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Original Article

Outcome patterns of cervical adenocarcinoma and squamous cell carcinoma following curative surgery: before and after propensity score matching analysis of a cohort study

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Abstract: To estimate the outcome patterns and predictors of curative surgery for cervical squamous cell carcinoma (SCC) and adenocarcinoma (ADC) for overall survival (OS), locoregional recurrence (LRR), and distant metastasis (DM), we enrolled 4628 patients who had received a diagnosis of cervical SCC or ADC and received curative surgery. Cox regression analysis was employed to calculate hazard ratios and confidence intervals (CIs); independent predictors were controlled for or stratified in the analysis, and the endpoint was all-cause death. Propensity score matching was conducted to create well-balanced groups. Multivariate Cox regression analysis indicated that the pathologic type of ADC, age ≥ 70 years, advanced pathologic stage, positive margin, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential chemotherapy and radiotherapy, earlier year of diagnosis, Charlson comorbidity index (CCI) = 1, CCI ≥ 2, low income levels, and treatment at a nonmedical center were significant independent poor prognostic factors for all-cause mortality in cervical cancer treated with curative surgery. Adjusted hazard ratios (95% CIs) for patients with cervical ADC who received curative surgery were 2.34 (1.96-2.79), 1.15 (0.89-1.49), and 2.16 (1.75-2.66) compared with cervical SCC for all-cause mortality, LRR, and DM, respectively. This study indicated that curative surgery for cervical ADC was associated with poorer OS and higher DM rates relative to cervical SCC, but no significant differences were identified in LRR.

Keywords: Surgery, cervical squamous cell carcinoma, cervical adenocarcinoma, survival, locoregional recurrence, metastasis

Introduction

Adenocarcinoma (ADC) and squamous cell carcinoma (SCC) of the cervix share many similarities, and they are treated with the same approach at most institutions following National Comprehensive Cancer Network (NCCN) guidelines [1]. However, several differences have been identified in epidemiology, prognostic factors, and patterns of failure after primary treatment and possibly in response to specific treatments [2]. Despite these differences, specific treatment strategies tailored to ADC have not yet emerged. Either curative surgery (usually radical hysterectomy, bilateral salpingo-oophorectomy, or pelvic lymph node dissection) or radiotherapy (RT), which is typically administered with concurrent chemoradiotherapy (CCRT), can cure stage IB and IIA cervical cancer (CC). The preference for surgery in cervical ADC is based on data from a prospective trial, in which 343 women with stage IB and IIA CC (14% ADC) were randomly assigned to primary surgery or RT alone [3, 4]. At a median follow-up

of 87 months, the 5-year overall and disease-free survival rates were the same for both treatment groups (83% and 74% for each group, respectively) [3, 4]. However, multivariate analysis demonstrated a survival advantage for patients with ADC who underwent primary surgery [3, 4]. Whether this result was due to the increased effectiveness of surgery or the absence of a benefit from RT (possibly due to the lack of concurrent chemotherapy [CT]) in women with ADC [5] remains to be determined. As noted, some data raise the possibility that ADC has poorer outcomes with RT alone than do SCCs, but this relative radioresistance may be overcome through the use of concurrent CT [5]. Thus, when RT is administered for ADC, patients are usually administered concurrent cisplatin-based CT. Presently, curative surgery appears to have preferable outcomes in cervical ADC based on retrospective studies with a small sample size [3, 4].

For women with locoregionally advanced International Federation of Gynecology and Obstetrics (FIGO) clinical stage IIB-IVA cervical SCC, primary CCRT has been the treatment of choice at most institutions, although the treatment of choice varies across institutions. In this setting, NCCN guidelines recommend either radical hysterectomy or initial CCRT [1]. However, these patients are initially treated with CCRT because evidence level category 2B is provided for surgery for advanced CC in NCCN guidelines [1]. One of the main arguments against a primary surgical approach to advanced stages is the high potential for multimodal therapy, given that the majority of women will have a high- or intermediate-risk disease, for which adjuvant CCRT is recommended [5]. However, some studies have demonstrated radioresistance in cervical ADC; thus, curative surgery might improve the survival of patients advanced ADC [5, 6]. Thus, some patients with advanced stage CC continue to receive curative surgery in Taiwan [6], although adjuvant treatments usually cannot be avoided [1, 5].

Patterns of overall survival (OS), locoregional recurrence (LRR), and distant metastasis (DM) in cervical SCC and ADC following curative surgery with or without adjuvant treatments may differ, but the difference remains unclear because no large-scale head-to-head study has estimated outcome patterns of curative surgery for cervical pathologic types of SCC and ADC. In this study, we aimed to determine outcome patterns and predictors of curative surgery for cervical SCC and ADC at pathologic stages I-IIA (early stages) and IIB-IVA (advanced stages) for OS, LRR, and DM.

Patients and methods

We established a cohort by using data from the Taiwan Cancer Registry Database. We enrolled patients who had received a diagnosis of resectable cervical SCC or ADC and underwent curative surgery (radical hysterectomy, bilateral salpingo-oophorectomy, or pelvic lymph node dissection) between January 1, 2007, and December 31, 2015. The index date was the date of the surgery. The follow-up duration was from the index date to December 31, 2014. The Taiwan Cancer Registry Database of the Collaboration Center of Health Information Application contains the detailed cancer-related information of patients, including clinical and pathologic stages, treatment modalities, pathologic characteristics, surgical procedures, RT doses including dose of external beam radiotherapy (EBRT) and intracavitary brachytherapy, and the CT regimens used [7-14]. Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. The diagnoses of the enrolled patients were confirmed using their pathological data, and the patients who received a new diagnosis of resectable cervical SCC or ADC were confirmed to have no other cancer. Patients with a diagnosis of resectable cervical SCC or ADC, aged ≥ 20 years, and clinical cancer stage I-IVA as per the FIGO staging system were included. Pathologic staging according to the American Joint Committee on Cancer (AJCC) staging system, 7th edition, after curative surgery was also used. Patients with a history of cancer before cervical SCC or ADC, distant metastasis, missing sex data, an age of <20 years, nonstandard surgical procedures, nonplatinum-based adjuvant CT or CCRT, hypofraction RT dose of adjuvant RT, adenosquamous cell carcinoma, small cell carcinoma, or unclear staging were excluded. In addition, we excluded patients with cervical SCC or ADC who did not receive surgery within 3 months after the diagnosis date of CC, received CT alone, received neoadjuvant CT, received RT alone, receiv-

ed definitive CCRT, or underwent neoadjuvant CCRT followed by surgery. Finally, we enrolled patients with CC who received curative surgery and categorized them into 2 groups according to the pathologic type and pathologic stage to compare their outcomes. The median total dose and fraction size of adjuvant RT were 50 and 2 Gy per fraction, respectively, in the SCC and ADC groups (**Table 1**). Comorbidities were scored using the Charlson comorbidity index (CCI) [15, 16]. Only comorbidities observed within 6 months before the index date were included; comorbidities were identified and included according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) main diagnosis codes for a first admission or 3 or more repeat codes main diagnosis codes for outpatient visits.

