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Original Article

Overall survival, locoregional recurrence, and distant metastasis of definitive concurrent chemoradiotherapy for cervical squamous cell carcinoma and adenocarcinoma: before and after propensity score matching analysis of a cohort study

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Abstract: Purpose: To estimate the outcomes of definitive concurrent chemoradiotherapy (CCRT) for bulky or advanced-stage cervical squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Patients and methods: We enrolled patients who had been diagnosed as having cervical SCC or ADC and received definitive CCRT. A Cox regression analysis was performed to determine the hazard ratio (HR) and 95% confidence intervals (95% CI); independent predictors were stratified or controlled for in the analysis, and the endpoint was all-cause mortality among patients with cervical SCC and ADC who received CCRT. Propensity score matching was performed to create well-balanced groups. Results: we enrolled 3258 patients who had International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IVA cervical cancer without distant metastasis. Among them, 2927 patients with cervical SCC and 331 patients with cervical ADC received definitive CCRT. The results of multivariate Cox regression analysis indicated that ADC, advanced FIGO stage, no intracavitary brachytherapy, old age, earlier year of diagnosis, and higher comorbidity scores were significant independent poor prognostic factors of all-cause mortality in patients with cervical cancer who received definitive CCRT. Patients with cervical ADC who received definitive CCRT had higher all-cause mortality, locoregional recurrence (LRR), and distant metastasis (DM) (adjusted HR [95% CI]: 2.10 [1.79-2.46], 1.79 [1.35-2.37], and 1.97 [1.54-2.53] for all-cause mortality, LRR, and DM, respectively) compared with patients with cervical SCC who received CCRT. Conclusion: Definitive CCRT in patients with cervical ADC resulted in lower overall survival, higher LRR, and higher DM rate compared with patients with cervical SCC.

Keywords: Cervical cancer, squamous cell carcinoma, adenocarcinoma, concurrent chemoradiotherapy, survival

Introduction

Cervical adenocarcinoma (ADC) and squamous cell carcinoma (SCC) account for 25% and 75% of invasive cervical cancers (CCs), respectively [1]. In Taiwan, approximately 18% of all invasive CCs are cervical ADC [2]. Treatment for CC is mostly based on data from randomized trials in which the majority of subjects were patients with SCC; ADC comprises, on average, 10% of cases [3-5]. No study has reported separate outcomes for ADC, and no prospective study has focused on the treatment of ADC as the sole histology. Consequently, in most institutions, treatment for ADC follows the principles established for cervical SCC [3]. Furthermore, no studies have reported on the effects of different management approaches for cervical

ADC and SCC. Initial concurrent chemoradiotherapy (CCRT) rather than surgery is still recommended by the National Comprehensive Cancer Network (NCCN) guidelines in Taiwan for certain subsets of women with invasive cervical ADC, such as patients who display locoregionally advanced-stage IIB to IVA disease, bulky early-stage disease stage IB2-IIA, or evidence of lymph node involvement during imaging or clinical exams [3].

Whether histologic type is an independent prognostic factor in CC remains controversial [6-13]. After adjustment for the stage, some series have supported the prognostic equivalence of cervical ADC and cervical SCC [6-9], whereas others have reported that ADC has a less favorable prognosis [10-13]. One of the largest studies on CC from the Surveillance, Epidemiology, and End Results database, that comprised 77% and 17% patients with SCC and ADC, respectively [13], reported that women with early-stage CC (stage IB1 to IIA) and late-stage disease (stage IIB to IVA) ADC had a higher mortality risk than women with SCC. However, no further details were available regarding the outcomes of stages I-IV, locoregional recurrence (LRR), distant metastasis (DM), or the effects of various treatments for cervical ADC and SCC [13]. A few articles with small sample sizes (ADC < 100 patients) reported that patients with early-stage IB cervical ADC, identified according to the International Federation of Gynecology and Obstetrics (FIGO), who received surgery and adjuvant radiotherapy (RT) exhibited worse outcomes and higher distant metastasis rates [14, 15]. An intergroup trial in the United States compared CCRT and RT in 243 patients (50 patients with ADC) with resected stage IA2, IB, or IIA CC and high-risk features [16]. The subgroup analysis revealed that patients with ADC had a less favorable prognosis than patients with SCC when treated with RT alone [16]; however, we did not identify a difference between the patients with ADC and SCC who were concurrently treated with chemotherapy (CT) and RT. Therefore, treatments that combine CT and RT, such as CCRT, may be more effective for treating cervical ADC than RT alone [16].

