRFS, locoregional recurrence-free survival; LVI, lymphovascular invasion; MD, moderately differentiated; PALN, para-aortic lymph node; PD, poorly differentiated; PLN, pelvic lymph node; RT, radiation therapy; WD, well-differentiated; WP, whole pelvis.

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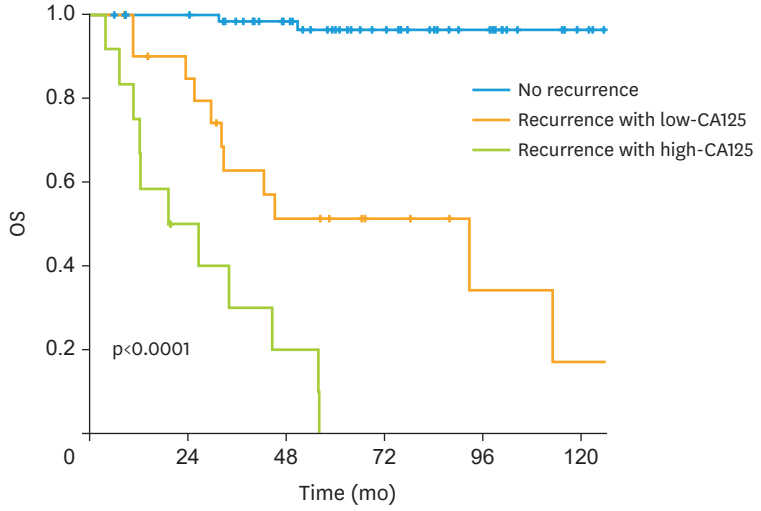
Table 4. Prognostic factors of overall survival

Variables	(Ref. vs.)*	Univariable analysis			Multivariable analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Age	(<45 vs. ≥45)	2.09	0.90–4.88	0.090			
Differentiation	(WD/MD vs. PD)	1.14	0.32–4.09	0.840			
Tumor size	(<4 cm vs. 4–6 cm)	1.75	0.75–4.11	0.200			
	(<4 cm vs ≥6 cm)	2.55	0.98–6.61	0.060			
Depth of invasion	(<1/2 vs. ≥1/2 of stroma)	2.13	0.51–8.96	0.300			
LVI	(Negative vs. positive)	1.81	0.84–3.86	0.130			
Resection margin	(Negative vs. positive)	1.99	0.60–6.58	0.260			
Parametrium	(Free vs. involvement)	2.44	1.16–5.14	0.020	2.19	0.96–4.99	0.061
Positive LN	(No vs. yes)	3.96	1.75–8.92	<0.001	2.66	0.94–7.53	0.066
Positive PLN	(No vs. yes)	1.10	0.54–2.26	0.790			
Positive PALN	(No vs. yes)	2.50	0.59–10.65	0.210			
Adjuvant treatment	(RT vs. CCRT)	2.78	1.19–6.48	0.020	0.94	0.31–2.83	0.910
RT field	(WP vs. extended field)	2.69	0.81–8.97	0.110			
Preoperative CA125	(Continuous)	1.02	1.01–1.03	<0.001			
Preoperative CA125	(<50 vs. ≥50 U/mL)	3.14	1.49–6.62	<0.001	2.27	1.02–5.31	0.042

*The foreparts of parentheses are set as the reference group.
CA125, carbohydrate antigen 125; CCRT, concurrent chemoradiation therapy; LN, lymph node; LVI, lymphovascular invasion; MD, moderately differentiated; PALN, para-aortic lymph node; PD, poorly differentiated; PLN, pelvic lymph node; RT, radiation therapy; WD, well-differentiated; WP, whole pelvis.

5. CA125 levels at recurrence

Among the 41 patients with progressive disease, CA125 levels at recurrence were evaluated in 33. The median CA125 level at recurrence was 19.4 (IQR=6.5–62.8) U/mL; patients with high preoperative CA125 levels had higher CA125 levels at recurrence than those with low preoperative CA125 levels (**Table S1**). Based on the cutoff value of 50 U/mL, 21 and 12 patients presented with CA125 levels <50 U/mL and CA125 levels ≥50 U/mL, respectively, at recurrence. There was no difference in the pattern of failure between these patients (**Table S1**). However, CA125 levels ≥50 U/mL at recurrence was associated with lower 5-year OS rates than CA125 levels <50 U/mL at recurrence (0.0% vs. 51.3%, p=0.003, **Fig. 2**).



No. at risk						
No recurrence	64	62	50	33	24	15
Recurrence with low-CA125	21	16	9	5	2	1
Recurrence with high-CA125	12	5	2	0	0	0

Fig. 2. Survival outcomes stratified by recurrence and CA125 level at recurrence.
The remaining eight patients who experienced treatment failures were excluded from the analysis because the level of CA125 at recurrence was not available.
CA125, carbohydrate antigen 125; OS, overall survival.