Significant independent predictors, such as pathologic type, age, AJCC pathologic stage, surgical margin, grade of differentiation, adjuvant treatment, intracavitary brachytherapy, year of diagnosis, CCI score, income level, hospital level, and hospital region, were determined using multivariate Cox regression analysis to determine the hazard ratio (HR); independent predictors were controlled for or stratified in the analysis, and the endpoint was all-cause death among patients with cervical SCC or ADC who received curative surgery. The cumulative incidence of all-cause mortality was estimated using the Kaplan-Meier method, and differences between cervical SCC and ADC were determined using the log-rank test. After adjustment for confounders, the Cox proportional hazard method was used to model the time from the index date to all-cause mortality incidence among patients. In multivariate analysis, HRs were adjusted for pathologic type, age, AJCC pathologic stage, surgical margin, grade of differentiation, adjuvant treatment, intracavitary brachytherapy, year of diagnosis, CCI score, income level, hospital level, and hospital area. Stratified analyses were performed to evaluate the risks of mortality, LRR, and DM associated with resectable cervical SCC or ADC at various AJCC pathologic stages. All analyses were performed using SAS 9.3 software (SAS, Cary, NC, USA). Two-sided $P<.05$ was considered significant.

To reduce the effects of potential confounders, propensity score matching (PSM) was employed to create well-balanced groups. PSM scores were adjusted using a multivariable logistic regression model, in which the SCC and ADC groups were dependent variables and potential confounders were covariates. The following confounders were included in PSM: pathologic type, age, AJCC pathologic stage, surgical margin, grade of differentiation, adjuvant treatment, intracavitary brachytherapy, RT cumulative dose, platinum cumulative dose, intracavitary brachytherapy dose, year of diagnosis, CCI score, income level, hospital level, and hospital area. All patients with cervical ADC were matched at a ratio of 1:2 to patients with cervical SCC (if ADC cannot be matched at a ratio of 1:2 to SCC, ADC might be matched at a ratio of 1:1 to SCC). The independent predictors were controlled for in the analysis.

Results

We enrolled 4628 patients who had FIGO stage I-IVA CC without distant metastasis (**Table 1**). Of these, 3588 patients with cervical SCC received curative surgery, and 1040 patients with cervical ADC received curative surgery. Overall, 3578 patients received curative surgery at pathologic stages I-IIA, and 1050 patients received curative surgery at pathologic stages IIB-IVA. The mean follow-up duration after the index date was 79.5 and 75.0 months for pathologic stages I-IIA and IIB-IVA cervical SCC, respectively, and 66.2 and 46.0 months for pathologic stages I-IIA and IIB-IVA cervical ADC, respectively. Relative to patients with cervical SCC, patients with cervical ADC were significantly younger and more frequently received treatment at a medical center; had higher income levels, lower incidence of pathologic stage IIB, and more frequent well-differentiated or undifferentiated cancer; and were more likely to be margin clear in the early pathologic stage, more likely to receive adjuvant treatment, more likely to receive adjuvant sequential CT and RT in early pathologic stages, and more likely to live in northern Taiwan (**Table 1**). Incidence rates of DM and death for ADC were also higher. No statistically significant differences were identified in the platinum cumulative dose, RT cumulative dose, intracavitary brachytherapy dose, CCI score, or FIGO stage; however, we identified significant stage variation (from FIGO stage to AJCC pathologic stage) and significant differences in FIGO stage IIB (Supplementary Table 1). Clinical and pathologic stages were significantly inconsistent for

Table 1. Characteristics of patients with cervical adenocarcinoma or squamous cell carcinoma who received curative surgery

		AJCC pathologic stages I-IIA			AJCC pathologic stages IIB-IVA		
		SCC (N = 2790)	*Adenocarcinoma* (N = 788)	*P*-value	*SCC* (N = 798)	*Adenocarcinoma* (N = 252)	*P*-value
		n (%)	n (%)		n (%)	n (%)	
Age, years	Mean (SD)	51.3 (12.3)	48.6 (10.2)	<.0001	55.1 (11.8)	51.5 (10.4)	<.0001
	Median (IQR: Q1, Q3)	51 (20, 90)	48 (25, 83)		54 (24, 88)	52 (27, 83)	
Age group	20-39	508 (18.2)	138 (17.5)	<.0001	73 (9.1)	31 (12.3)	.0015
	40-49	772 (27.7)	304 (38.6)		167 (20.9)	70 (27.8)	
	50-59	811 (29.1)	235 (29.8)		296 (37.1)	91 (36.1)	
	60-69	475 (17.0)	86 (10.9)		164 (20.6)	49 (19.4)	
	70+	224 (8.0)	25 (3.2)		98 (12.3)	11 (4.4)	
Year of diagnosis	2007-2009	1106 (39.6)	265 (33.6)	.0085	306 (38.3)	71 (28.2)	.0129
	2010-2012	945 (33.9)	298 (37.8)		279 (35.0)	105 (41.7)	
	2013-2015	739 (26.5)	225 (28.6)		213 (26.7)	76 (30.2)	
FIGO stages	I-IIA	2764 (99.1)	780 (99.0)	.8314	630 (78.9)	185 (73.4)	.0661
	IIB-IVA	26 (0.9)	8 (1.0)		168 (21.1)	67 (26.6)	
AJCC pathologic stage	I	2594 (93.0)	744 (94.4)	.1532			
	IIA	196 (7.0)	44 (5.6)				
	IIIB				199 (24.9)	28 (11.1)	<.0001
	IVA				515 (64.5)	167 (66.3)	
	4				84 (10.5)	57 (22.6)	
Grade	I (well differentiated)	149 (5.3)	237 (30.1)	<.0001	21 (2.6)	40 (15.9)	<.0001
	II (moderately differentiated)	1287 (46.1)	332 (42.1)		512 (64.2)	133 (52.8)	
	III (poorly differentiated)	449 (16.1)	98 (12.4)		174 (21.8)	56 (22.2)	
	IV (undifferentiated)	9 (0.3)	6 (0.8)		3 (0.4)	5 (2.0)	
	Missing	896 (32.1)	115 (14.6)		88 (11.0)	18 (7.1)	
Surgical margin	No residual	2457 (88.1)	725 (92.0)	<.0001	590 (73.9)	185 (73.4)	.3999
	Residual	179 (6.4)	19 (2.4)		137 (17.2)	50 (19.8)	
	Unknown	154 (5.5)	44 (5.6)		71 (8.9)	17 (6.7)	
Adjuvant treatment	Adjuvant CCRT	179 (6.4)	71 (9.0)	.0080	408 (51.1)	120 (47.6)	.0126
	Adjuvant sequential CT and RT	24 (0.9)	14 (1.8)		53 (6.6)	33 (13.1)	
	Adjuvant RT	339 (12.2)	97 (12.3)		164 (20.6)	51 (20.2)	
	No adjuvant	2248 (80.6)	606 (76.9)		173 (21.7)	48 (19.0)	
RT cumulative dose, Gy	Mean (SD)	45.8 (11.6)	45.9 (11.7)	.9971	48.8 (14.9)	48.8 (15.4)	.4020
	Median (IQR: Q1, Q3)	50 (37, 56)	50 (36, 56)		50 (37, 56)	50 (37, 56)	
EBRT cumulative dose	No EBRT	2272 (81.4)	620 (78.7)	.2146	226 (28.3)	81 (32.1)	.4015
	<50 Gy	250 (9.0)	83 (10.5)		247 (31.0)	79 (31.3)	