Our literature review suggested that no large study has estimated the outcomes of definitive CCRT for bulky or advanced stages of cervical SCC and ADC in terms of overall survival, LRR, or DM. Prognostic factors have not been reported either. Therefore, we evaluated the prognostic factors, overall survival (OS), LRR, and DM of definitive CCRT at different stages of cervical SCC and ADC, and we evaluated whether the current definitive CCRT with the platinum-based regimen is also effective for cervical ADC.

Patients and methods

A cohort was established using data from the Taiwan Cancer Registry database. Patients who were diagnosed as having cervical SCC or ADC and received definitive CCRT between January 1, 2007, and December 31, 2015, were enrolled. The follow-up duration was from the index date to December 31, 2014. The Cancer Registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information for each patient, including the clinical stage, treatment modalities, pathology, radiation doses (dose of external beam radiotherapy [EBRT] and intracavitary brachytherapy), and CT regimens [17, 18]. The 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 were newly diagnosed as having cervical SCC or ADC were confirmed to have no other cancer. Patients were included if they had been diagnosed as having cervical SCC or ADC, they were aged ≥ 20 years, and if their datafile contained a FIGO staging system classification (clinical cancer stage IB-IVA were included). Patients with a history of cancer before cervical SCC or ADC, with DM, missing sex data, undergoing hypofractionation or stereotactic body RT, treated with non-platinum-based chemotherapy, with adenosquamous or small cell carcinoma, or with unclear staging data were excluded. Furthermore, patients with cervical SCC or ADC were excluded if they did not receive definitive CCRT, CT alone, RT alone, or surgical tumor resection.

Patients with CC were enrolled and categorized into two groups according to differences in pathology to compare their definitive CCRT outcomes. The median total dose and fraction size of RT were 52 and 2 Gy per fraction in SCC and ADC groups (**Table 1**). Comorbidities were scored using the Charlson comorbidity index (CCI) [19, 20]. Comorbidities noted within 6

Table 1. Characteristics of patients with cervical adenocarcinoma or squamous cell carcinoma who received definitive concurrent chemoradiotherapy