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DISCUSSION

By analyzing the prognostic value of preoperative CA125 levels in surgically resected cervix ADC with either intermediate or high-risk features, we demonstrated a positive correlation between preoperative high-CA125 levels (≥50 U/mL) and the extent of disease, including tumor size, positive LNs, and pathological stage. In addition, high-CA125 was significantly associated with locoregional progression, distant metastasis, and inferior survival outcomes in comparison to low-CA125. We also found that CA125 levels ≥50 U/mL at recurrence were related to inferior survival outcomes in patients with CA125 levels <50 U/mL at recurrence.

Several studies have investigated various cutoff values for CA125 in cervical ADC. Tsai et al. discovered that CA125 level ≥26 U/mL was deemed as a predictive factor for LVI and deep stromal invasion in patients with early-stage cervical ADC treated with surgery [9]. Bender et al. [10] reported that CA125 level ≥30 U/mL was a significant unfavorable factor for survival in patients treated with definitive RT or surgery. In our study, we observed the effect of elevated CA125 levels in patients after radical hysterectomy and adjuvant RT on disease status and survival outcomes. We found that a higher CA125 levels (>50 U/mL) were significantly associated with an unfavorable pathological status and poor survival outcomes.

Since patients with ADC more frequently experience distant metastasis than those with SCC, early detection of relapse based on serum tumor markers is essential for improving treatment outcomes by eradicating microscopic metastatic disease. Although a standard cutoff level of 1.5 ng/mL for SCC-Ag can detect 70%–86% of relapses during surveillance, there is no useful criterion for CA125 in cervical ADC [17-19]. Although there was no difference in patterns of failure according to the CA125 level at recurrence, patients with high CA125 levels at recurrence had poorer OS than those with low CA125 levels at recurrence in our study. Elevated CA125 levels at recurrence could be a surrogate for tumor aggressiveness. There was no difference in patterns of recurrence between patients with high or low CA125 levels at recurrence, but rapid disease progression after initial recurrence may account for the low survival rate in patients with high CA125 levels at recurrence. Although a randomized trial in patients with ovarian cancer failed to prove the survival benefit of early intervention based on elevated CA125 levels during follow-up, detection of CA125 levels may help physicians to be preemptively informed of potential disease recurrence [20,21].

According to whole-exome sequencing and genotyping analysis, cervical ADC is characterized by distinct genomic alterations from those in cervical SCC [22,23]. Furthermore, revised classifications for cervical ADC endorsed by the International Endocervical Adenocarcinoma Criteria and the World Health Organization also highlight the heterogeneity of cervical ADC [24,25]. Recent studies based on the new categorization reported distinct clinical outcomes in patients with ADC [26-28]. However, there are no reports on the clinical implications of serum CA125 levels in various types of cervical ADC. Although we observed the detrimental effect of high-CA125 in ADC, appropriate serum tumor markers and cutoff values for detecting early recurrence in each ADC subtype need to be further analyzed.

Our study has several limitations. First, the lack of serial monitoring of CA125 levels after initial treatment provides limited information regarding the post-operative CA125 nadir and early detection of failure. Determining the dynamics of CA125 levels between pre-operative and post-operative assessment might allow more refined pre-operative estimation of the

prognosis than conventional pathological parameters. Secondly, the information on profiles of CA125 in patients without adverse features was lacking in the current study. Since we only included patients with intermediate to high-risk pathologic features, current cutoff value of 50 U/mL possibly applied to specific subgroup of patients treated with radical surgery. However, the strength of this study is a large number of patients with ADC were treated homogeneously, including treatment with radical hysterectomy followed by adjuvant RT/CCRT. A further study including both intermediate/high-risk and low-risk cervical cancer could help physicians to identify the prognostic impact of patients with cervical ADC. Lastly, due to the lack of pathological review of surgical specimens, we were unable to provide detailed information on the revised subgroups of ADC.

In summary, we demonstrated that preoperative high-CA125 directly relates to aggressive tumor features and poor outcomes in patients with cervical ADC presenting with adverse pathologic factors. In addition, CA125 level ≥50 U/mL at first recurrence was associated with poor survival outcomes in those patients. Preoperative high-CA125 may help stratify high-risk patients who require more intensive systematic treatment. In further investigations, the optimal cutoff value of CA125 in cervical ADC should be studied on a large scale because it is inconsistent and only a few reports have evaluated it thus far. In addition, the cutoff value of CA125 according to the subtype of cervical ADC might be needed to define its association with prognosis.

SUPPLEMENTARY MATERIALS

Table S1
Pre-operative CA125 level and patterns of failure stratified by CA 125 level at first recurrence

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Fig. S1
CONSORT diagram.

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Fig. S2
Results of maximally selected rank statistics regarding pre-operative CA125 level.

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Fig. S3
Survival outcomes of the entire patients.

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Fig. S4
Survival outcomes for patients in the high-risk group* according to CA125 elevation: Locoregional recurrence-free survival (A), distant metastasis-free survival (B), and overall survival (C).

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