	50+ Gy	268 (9.6)	85 (10.8)		325 (40.7)	92 (36.5)	
Platinum cumulative dose, MG	Mean (SD)	446.0 (224.3)	533.2 (428.8)	.5141	488.4 (317.0)	628.3 (614.7)	.1517
	Median (IQR: Q1, Q3)	420 (300, 600)	420 (300, 600)		450 (300, 600)	500 (300, 600)	
Platinum cumulative dose	No CT	2587 (92.7)	703 (89.2)	.0058	337 (42.2)	99 (39.3)	.5886
	<500 MG	115 (4.1)	47 (6.0)		239 (29.9)	75 (29.8)	
	500+ MG	88 (3.2)	38 (4.8)		222 (27.8)	78 (31.0)	
Intracavitary brachytherapy dose, cGy	Mean (SD)	2275.2 (943.9)	2213.7 (794.8)	.3015	2043.2 (812.6)	2267.2 (753.3)	.8284
	Median (IQR: Q1, Q3)	2500 (1500, 3000)	2000 (1500, 2500)		2000 (1500, 3000)	2000 (1500, 2500)	
Intracavitary brachytherapy dose	No intracavitary brachytherapy	2167 (77.7)	614 (77.9)	.3963	241 (30.2)	89 (35.3)	.3123
	<2500 cGy	490 (17.6)	145 (18.4)		454 (56.9)	133 (52.8)	
	2500+ cGy	133 (4.8)	29 (3.7)		103 (12.9)	30 (11.9)	
CCI Score	Mean (SD)	0.3 (0.7)	0.3 (0.7)	.1054	0.3 (0.7)	0.4 (0.8)	.2343
	0	2216 (79.4)	647 (82.1)	.2362	637 (79.8)	192 (76.2)	.4216
	1	396 (14.2)	95 (12.1)		105 (13.2)	41 (16.3)	
	2+	178 (6.4)	46 (5.8)		56 (7.0)	19 (7.5)	
Income	<NTD 18,000	695 (24.9)	148 (18.8)	.0002	218 (27.3)	62 (24.6)	.5471
	NTD 18,000-22,500	995 (35.7)	283 (35.9)		266 (33.3)	82 (32.5)	
	NTD 22,500-30,000	398 (14.3)	108 (13.7)		118 (14.8)	35 (13.9)	
	NTD 30,000+	702 (25.2)	249 (31.6)		196 (24.6)	73 (29.0)	
Hospital level	Medical center	1950 (69.9)	579 (73.5)	.0509	509 (63.8)	186 (73.8)	.0034
	Other	840 (30.1)	209 (26.5)		289 (36.2)	66 (26.2)	
Hospital area	North	1388 (49.7)	435 (55.2)	.0238	332 (41.6)	130 (51.6)	.0003
	Middle	601 (21.5)	147 (18.7)		141 (17.7)	55 (21.8)	
	South/East	801 (28.7)	206 (26.1)		325 (40.7)	67 (26.6)	
Mean follow-up time, months (SD)		79.5 (31.8)	75.0 (31.1)		66.2 (35.4)	46.0 (31.0)	
Death		206 (7.38)	79 (10.03)		245 (30.70)	143 (56.75)	
Local recurrence		207 (7.42)	52 (6.60)		94 (11.78)	38 (15.08)	
Distant metastasis		103 (3.69)	68 (8.63)		180 (22.56)	91 (36.11)	

CCRT, concurrent chemoradiotherapy; cGy, centigray; Gy, gray; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; CT, chemotherapy; RT, radiotherapy; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; MG, milligrams; SD, standard deviation; IQR, interquartile range; NTD, New Taiwan dollar, AJCC, American Joint Committee on Cancer.

Table 2. Results of Cox proportional hazard regression analysis of the risk of all-cause mortality among patients with cervical adenocarcinoma or squamous cell carcinoma who received curative surgery

		Crude HR (95% CI)	Adjusted HR* (95% CI)	*P*-value
Pathologic type	SCC	1	1	<.0001
	Adenocarcinoma	1.88 (1.60, 2.21)	2.34 (1.96, 2.79)	
Age	0-39	1	1	<.0001
	40-49	1.17 (0.87, 1.57)	1.01 (0.75, 1.36)	
	50-59	1.57 (1.19, 2.07)	1.07 (0.81, 1.43)	
	60-69	2.04 (1.52, 2.74)	1.25 (0.91, 1.70)	
	70+	4.71 (3.50, 6.33)	2.89 (2.10, 3.99)	
AJCC pathologic stage	I	1	1	<.0001
	IIA	2.75 (2.00, 3.80)	2.05 (1.46, 2.87)	
	IIB	3.49 (2.58, 4.73)	2.31 (1.66, 3.22)	
	III	6.18 (5.17, 7.38)	4.76 (3.79, 5.98)	
	IVA	16.95 (13.31, 21.59)	10.07 (7.54, 13.46)	
Surgical margin	No residual	1	1	<.0001
	Residual	3.33 (2.74, 4.06)	1.80 (1.45, 2.24)	
	Unknown	1.89 (1.45, 2.48)	1.38 (1.04, 1.83)	
Grade	I (well differentiated)	1	1	.0017
	II (moderately differentiated)	1.30 (0.98, 1.72)	1.19 (0.88, 1.61)	
	III (poorly differentiated)	1.63 (1.20, 2.22)	1.41 (1.01, 1.95)	
	IV (undifferentiated)	4.69 (2.32, 9.50)	3.21 (1.56, 6.60)	
	Missing	0.62 (0.45, 0.87)	0.96 (0.68, 1.37)	
Adjuvant treatment	No adjuvant	1	1	.0381
	Adjuvant CCRT	3.41 (2.84, 4.09)	0.96 (0.76, 1.22)	
	Adjuvant sequential CT and RT	5.66 (4.17, 7.70)	1.52 (1.08, 2.15)	
	Adjuvant RT	2.92 (2.40, 3.56)	1.11 (0.88, 1.41)	
IC brachytherapy		2.81 (2.41, 3.27)	1.14 (0.92, 1.50)	.1307
Year of diagnosis	2007-2009	1	1	.0553
	2010-2012	1.05 (0.88, 1.25)	0.86 (0.72, 1.02)	
	2013-2015	0.96 (0.77, 1.21)	0.77 (0.61, 0.97)	
CCI score	0	1.00	1	<.0001
	1	1.52 (1.24, 1.85)	1.24 (1.00, 1.53)	
	2+	2.27 (1.79, 2.88)	1.76 (1.37, 2.28)	
Income	<NTD 18,000	1	1	.0051
	NTD 18,000-22,500	0.78 (0.65, 0.94)	0.74 (0.61, 0.89)	
	NTD 22,500-30,000	0.73 (0.57, 0.95)	0.73 (0.62, 0.85)	
	NTD 30,000+	0.72 (0.58, 0.88)	0.72 (0.58, 0.89)	
Hospital level	Medical center	1	1	.0422
	Nonmedical center	1.36 (1.16, 1.59)	1.19 (1.01, 1.41)	
Region	North	1	1	.2881
	Central	1.06 (0.86, 1.30)	1.05 (0.85, 1.30)	
	South/East	1.31 (1.10, 1.55)	1.16 (0.96, 1.39)	

*All the variables included in **Table 2** were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; Gy, gray; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; MG, milligrams; HR, hazard ratio; CI, confidence intervals; NTD, New Taiwan dollar; IC, intracavitary; AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiotherapy.

cervical ADC relative to SCC. In addition, clinical stage IIB for cervical ADC is usually underestimated; up-pathologic stages were identified in 62.2% of patients.