		Total (N = 3258)	*SCC (N = 2927)*	*Adenocarcinoma (N = 331)*	*P value*
		n (%)	*n (%)*	*n (%)*	
Age, years	Mean (SD)	57.6 (12.0)	57.9 (12.0)	55.3 (11.6)	.0001
	Median (min, max)	57.0 (25, 91)	57.0 (25, 91)	54.0 (28, 88)	
Age group	20-49	821 (25.2)	711 (24.3)	110 (33.2)	.0013
	50-59	1125 (34.5)	1013 (34.6)	112 (33.8)	
	60-69	685 (21.0)	622 (21.3)	63 (19.0)	
	≥ 70	627 (19.2)	581 (19.8)	46 (13.9)	
Year of diagnosis	2007-2009	1048 (32.2)	944 (32.3)	104 (31.4)	.1124
	2010-2012	1058 (32.5)	964 (32.9)	94 (28.4)	
	2013-2015	1152 (35.4)	1019 (34.8)	133 (40.2)	
FIGO stage	IB2	506 (15.5)	438 (15.0)	68 (20.5)	.0154
	II	1575 (48.3)	1426 (48.7)	149 (45.0)	
	III	764 (23.4)	699 (23.9)	65 (19.6)	
	IVA	413 (12.7)	364 (12.4)	49 (14.8)	
EBRT cumulative dose, Gy	Mean (SD)	51.8 (18.7)	51.9 (18.8)	50.8 (17.0)	.6814
	Median (Q1, Q3)	52 (38, 60)	52 (38, 60)	52 (37, 60)	
EBRT cumulative dose	< 50 Gy	1404 (43.1)	1262 (43.1)	142 (42.9)	.9402
	≥ 50 Gy	1854 (56.9)	1665 (56.9)	189 (57.1)	
Platinum cumulative dose, mg	Mean (SD)	558.3 (480.1)	555.3 (467.6)	584.2 (578.8)	.8719
	Median (IQR, Q1, Q3)	500 (300, 600)	490 (300, 600)	500 (300, 600)	
Platinum cumulative dose	< 500 mg	1628 (50.0)	1470 (50.2)	158 (47.7)	.3909
	≥ 500 mg	1630 (50.0)	1457 (49.8)	173 (52.3)	
IC Brachytherapy	No	554 (17.0)	485 (16.6)	69 (20.8)	.0497
	Yes	2704 (83.0)	2442 (83.4)	262 (79.2)	
IC Brachytherapy dose, cGy	Mean (SD)	2390.6 (675.8)	2405.0 (672.5)	2362.9 (692.9)	.1009
	Median (IQR, Q1, Q3)	2500 (2000, 3000)	2500 (2000, 3000)	2500 (2000, 3000)	
IC Brachytherapy dose	No IC Brachytherapy	554 (17.0)	485 (16.6)	69 (20.8)	.1124
	< 2500 cGy	1119 (34.3)	1005 (34.3)	114 (34.4)	
	≥ 2500 cGy	1585 (48.6)	1437 (49.1)	148 (44.7)	
CCI Scores	Mean (SD)	0.4 (0.9)	0.4 (0.9)	0.4 (0.9)	.4343
	0	2464 (75.6)	2220 (75.8)	244 (73.7)	.6608
	1	481 (14.8)	427 (14.6)	54 (16.3)	
	≥ 2	313 (9.6)	280 (9.6)	33 (10.0)	
Income	< 18,000 NTD	931 (28.6)	847 (28.9)	84 (25.4)	.0275
	18,000-22,500 NTD	1067 (32.8)	972 (33.2)	95 (28.7)	
	22,500-30,000 NTD	465 (14.3)	414 (14.1)	51 (15.4)	
	≥ 30,000 NTD	795 (24.4)	694 (23.7)	101 (30.5)	
Hospital type	Medical center	2391 (73.4)	2142 (73.2)	249 (75.2)	.4247
	others	867 (26.6)	785 (26.8)	82 (24.8)	
Hospital location	North	1629 (50.0)	1476 (50.4)	153 (46.2)	.0792
	Middle	710 (21.8)	622 (21.3)	88 (26.6)	
	South/East	919 (28.2)	829 (28.3)	90 (27.2)	
Mean of follow-up time, months (SD)		54.6 (35.5)	56.2 (35.4)	41.1 (33.6)	
Death		1264 (38.8)	1081 (36.9)	183 (55.3)	< .0001
Local recurrence		422 (13.0)	364 (12.4)	58 (17.5)	< .0001
Distant metastasis		503 (15.4)	428 (14.6)	75 (22.7)	< .0001

Gy, gray; cGy, centigray; SCC, squamous cell carcinoma; ADC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; mg, milligrams; SD, standard deviation; IQR, interquartile range; NTD, New Taiwan dollar; IC, intracavitary.

months before the index date were included. Comorbidities were identified on the basis of two separate diagnoses during visits to outpatient clinics and categorized according to the

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Significant independent predictors, such as age, CCI scores, FIGO clinical stage, year of diagnosis, RT cumulative dose, platinum cumulative dose, intracavitary brachytherapy dose, CCI Scores, income, hospital types, and hospital locations, were determined through multivariate Cox regression analysis to determine the hazard ratio (HR). Independent predictors were stratified or controlled for in the analysis, and the endpoint was all-cause mortality among patients with cervical SCC and ADC who received CCRT. The cumulative incidence of all-cause mortality was estimated using the Kaplan-Meier method, and differences between cervical SCC and ADC were determined according to a log-rank test. The Cox proportional hazards method was adjusted for confounders and used to model the time from the index date until all-cause mortality among patients with cervical SCC or ADC who received CCRT. In the multivariate analysis, HRs were adjusted for age, CCI score, FIGO clinical stage, year of diagnosis, RT cumulative dose, platinum cumulative dose, intracavitary brachytherapy dose, CCI score, income, hospital type, and hospital location. Stratified analyses were performed to evaluate the risk of mortality, LRR, and DM associated with cervical SCC or ADC and FIGO clinical stages. All analyses were performed using SAS statistical software (version 9.3; SAS, Cary, NC, USA). A 2-tailed *P* value < .05 was considered statistically significant.