The results of multivariate Cox regression analysis indicated that the pathologic type of ADC, age ≥ 70 years, advanced AJCC pathologic stage, positive margin, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential CT and RT, earlier year of diagnosis, CCI = 1, CCI ≥ 2, low income level, and treatment at a nonmedical center were significant independent poor prognostic factors for all-cause mortality in CC treated with curative surgery (**Table 2**). Cervical ADC with curative surgery (adjusted HR [aHR], 2.34; 95% confidence interval [CI], 1.96-2.79) was a significant independent prognostic factor for OS (*P* <.0001) (**Table 2**). The aHRs (95% CIs) of age ≥ 70 years and AJCC pathologic stages IIA, IIB, III, and IVA were 2.89 (2.10-3.99), 2.05 (1.46-2.87), 2.31 (1.66-3.22), 4.76 (3.79-5.98), and 10.07 (7.54-13.46), respectively. The aHRs (95% CIs) of positive margin, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential CT and RT, 2013-2015 as year of diagnosis, CCI = 1, CCI ≥ 2, higher income (≥ 30,000 NTD), and treatment at a nonmedical center were 1.80 (1.45-2.24), 1.41 (1.01-1.95), 3.21 (1.56-6.60), 1.52 (1.08-2.15), 0.77 (0.61-0.97), 1.24 (1.00-1.53), 1.76 (1.37-2.28), 0.72 (0.58, 0.89), and 1.19 (1.01-1.41), respectively.

Stratified analyses were performed to evaluate the risk of mortality among patients for different AJCC pathologic stages, and a stratified Cox proportional hazard model was used to analyze the risk of mortality associated with different pathologic stages (**Table 3**). After adjustment for the pathologic type, age, AJCC pathologic stage, surgical margin, grade of differentiation, adjuvant treatment, intracavitary brachytherapy, year of diagnosis, CCI score, income level, hospital level, and hospital area, the aHRs (95% CIs) of pathologic stage I-IIA for overall mortality in ADC, age ≥ 70 years, pathologic stage IIA, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential CT and RT, CCI = 1, and CCI ≥ 2 were 1.93 (1.45-2.57), 3.68 (2.32-5.82), 1.62 (1.14, 2.31), 2.02 (1.23-3.32), 1.96 (1.45-3.46), 2.83 (1.30-6.16), 1.62 (1.20-2.20), and 2.56 (1.82-3.60), respectively (**Table 3**). In pathologic stages IIB-IVA, the aHRs (95% CIs) of ADC, age ≥ 70 years, pathologic stage III, pathologic stage IVA, positive margin, poorly differentiated cancer, undifferentiated cancer, adjuvant CCRT, 2013-2015 year of diagnosis, and income ≥ 30,000 NTD were 2.59 (2.05-3.28), 2.00 (1.27-3.16), 1.79 (1.30-2.45), 3.79 (2.62-5.47), 2.08 (1.61-2.69), 1.09 (1.01-1.41), 2.77 (1.17-6.52), 0.70 (0.53-0.92), 0.71 (0.53-0.96), and 0.73 (0.55-0.98), respectively (**Table 3**).

Stratified Cox proportional hazard model results for the risks of all-cause mortality, LRR, and DM are presented in **Table 4**. Without stratification by stage, patients with cervical ADC had higher all-cause mortality and DM; aHRs (95% CIs) were 2.34 (1.96-2.79) and 2.16 (1.75-2.66) for all-cause mortality and DM (**Table 4**), respectively. After multivariate analysis, patients with pathologic stages I-IIA cervical ADC had higher all-cause mortality, with aHRs (95% CIs) of 1.93 (1.45-2.57) and 2.50 (1.78-3.51) for all-cause mortality and DM, respectively. Patients with pathologic stages IIB-IVA cervical ADC also had higher all-cause mortality, with aHRs (95% CIs) of 2.59 (2.05-3.28) and 1.84 (1.39-2.42) for all-cause mortality and DM, respectively (**Table 4**).

Kaplan-Meier OS curves for patients with ADC or SCC at all pathologic stages, stage I-IIA, and IIB-IVA are provided in **Figure 1**. The OS rate was higher for patients with cervical SCC (log-rank test: *P*<.0001, *P* = .0059, and *P*<0.0001, respectively). The 5-year OS rates of patients with cervical SCC or ADC who received CCRT were 90% and 80%, 95% and 92%, and 74% and 42% for all pathologic stages, stages I-IIA, and stages IIB-IVA, respectively (Supplementary Table 2).

The matching process yielded a final cohort of 2479 patients (1218 vs. 667 patients with cervical SCC or cervical ADC at pathologic stages I-IIA and 384 vs. 210 patients with cervical SCC or cervical ADC at pathologic stages IIB-IVA) eligible for further analysis. Patient characteristics for PSM were identified, and all confounders were well matched (Supplementary Table 3). Cox proportional hazard regression analysis of the all-cause mortality, LRR, and DM of our PSM cohorts with cervical SCC or ADC was conducted (Supplementary Table 4). After PSM, the trends for all-cause death, LRR, and DM were similar to those in the non-PSM cohort (**Table 4**). Patients with cervical ADC who received curative surgery had higher all-cause death and DM than those with cervical SCC at both early and advanced pathologic stages. No sig-

Table 3. Results of Cox proportional hazard regression analysis of the risk of all-cause mortality, stratified by AJCC pathologic stage

		Stages I-IIA		Stages IIB-IV	
		Adjusted HR (95% CI)	*P*-value	Adjusted HR* (95% CI)	*P*-value
Pathologic type	SCC	1	<.0001	1	<.0001
	Adenocarcinoma	1.93 (1.45, 2.57)		2.59 (2.05, 3.28)	
Age	0-39	1	<.0001	1	.0019
	40-49	0.72 (0.46, 1.15)		1.20 (0.81, 1.79)	
	50-59	0.86 (0.55, 1.34)		1.09 (0.75, 1.60)	
	60-69	1.49 (0.94, 2.36)		0.99 (0.64, 1.52)	
	70+	3.68 (2.32, 5.82)		2.00 (1.27, 3.16)	
AJCC pathologic stage	I	1	.0075	-	<.0001
	IIA	1.62 (1.14, 2.31)		-	
	IIB	-		1	
	III	-		1.79 (1.30, 2.45)	
	IVA	-		3.79 (2.62, 5.47)	
Surgical margin	No residual	1	.5868	1	<.0001
	Residual	1.16 (0.72, 1.88)		2.08 (1.61, 2.69)	
	Unknown	1.23 (0.79, 1.92)		1.47 (1.01, 2.12)	
Grade	I (well differentiated)	1	.0007	1	.0305
	II (moderately differentiated)	1.46 (0.92, 2.31)		0.93 (0.62, 1.38)	
	III (poorly differentiated)	2.02 (1.23, 3.32)		1.09 (1.01, 1.41)	
	IV (undifferentiated)	1.96 (1.45, 3.46)		2.77 (1.17, 6.52)	
	Missing	0.90 (0.54, 1.52)		1.07 (0.66, 1.75)	
Adjuvant treatment	No adjuvant	1	.0747	1	.0558
	Adjuvant CCRT	1.05 (0.67, 1.63)		0.70 (0.53, 0.92)	
	Adjuvant sequential CT and RT	2.83 (1.30, 6.16)		0.95 (0.64, 1.40)	
	Adjuvant RT	1.03 (0.72, 1.47)		0.84 (0.61, 1.14)	
Intracavitary brachytherapy		1.93 (0.40, 2.67)	.3301	0.87 (0.69, 1.09)	.2309
Year of diagnosis	2007-2009	1	.3536	1	.0755
	2010-2012	0.82 (0.62, 1.09)		0.95 (0.75, 1.20)	
	2013-2015	0.99 (0.68, 1.43)		0.71 (0.53, 0.96)	
CCI score	0	1.00	<.0001	1	.6955
	1	1.62 (1.20, 2.20)		0.97 (0.71, 1.32)	
	2+	2.56 (1.82, 3.60)		1.18 (0.78, 1.79)	
Income	<NTD 18,000	1	.1167	1	.1359
	NTD 18,000-22,500	0.72 (0.54, 0.97)		0.84 (0.64, 1.09)	
	NTD 22,500-30,000	0.67 (0.43, 1.05)		0.99 (0.71, 1.37)	
	NTD 30,000+	0.83 (0.60, 1.15)		0.73 (0.55, 0.98)	
Hospital level	Medical center	1	.0717	1	.2800
	Other	1.27 (0.98, 1.64)		1.13 (0.90, 1.42)	
Area	North	1	.3236	1	.6597
	Central	1.04 (0.76, 1.44)		0.98 (0.73, 1.31)	
	South/East	1.23 (0.93, 1.62)		1.11 (0.87, 1.41)	

*All the variables included in **Table 2** were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; Gy, gray; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; MG, milligrams; HR, hazard ratio; CI, confidence intervals; NTD, New Taiwan dollar; IC, intracavitary; AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiotherapy.

nificant difference was observed in LRR for either early or advanced pathologic stages.