To reduce the effects of potential confounding factors in the comparison of CCRT outcomes between the two groups, the groups were propensity score matched (PSM). Propensity score matching was performed using a multivariable logistic regression model in which the SCC and ADC groups were the dependent variables and potential confounders were covariates. The following confounders were included in the PSM: age, FIGO stage, year of diagnosis, RT cumulative dose, platinum cumulative dose, intracavitary brachytherapy dose, CCI score, income, hospital type, and hospital location. All patients with cervical ADC were matched with patients with cervical SCC at a ratio of 1:2. Independent predictors were controlled in the analysis, and the endpoint was the mortality rate among patients with cervical SCC and ADC.

Results

We enrolled 3258 patients who had FIGO stage IB-IVA CC without DM (**Table 1**). Among them, 2927 patients with cervical SCC and 331 patients with cervical ADC received definitive CCRT. The mean follow-up duration after the index date was 54.6 months (standard deviation = 35.5 months). The patients with cervical ADC were significantly younger, had a higher income, and had an earlier disease stage. Furthermore, fewer patients with ADC received intracavitary brachytherapy than did patients with cervical SCC (**Table 1**). The rates of LRR, DM, and mortality after definitive CCRT were higher in patients with cervical ADC than in patients with cervical SCC (LRR: 17.5% and 12.4%, DM: 22.7% and 14.6%, and mortality: 55.3% and 36.9% in patients with cervical ADC and SCC, respectively). The years of diagnosis, EBRT cumulative dose, intracavitary brachytherapy dose, platinum cumulative dose, CCI score, hospital type, and hospital location were not significantly different between the two groups. We further investigated Elixhauser Comorbidities between cervical SCC and ADC, and we did not identify statistically significant differences between the two groups receiving definitive CCRT (Supplemental Table 1) [21, 22].

The results of multivariate Cox regression analysis indicated that ADC pathology, advanced FIGO stage, no intracavitary brachytherapy, old age, early year of diagnosis, and high CCI score were significant independent poor prognostic factors of all-cause mortality in patients with CC receiving definitive CCRT (**Table 2**). Cervical ADC (adjusted HR [aHR], 2.10; 95% confidence interval [CI], 1.79-2.46) was a significant independent prognostic factor for OS (P < .0001) (**Table 2**). The aHR of intracavitary brachytherapy at ≥ 2500 cGy and < 2500 cGy compared with no intracavitary brachytherapy was 2.27 (95% CI, 1.85-2.79) and 3.85 (95% CI, 3.09-4.80), respectively.

The patient's FIGO clinical stage was identified as a crucial, independent predictor. Furthermore, aHRs increased with advancement from FIGO stages II through IV (aHR: 1.39, 2.27, and 3.85 for stages II, III, and IV, respectively) (**Table 2**). Stratified analyses were performed to evaluate the risk of mortality among patients with cervical ADC and SCC receiving CCRT at different FIGO clinical stages, and a stratified Cox propor-

Table 2. Cox proportional hazards regression analysis of the risk of all-cause mortality among patients with cervical adenocarcinomas or squamous cell carcinoma and received definitive concurrent chemoradiotherapy

		Crude HR (95% CI)	Adjusted HR* (95% CI)	*P* value
Pathologic type	SCC	1	1	< .0001
	adenocarcinoma	1.93 (1.65-2.26)	2.10 (1.79-2.46)	
FIGO stage	I	1	1	< .0001
	II	1.33 (1.09-1.61)	1.39 (1.14-1.69)	
	III	2.46 (2.01-3.01)	2.27 (1.85-2.79)	
	IV	4.86 (3.93-6.00)	3.85 (3.09-4.80)	
EBRT cumulative dose	< 50 Gy	1	1	.5315
	≥ 50 Gy	1.20 (1.07-1.34)	0.96 (0.85-1.09)	
Platinum cumulative dose	< 500 mg	1	1	.2706
	≥ 500 mg	0.94 (0.84-1.04)	0.94 (0.84-1.05)	
IC Brachytherapy dose	No IC Brachytherapy	1	1	< .0001
	< 2500 cGy	0.35 (0.30-0.40)	0.45 (0.39-0.53)	
	≥ 2500 cGy	0.29 (0.25-0.33)	0.42 (0.36-0.49)	
Age, years	≥ 70	1	1	< .0001
	60-69	0.93 (0.80-1.07)	0.85 (0.74-0.99)	
	50-59	0.85 (0.72-1.01)	0.73 (0.61-0.87)	
	20-49	1.35 (1.15-1.58)	1.10 (0.93-1.30)	
Year of diagnosis	2007-2009	1	1	.0199
	2010-2012	0.95 (0.83-1.08)	0.94 (0.83-1.08)	
	2013-2015	0.84 (0.72-0.97)	0.81 (0.70-0.94)	
CCI score	0	1	1	< .0001
	1	1.33 (1.15-1.55)	1.34 (1.15-1.56)	
	≥ 2	1.71 (1.45-2.02)	1.51 (1.27-1.80)	
Income	< 18,000 NTD	1	1	.0686
	18,000-22,500 NTD	0.86 (0.75-0.98)	0.93 (0.81-1.07)	
	22,500-30,000 NTD	0.81 (0.67-0.97)	0.89 (0.74-1.07)	
	≥ 30,000 NTD	0.75 (0.65-0.88)	0.81 (0.70-0.95)	
Hospital type	Medical center	1	1	.7094
	others	1.14 (1.01-1.29)	0.98 (0.86-1.11)	
Area	North	1	1	.0657
	Middle	0.97 (0.84-1.12)	1.08 (0.93-1.25)	
	South/East	1.18 (1.04-1.35)	1.17 (1.03-1.33)	

*All variables presented in **Table 2** were used in the multivariate analysis. Gy, gray; SCC, squamous cell carcinoma; ADC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; mg, milligrams; HR, hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; IC, intracavitary.

tional hazard model was used to analyze the risk of mortality at different FIGO stages among patients with CC (**Table 3**). The aHRs after definitive CCRT for CC were calculated after adjusting for pathologic type, RT cumulative dose, platinum cumulative dose, intracavitary brachytherapy dose, age, year of diagnosis, CCI score, income, hospital type, and hospital location. Compared with the aHRs (95% CIs) of cervical SCC, those of cervical ADC for overall mortality in FIGO clinical stages I, II, and III-IV were 2.21 (95% CI, 1.43-3.42; P = .0004), 2.26 (95% CI, 1.75-2.92; P < .0001), and 2.05 (95% CI, 1.26-2.59; P < .0001), respectively (**Table 3**). Patients with CC who received intracavitary brachytherapy exhibited better OS compared with patients who did not receive intracavitary brachytherapy, regardless of FIGO stage. Old age and high CCI scores (1 or ≥ 2 compared with 0) in patients with CC receiving definitive CCRT were signifi-

Table 3. Cox proportional hazards regression analysis of the risk of all-cause mortality, stratified by disease stage