Supplementary Figure 1 presents the survival curves for all-cause death, as calculated using

Table 4. Results of Cox proportional hazard model for the risk of all-cause mortality, locoregional recurrence, and distant metastasis, stratified by AJCC pathologic stage

AJCC pathologic stage	Event	Pathologic type	Patient (n)	Event (n) (%)	Adjusted HR* (95% CI)	*P*-value
All patients	All-cause mortality	SCC	3588	451 (12.57)	1	<.0001
		Adenocarcinoma	1040	222 (21.35)	2.34 (1.96, 2.79)	
	Locoregional recurrence	SCC	3588	301 (8.39)	1	.2905
		Adenocarcinoma	1040	90 (8.65)	1.15 (0.89, 1.49)	
	Distant metastasis	SCC	3588	283 (7.89)	1	<.0001
		Adenocarcinoma	1040	159 (15.29)	2.16 (1.75, 2.66)	
Stages I-IIA	All-cause mortality	SCC	2790	206 (7.38)	1	<.0001
		Adenocarcinoma	788	79 (10.03)	1.93 (1.45, 2.57)	
	Locoregional recurrence	SCC	2790	207 (7.42)	1	.9737
		Adenocarcinoma	788	52 (6.60)	1.01 (0.72, 1.41)	
	Distant metastasis	SCC	2790	103 (3.69)	1	<.0001
		Adenocarcinoma	788	68 (8.63)	2.50 (1.78, 3.51)	
Stages IIB-IVA	All-cause mortality	SCC	798	245 (30.70)	1	<.0001
		Adenocarcinoma	252	143 (56.75)	2.59 (2.05, 3.28)	
	Locoregional recurrence	SCC	798	94 (11.78)	1	.2891
		Adenocarcinoma	252	38 (15.08)	1.26 (0.82, 1.92)	
	Distant metastasis	SCC	798	180 (22.56)	1	<.0001
		Adenocarcinoma	252	91 (36.11)	1.84 (1.39, 2.42)	

*All the variables included in **Table 2** were used in the multivariate analysis. SCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence intervals; AJCC, American Joint Committee on Cancer.

the Kaplan-Meier method, for the PSM cohort in different stages. After PSM, those with cervical SCC still exhibited superior OS for all pathologic stages, stages I-IIA, and stages III-IVA.

Discussion

No large-scale, head-to-head study estimating outcome patterns for cervical ADC and SCC treated with curative surgery has been conducted. Our study is the first to describe and compare the failure and survival patterns of patients with different pathologic types of CC who received surgery. Our findings can be confirmed in further research on CC with SCC or ADC types. According to our literature review, this study is the largest cohort study to estimate predictors, patterns of failure, and survival for cervical ADC and SCC treated with surgery. PSM was also used to control for numerous confounders.

The significant characteristics of cervical ADC and SCC treated with curative surgery are compatible with those reported in previous studies, including younger age and higher income level of patients with ADC than those with SCC [17-19]. However, significant clinical characteristics not mentioned in previous reports were also identified, including the gradual increase in the incidence of cervical ADC in recent years, high inconsistency in clinic and pathologic stages of ADC, more advanced pathologic stages of ADC, more well-differentiated and undifferentiated ADC, more adjuvant CCRT for patients with ADC at early pathologic stages, more positive margin with ADC, higher prevalence of ADC in northern Taiwan, and more patients with ADC who underwent surgery at a medical center relative to patients with cervical SCC. A higher proportion of ADC patients with a positive margin and adjuvant CCRT might be associated with more advanced pathologic stages in ADC patients compared with SCC patients (**Table 1**). That cervical ADC was associated with higher income levels, living in northern Taiwan, and surgery at medical centers may be because northern Taiwanese people are wealthier than southern Taiwanese people [20]. The most notable clinical findings of our study were the stage variation from FIGO stage to AJCC pathologic stage, especially for cervical ADC at FIGO stage IIB (Supplementary Table 1). FIGO stages IIB of cervical ADC were usually underestimated, with 62.2% up-staging. This inconsistency and underestimation in FIGO and pathologic