		Stage I		Stage II		Stage III-IV	
		aHR* (95% CI)	*P* value	aHR* (95% CI)	*P* value	aHR* (95% CI)	*P* value
Pathologic type	SCC	1	.0004	1	< .0001	1	< .0001
	adenocarcinoma	2.21 (1.43-3.42)		2.26 (1.75-2.92)		2.05 (1.62-2.59)	
RT cumulative dose	< 50 Gy	1	.1652	1	.3748	1	.8335
	≥ 50 Gy	1.32 (0.89-1.96)		0.91 (0.75-1.12)		0.98 (0.82-1.17)	
Platinum cumulative dose	< 500 mg	1	.2098	1	.8533	1	.5603
	≥ 500 mg	0.80 (0.56-1.14)		1.02 (0.85-1.22)		0.95 (0.81-1.12)	
IC Brachytherapy dose	No IC Brachytherapy	1	.0009	1	< .0001	1	< .0001
	< 2500 cGy	0.42 (0.23-0.74)		0.34 (0.25-0.44)		0.45 (0.37-0.55)	
	≥ 2500 cGy	0.35 (0.20-0.60)		0.29 (0.23-0.38)		0.46 (0.38-0.56)	
Age, years	≥ 70	1	.3747	1	< .0001	1	.0352
	60-69	0.98 (0.67-1.68)		0.98 (0.76-1.25)		0.78 (0.63-0.96)	
	50-59	0.96 (0.55-1.75)		0.72 (0.54-0.97)		0.72 (0.56-0.92)	
	20-49	1.49 (0.89-2.49)		1.43 (1.10-1.87)		0.85 (0.66-1.09)	
Year of diagnosis	2007-2009	1	.3969	1	.0854	1	.0966
	2010-2012	0.73 (0.46-1.16)		0.86 (0.69-1.07)		1.04 (0.86-1.25)	
	2013-2015	0.93 (0.57-1.49)		0.76 (0.59-0.97)		0.84 (0.68-1.03)	
CCI score	0	1	.1463	1	< .0001	1	.0034
	1	1.59 (0.95-2.65)		1.18 (0.92-1.50)		1.43 (1.15-1.78)	
	≥ 2	1.43 (0.82-2.50)		1.98 (1.51 2.60)		1.27 (0.99-1.63)	
Income	< 18,000 NTD	1	.3768	1	.7504	1	.0566
	18,000-22,500 NTD	1.17 (0.75-1.82)		0.95 (0.76-1.19)		0.85 (0.70-1.03)	
	22,500-30,000 NTD	0.68 (0.36-1.31)		0.97 (0.71-1.32)		0.87 (0.68-1.12)	
	≥ 30,000 NTD	0.92 (0.55-1.54)		0.87 (0.67-1.12)		0.75 (0.60-0.93)	
Hospital type	Medical center	1	.4386	1	.4019	1	.9634
	others	0.84 (0.54-1.31)		0.91 (0.74-1.13)		1.00 (0.84-1.20)	
Area	North	1	.1374	1	.7420	1	.1478
	Middle	0.86 (0.53-1.38)		1.08 (0.85-1.36)		1.08 (0.87-1.34)	
	South/East	1.40 (0.91-2.14)		1.07 (0.87-1.33)		1.26 (0.95-1.51)	

*All variables presented in **Table 2** were used in the multivariate analysis. Gy, gray; SCC, squamous cell carcinoma; ADC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; mg, milligrams; HR, hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; IC, intracavitary; aHR, adjusted hazard ratio.

cant poor prognostic factors in stages II and III-IV FIGO (**Table 3**).

The results of using a stratified Cox proportional hazard model to determine the risk of all-cause mortality, LRR, and DM among patients with cervical ADC or SCC who received definitive CCRT are presented in **Table 4**. Patients with cervical ADC had higher all-cause mortality, LRR, and DM (aHR: 2.10, 1.79, and 1.97, respectively) compared with patients with cervical SCC when the model was not stratified by age (**Table 4**). Patients with cervical ADC exhibited higher all-cause mortality compared with patients with cervical SCC; the results of multivariate analysis revealed that the aHRs were 2.21, 2.26, and 2.05 in FIGO stage I, II, and III-IV, respectively. Patients with cervical ADC exhibited higher LRR in stages I-II (aHR: 2.58 and 1.84 for stage I, and II, respectively) but no significant difference in FIGO stages III-IV compared with patients with cervical SCC. Compared with patients with cervical SCC, patients with cervical ADC had higher DM in FIGO stages II and III-IV (aHR: 2.31 and 1.90 for stages II and III-IV, respectively) but no significant difference in FIGO stage I.