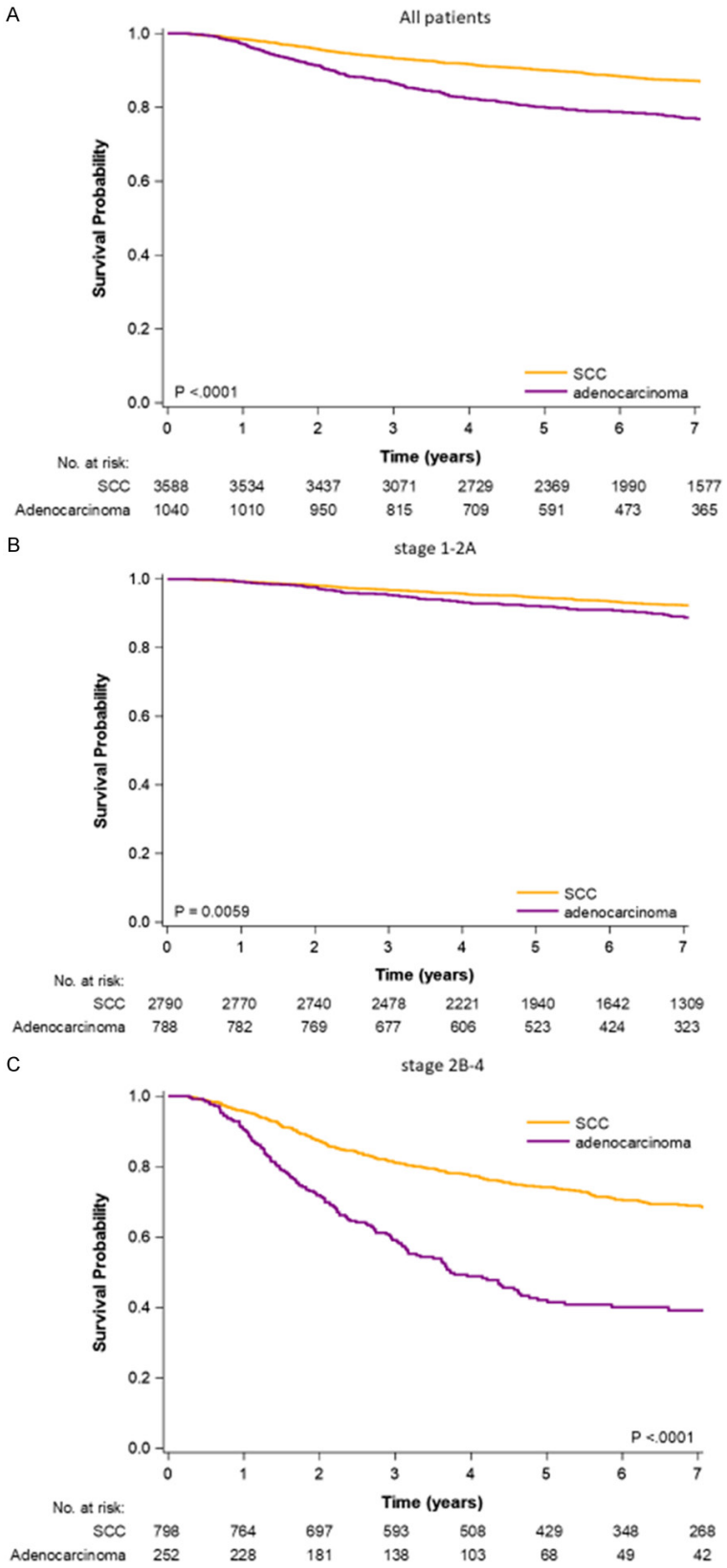

Figure 1. Kaplan-Meier survival curves of all-cause death for patients with cervical adenocarcinoma or squamous cell carcinoma who received curative surgery. A. All study patients. B. AJCC pathologic stages I-IIA. C. AJCC pathologic stages IIB-IV.

stages in cervical ADC is a novel finding. The clinical FIGO stages of cervical ADC were underestimated, which may partially explain why patients with cervical ADC at early clinic stages receiving RT or CCRT had poorer survival than those with cervical SCC [4, 5, 21].

We also estimated predictors of all-cause mortality using Cox proportional hazard regression analysis. The risk factors identified were ADC, age ≥ 70 years, advanced pathologic stage (with aHRs increasing gradually from IIA to IVA), positive margin, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential CT and RT, earlier year of diagnosis, high CCI, low income, and nonmedical center treatment. These factors were compatible with those described in previous studies, for example, ADC, old age, advanced stages, positive margin, poorly differentiated cancer, undifferentiated cancer, and earlier year of diagnosis [22-29]. However, age ≥ 70 years, low income level, CCI = 1 or ≥ 2, and treatment at nonmedical centers have been reported for first time. The higher risk of all-cause mortality for treatment at a nonmedical center might be associated with the hospital case volume [30-32]. That adjuvant sequential CT and RT were poor prognostic factors for survival may be because adjuvant sequential CT and RT are insufficient adjuvant treatments for CC patients with high pathologic risk factors when compared with adjuvant CCRT or adjuvant RT [33-35].

Cox proportional hazard regression analysis stratified by AJCC pathologic early and advanced stages was conducted for examining the risk of all-

cause mortality (**Table 3**). The risk factors were similar to non-stage-stratified outcomes. The risk factors for pathologic stages I-IIA were ADC, age ≥ 70 years, CCI = 1, CCI ≥ 2, pathologic stage IIA, poorly differentiated cancer, undifferentiated cancer, adjuvant sequential CT and RT, and low income level. The predictors in pathologic stage I-IIA CC were similar to all stages-CC (**Tables 2** and **3**). No significant differences in medical versus nonmedical center, year of diagnosis, or positive margin were noted, possibly because they might be associated with adjuvant treatments, which could cover these risk factors at early pathologic stages (**Table 3**) [5, 36]. In advanced pathologic stages, adjuvant CCRT results in better OS of pathologic IIB-IVA CC, which is compatible with the finding of previous studies [5, 36]. Our results support that adjuvant CCRT is an effective adjuvant treatment for advanced pathologic stage CC (**Table 3**). Other nonsignificant factors, including high CCI, high grade of differentiated cancer, and treatment at a nonmedical center might be associated with the relatively small sample size of patients with pathologic stage IIB-IVA CC (798 SCC and 252 ADC cases) compared with early pathologic stage CC (**Table 1**).

Figure 1 displays Kaplan-Meier survival curves of all-cause death for patients with cervical ADC or SCC who received curative surgery. Although curative surgery is generally preferred over CCRT for cervical ADC [4, 21], this surgery resulted in inferior OS compared with SCC at all-stages, pathologic stages I-IIA, and stages IIB-IVA CC (**Figure 1** and Supplementary Table 2). The distances between the survival curves of SCC and ADC were larger in advanced pathologic stages than in early pathologic stages (**Figure 1B** and **1C**). Thus, relative to those with SCC, the OS of patients with ADC was poorer at advanced pathologic stages than at early pathologic stages (**Figure 1**). In early pathologic stages, the 5-year OS of SCC and ADC was similar (95% and 92%, respectively). By contrast, 5-year OS was poor for ADC at pathologic stages IIB-IVA relative to SCC (74% and 42%, respectively). The median OS of cervical ADC treated with curative surgery was only 3.73 years. According to our results, curative surgery with adjuvant treatments for cervical ADC is not optimal in improving OS. Other clinical trials with novel therapy would be necessary for advanced-stage cervical ADC.

Analysis stratified by the AJCC pathologic stage was performed to determine the risks of all-cause mortality, LRR, and DM (**Table 4**). In previous studies, radioresistance and higher LRR were noted for cervical ADC than for cervical SCC [5, 37]. In our study, curative surgery improved LRR for cervical ADC, and no significance differences were observed in LRR between the groups (**Table 4**) in either early or advanced pathologic stages. However, OS and DM were poorer for ADC. Curative surgery could improve LRR, but not OS or DM rates, for cervical ADC. Finding new therapeutic modalities to reduce the high DM rate in patients with cervical ADC is essential to improving OS. New therapeutic strategies such as induction CT with novel regimens, induction CCRT, or adjuvant CT with nonplatinum-based regimens might decrease DM and improve OS [38-42].

Many risk factors for all-cause death in patients with CC who received curative surgery were identified (**Table 2**). Therefore, we conducted a PSM cohort study to match the risk factors to estimate the outcome patterns of patients with cervical ADC or SCC with early or advanced pathologic types who received curative surgery (Supplementary Table 3). All covariates were matched well. After PSM, the outcomes (Supplementary Table 4) were similar to those of the non-PSM cohort (**Table 4**). We created non-PSM and PSM cohorts to compare clinical characteristics, risk factors of survival, and head-to-head outcomes patterns of cervical ADC and SCC (**Tables 1**, **2** and Supplementary Table 4). An advantage of our study is its view on overall characteristics of cervical SCC and ADC (**Tables 1** and **2**) and the effects of curative surgery after PSM with all covariates controlled for (Supplementary Table 3). The survival curves of ADC and SCC for the PSM cohort were also similar with those of the non-PSM cohort (**Figure 1** and Supplementary Figure 1). The distance of the survival curves was larger in advanced than in early pathologic stages. The finding means curative surgery for cervical ADC at early pathologic stages would be more helpful for OS than curative surgery for cervical ADC at advanced pathologic stages. Although curative surgery was performed for cervical ADC with advanced pathologic stages, OS remained poor (Supplementary Figure 1 and Supplementary Table 2). Hence, new translational medicine studies must be conducted to combine basic and clinic data and uncover

novel therapeutic strategies to overcome DM and further improve OS, because most failure patterns are associated with DM rather than LRR after curative surgery (Supplementary Table 4).

The strength of our study is the size of the cohorts, which allowed estimation of outcomes patterns of curative surgery for cervical SCC and ADC, including OS, LRR, and DM. The treatment was homogenous in our study, as curative surgical procedures were consistent. PSM was also conducted to eliminate possible confounders (Supplementary Table 3), preserve clinical characteristics (**Table 1**), and further evaluate the outcomes patterns (**Table 4** and Supplementary Table 4). The outcomes patterns for cervical ADC differed markedly from those of cervical SCC. Curative surgery might be suitable for patients with cervical SCC but might be insufficient for those with cervical ADC (Supplementary Table 2). Cervical ADC is unique regarding both OS and DM, and treatment should be modified accordingly. The patterns of failure in cervical ADC are related to DM; no significant differences were observed in LRR (**Table 4** and Supplementary Table 4). Novel therapeutic modalities such as novel CT regimens or other effective systemic treatments in a neoadjuvant or adjuvant setting to decrease DM would be necessary for patients with cervical ADC who received curative surgery [38-43]. These findings could be considered in future clinical practice and randomized controlled studies.

This study has limitations. First, because all the patients were enrolled from an East Asian population, corresponding ethnic susceptibility remains unclear; our results should be cautiously extrapolated to other populations. No evidence indicates differences between populations in outcomes following curative surgery for CC. Second, the diagnoses of all comorbid conditions were based on ICD-9-CM codes. Nevertheless, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of the diagnoses, and hospitals with outlier charges or practices may be audited and subsequently heavily penalized if malpractice or discrepancies are identified. Third, toxicity induced by curative surgeries and adjuvant treatments for advanced stages of CC could not be determined; therefore, treatment-related mortality estimates may have been biased. However, we conducted a PSM cohort study with well-matched stages and adjuvant treatments, and the outcomes were compatible to those of our non-PSM cohort. Accordingly, to obtain crucial information on population specificity and disease occurrence, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential. Finally, the Taiwan Cancer Registry database does not contain information regarding dietary habits, socioeconomic status, or body mass index, all of which may be risk factors for mortality. However, considering the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to affect the conclusions.

Conclusion

Curative surgery for patients with cervical ADC was associated with poorer OS and higher DM rates than those with cervical SCC, but no significant differences were observed in LRR at early or advanced pathologic stages. Novel therapeutic strategies are necessary for reducing DM in patients with cervical ADC who receive curative surgery.

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Disclosure of conflict of interest

None.

Abbreviations

aHR, adjusted hazard ratio; CCRT, concurrent chemoradiotherapy; Gy, gray; US, United States; SCC, squamous cell carcinoma; ADC, adenocarcinoma; HR, hazard ratio; CI, confidence intervals; FIGO, the International Federation of Gynecology and Obstetrics; LRR, locoregional recurrence; DM, distant metastasis; NCCN, National Comprehensive Cancer Network; CC, cervical cancers; SEER, Surveillance, Epidemiology and End Results; CT, chemotherapy; RT, radiotherapy; OS, overall survival; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; ICD-9-CM, International Cl-

assification of Diseases, Ninth Revision, Clinical Modification; PSM, Propensity scores matched; AJCC, The American Joint Committee on Cancer.

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Supplementary Table 1. Stage variation from FIGO stage to AJCC pathologic stage

FIGO stage		*All patients* (N = 4628)	*SCC* (N = 3588)	*Adenocarcinoma* (N = 1040)	*P*-value
		n (%)	n (%)	n (%)	
Stage I	Unchanged pathologic stage	3234 (81.0)	2512 (81.2)	722 (80.2)	.5038
	Up-pathologic stage	759 (19.0)	581 (18.8)	178 (19.8)	
Stage IIA	Down-pathologic stage	78 (21.3)	63 (20.9)	15 (23.1)	.7841
	Unchanged pathologic stage	162 (44.3)	132 (43.9)	30 (46.2)	
	Up-pathologic stage	126 (34.4)	106 (35.2)	20 (30.8)	
Stage IIB	Down-pathologic stage	19 (12.6)	13 (11.4)	6 (16.2)	.0005
	Unchanged pathologic stage	74 (49.0)	66 (57.9)	8 (21.6)	
	Up-pathologic stage	58 (38.4)	35 (30.7)	23 (62.2)	
Stage III-IVA	Down-pathologic stage	12 (10.2)	74 (92.5)	35 (92.1)	.4774
	Unchanged pathologic stage	97 (82.2)			
	Up-pathologic stage	9 (7.6)	6 (7.5)	3 (7.9)	

SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics.

Supplementary Table 2. Survival rate of all-cause mortality by the Kaplan-Meier method

	Patient (n)	Event (n) (%)	Survival rate			Survival time (month)	
			1 y	3 y	5 y	Median	95% CI
All patients							
SCC	3588	451 (12.57)	.98	.93	.90		
Adenocarcinoma	1040	222 (21.35)	.97	.87	.80		
AJCC pathologic Stages I-IIA							
SCC	2790	206 (7.38)	.99	.97	.95	-	
Adenocarcinoma	788	79 (10.03)	.99	.95	.92	-	
AJCC pathologic Stages IIB-IVA							
SCC	798	245 (30.70)	.96	.81	.74	-	-
Adenocarcinoma	252	143 (56.75)	.90	.59	.42	3.73	(3.16, 4.66)

SCC, squamous cell carcinoma; CI, confidence intervals; AJCC, American Joint Committee on Cancer.

Supplementary Table 3. Patient Characteristics of the propensity score matching cohort

		AJCC pathologic stages I-IIA			AJCC pathologic stages IIB-IVA		
		SCC (N = 1218)	*Adenocarcinoma* (N = 667)	*P*-value	*SCC* (N = 384)	*Adenocarcinoma* (N = 210)	*P*-value
		n (%)	n (%)		n (%)	n (%)	
Age, years	0-39	213 (17.5)	119 (17.8)	-	44 (11.5)	23 (11.0)	-
	40-49	437 (35.9)	246 (36.9)		107 (27.9)	59 (28.1)	
	50-59	372 (30.5)	198 (29.7)		147 (38.3)	78 (37.1)	
	60-69	152 (12.5)	82 (12.3)		72 (18.8)	40 (19.0)	
	70+	44 (3.6)	22 (3.3)		14 (3.6)	10 (4.8)	
AJCC pathologic stage	1	1156 (94.9)	633 (94.9)	-			
	2A	62 (5.1)	34 (5.1)				
	2B				45 (11.7)	24 (11.4)	-
	3				289 (75.3)	151 (71.9)	
	4				50 (13.0)	35 (16.7)	
Year of diagnosis	2007-2009	438 (36.0)	207 (31.0)	.1483	122 (31.8)	62 (29.5)	.8714
	2010-2012	443 (36.4)	266 (39.9)		154 (40.1)	86 (41.0)	
	2013-2015	337 (27.7)	194 (29.1)		108 (28.1)	62 (29.5)	
Grade	I (well differentiated)	126 (10.3)	118 (17.7)	.1478	14 (3.6)	11 (5.2)	.9974
	II (moderately differentiated)	654 (53.7)	331 (49.6)		243 (63.3)	129 (61.4)	
	III (poorly differentiated)	194 (15.9)	98 (14.7)		91 (23.7)	51 (24.3)	
	IV (undifferentiated)	8 (0.7)	5 (0.7)		36 (9.4)	19 (9.1)	
	Missing	236 (19.4)	115 (17.2)		0	0	
Surgical margin	No residual	1124 (92.3)	615 (92.2)	.8654	291 (75.8)	159 (75.7)	.9009
	Residual	35 (2.9)	17 (2.5)		67 (17.4)	38 (18.1)	
	Unknown	59 (4.8)	35 (5.2)		26 (6.8)	13 (6.2)	
Adjuvant treatment	Adjuvant CCRT	101 (8.3)	61 (9.1)	.9998	204 (53.1)	104 (49.5)	.8408
	Adjuvant sequential CT and RT	15 (1.2)	10 (1.5)		35 (9.1)	26 (12.4)	
	Adjuvant RT	156 (12.8)	83 (12.4)		70 (18.2)	38 (18.1)	
	No adjuvant	946 (77.7)	513 (76.9)		75 (19.5)	42 (20.0)	
RT cumulative dose	No RT	961 (78.9)	523 (78.4)	.7930	110 (28.6)	68 (32.4)	.4556
	<50 Gy	119 (9.8)	70 (10.5)		109 (28.4)	65 (31.0)	
	50+ Gy	138 (11.3)	74 (11.1)		165 (43.0)	77 (36.7)	
Platinum cumulative dose	No CT	1102 (90.5)	596 (89.4)	.7525	145 (37.8)	80 (38.1)	.9099
	<500 MG	70 (5.7)	38 (5.7)		115 (29.9)	66 (31.4)	
	500+ MG	46 (3.8)	33 (4.9)		124 (32.3)	64 (30.5)	