The Kaplan-Meier OS curves for patients with ADC or SCC in stages I, II, III, and IV are provided in **Figure 1A-E**. The OS rate was higher in patients with cervical SCC who received CCRT than in patients with cervical ADC who received CCRT (log-rank test: P < .0001, P < .0001, P = .0004, P < .0001, and P = .0002 in all stages, stage I, II, III, and IV, respectively). The 3-year OS rates in patients with cervical SCC and ADC who received CCRT were 85% and 73%, 80% and 59%, 63% and 41%, and 43% and 18% in

Table 4. Stratified Cox proportional hazard model for the risk of all-cause mortality, locoregional recurrence, and distant metastasis among patients with cervical adenocarcinoma or squamous cell carcinoma who received definitive concurrent chemoradiotherapy

FIGO stage	Event	Pathologic type	Event no (%)	Adjusted HR* (95% CI)	*P* value
All patients	All-cause mortality	SCC	1081 (36.93)	ref.	< .0001
		adenocarcinoma	183 (55.29)	2.10 (1.79-2.46)	
	Locoregional recurrence	SCC	364 (12.44)	ref.	< .0001
		adenocarcinoma	58 (17.52)	1.79 (1.35-2.37)	
	Distant metastasis	SCC	428 (14.62)	ref.	< .0001
		adenocarcinoma	75 (22.66)	1.97 (1.54-2.53)	
Stage I	All-cause mortality	SCC	100 (22.83)	ref.	.0004
		adenocarcinoma	27 (39.71)	2.21 (1.43-3.42)	
	Locoregional recurrence	SCC	44 (10.05)	ref.	.0047
		adenocarcinoma	14 (20.59)	2.58 (1.37-4.86)	
	Distant metastasis	SCC	53 (12.10)	ref.	.2351
		adenocarcinoma	11 (16.18)	1.50 (0.77-2.93)	
Stage II	All-cause mortality	SCC	420 (29.45)	ref.	< .0001
		adenocarcinoma	71 (47.65)	2.26 (1.75-2.92)	
	Locoregional recurrence	SCC	178 (12.48)	ref.	.0026
		adenocarcinoma	29 (19.46)	1.84 (1.24-2.74)	
	Distant metastasis	SCC	175 (12.27)	ref.	< .0001
		adenocarcinoma	36 (24.16)	2.31 (1.61-3.32)	
Stage III-IV	All-cause mortality	SCC	561 (52.78)	ref.	< .0001
		adenocarcinoma	85 (74.56)	2.05 (1.62-2.59)	
	Locoregional recurrence	SCC	142 (13.36)	ref.	.1672
		adenocarcinoma	15 (13.16)	1.47 (0.85-2.52)	
	Distant metastasis	SCC	200 (18.81)	ref.	.0020
		adenocarcinoma	28 (24.56)	1.90 (1.27-2.86)	

*All variables presented in **Table 2** were used in the multivariate analysis. SCC, squamous cell carcinoma; ADC, adenocarcinoma; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio.

FIGO stage I, II, III, and IV, respectively (Supplemental Table 2). The 5-year OS rates in patients with cervical SCC and ADC who received CCRT were 80% and 61%, 74% and 50%, 55% and 33%, and 33% and 9% in FIGO stage I, II, III, and IV, respectively.

The matching process yielded a final cohort of 985 patients (655 and 330 patients in the cervical SCC and cervical ADC groups, respectively) who were eligible for further analysis. Patient characteristics for PSM are listed in Supplemental Table 3, and all confounding factors were well matched. Cox proportional hazards regression analysis for the PSM cohort revealed differences in all-cause mortality, LRR, and DM between patients with cervical SCC and ADC who received definitive CCRT (Supplemental Table 4). The trends in all-cause mortality, LRR, and DM after PSM were similar to the trends in the non-PSM cohort (**Table 4**). Patients with cervical ADC who received definitive CCRT had higher all-cause mortality, LRR, and DM compared with the cervical SCC cohort in all FIGO stages. All-cause mortality was higher in patients with cervical ADC who received CCRT in stages I, II, and III-IV. Patients with cervical ADC had higher LRR in stages I and II compared with patients with cervical ADC, but no significant difference was noted in stage III-IV. Patients with cervical ADC displayed higher DM compared with patients with cervical SCC in stages II and III-IV, but no significant difference was noted in stage I. Supplemental Figure 1 presents the survival curves for all-cause mortality in different stages using the Kaplan-Meier method for the PSM cohort. After propensity score matching, patients with cervical SCC who received CCRT continued to exhibit a higher OS than did patients with cervical ADC who received CCRT in all stages (stage I, II, III, and IV).