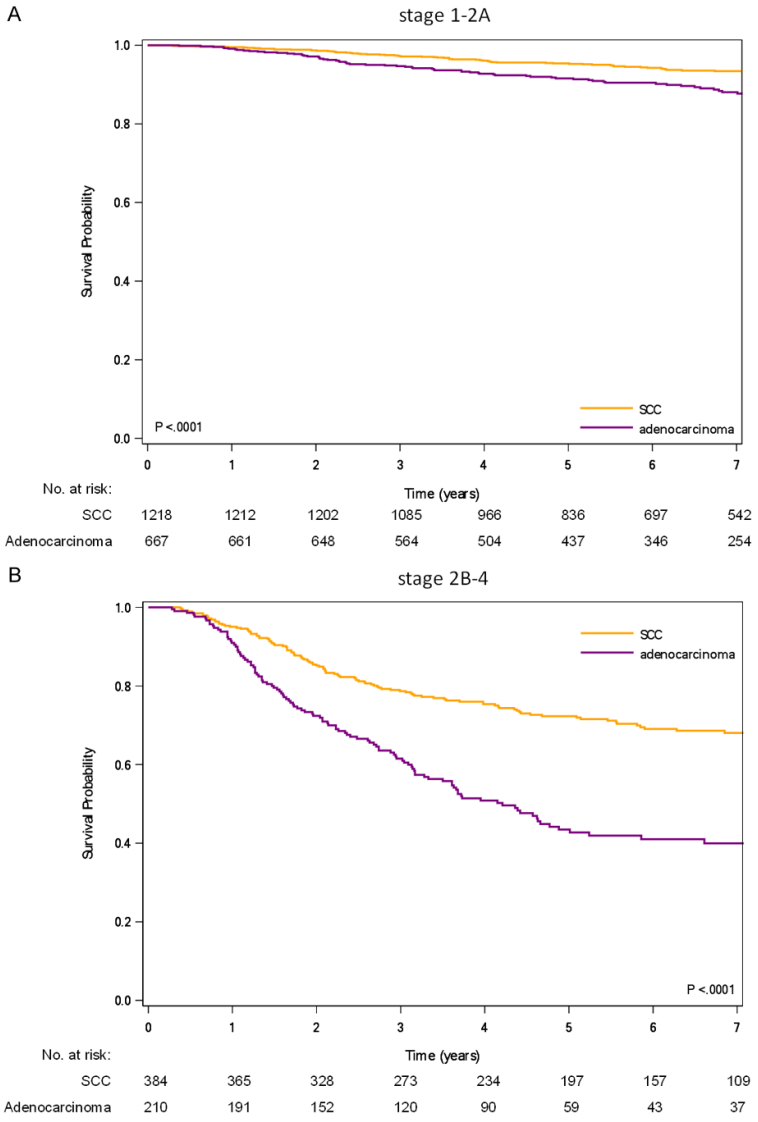
Intracavitary brachytherapy dose	No intracavitary brachytherapy	935 (76.8)	518 (77.7)	.6904	123 (32.0)	73 (34.8)	.8960
	<2500 cGy	233 (19.1)	127 (19.0)		212 (55.2)	110 (52.4)	
	2500+ cGy	50 (4.1)	22 (3.3)		49 (12.8)	27 (12.9)	
CCI Scores	0	1012 (83.1)	546 (81.9)	.5622	314 (81.8)	167 (79.5)	.9380
	1	148 (12.2)	85 (12.7)		44 (11.5)	28 (13.3)	
	2+	58 (4.8)	36 (5.4)		26 (6.8)	15 (7.1)	
Income	<NTD 18,000	250 (20.5)	132 (19.8)	.8744	94 (24.5)	54 (25.7)	.8204
	NTD 18,000-22,500	440 (36.1)	232 (34.8)		133 (34.6)	70 (33.3)	
	NTD 22,500-30,000	175 (14.4)	98 (14.7)		59 (15.4)	28 (13.3)	
	NTD 30,000+	353 (29.0)	205 (30.7)		98 (25.5)	58 (27.6)	
Hospital level	Medical center	899 (73.8)	488 (73.2)	.8751	272 (70.8)	150 (71.4)	.9226
	Other	319 (26.2)	179 (26.8)		112 (29.2)	60 (28.6)	
Hospital area	North	642 (52.7)	358 (53.7)	.9741	194 (50.5)	105 (50.0)	.7100
	Central	239 (19.6)	131 (19.6)		75 (19.5)	46 (21.9)	
	South/East	337 (27.7)	178 (26.7)		115 (29.9)	59 (28.1)	

CCRT, concurrent chemoradiotherapy; cGy, centigray; Gy, gray; SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; CT, chemotherapy; RT, radiotherapy; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; MG, milligrams; SD, standard deviation; IQR, interquartile range; NTD, New Taiwan dollar, AJCC, American Joint Committee on Cancer.

Supplementary Table 4. Results of Cox proportional hazard regression analysis of the propensity score matched cohort

AJCC pathologic stage	Event	Pathologic type	Patient (n)	Event (n) (%)	Adjusted HR (95% CI)	*P*-value
Stages 1-2A	All-cause mortality	SCC	1218	73 (5.99)	ref.	<.0001
		Adenocarcinoma	667	72 (10.79)	2.06 (1.48-2.88)	
	Locoregional recurrence	SCC	1218	92 (7.55)	ref.	.8558
		Adenocarcinoma	667	46 (6.90)	0.97 (0.67-1.39)	
	Distant metastasis	SCC	1218	50 (4.11)	ref.	<.0001
		Adenocarcinoma	667	60 (9.00)	2.75 (1.86-4.05)	
Stages 2B-4	All-cause mortality	SCC	384	116 (30.21)	ref.	<.0001
		Adenocarcinoma	210	117 (55.71)	2.54 (1.94-3.32)	
	Locoregional recurrence	SCC	384	49 (12.76)	ref.	.8027
		Adenocarcinoma	210	30 (14.29)	1.06 (0.66-1.72)	
	Distant metastasis	SCC	384	93 (24.22)	ref.	<.0001
		Adenocarcinoma	210	79 (37.62)	1.89 (1.39-2.57)	

*All the variables included in Supplemental Table 3 were used in the multivariate analysis. HR, hazard ratio; CI, confidence intervals; AJCC, American Joint Committee on Cancer.



Supplementary Figure 1. Kaplan-Meier survival curves for all-cause death in the propensity score matched cohort. A. Stages I-IIA. B. Stages IIB-IVA.