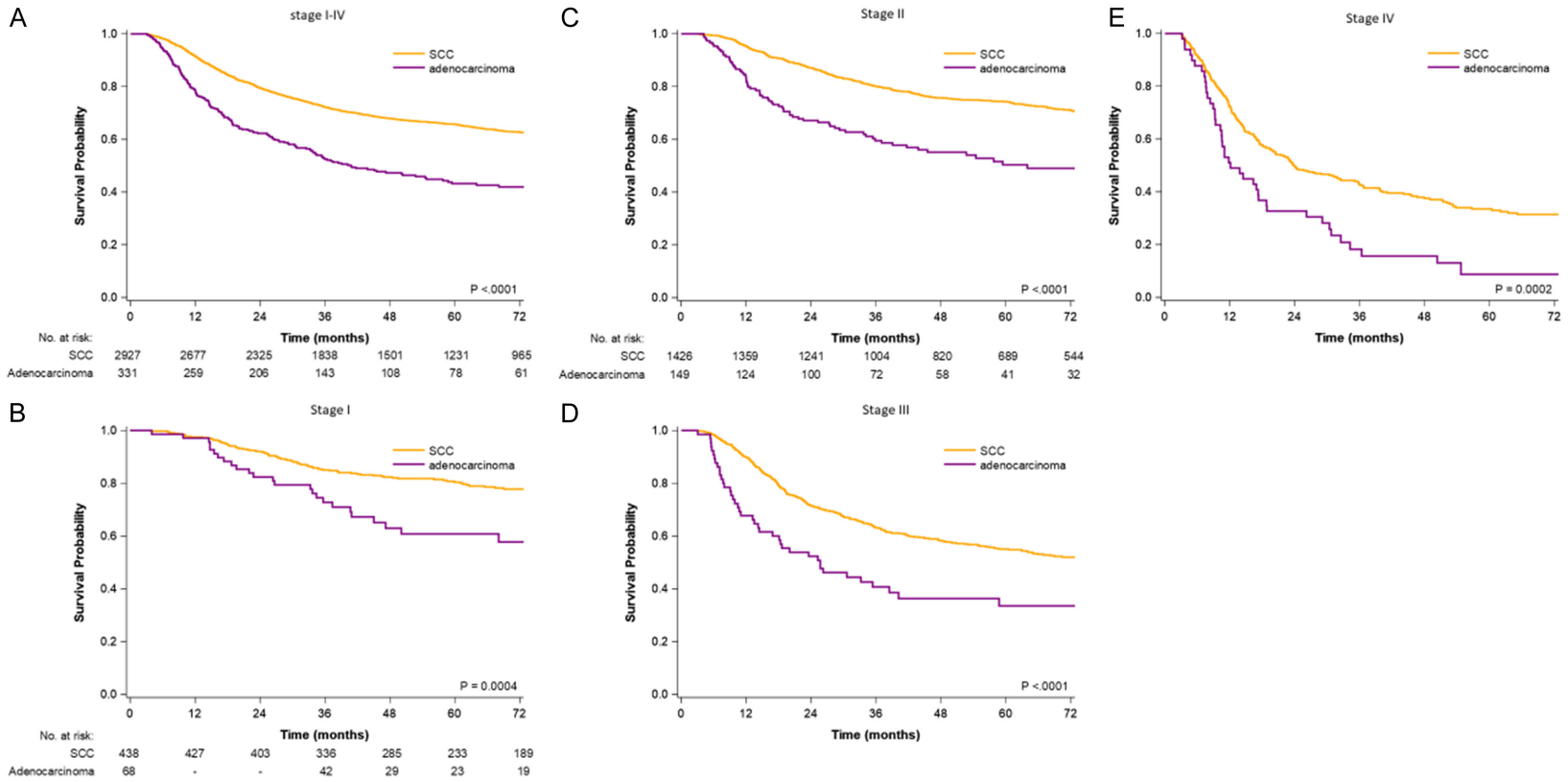

Figure 1. Survival curves for all-cause mortality determined using the Kaplan-Meier method (A) stage I-IV (B) stage I (C) stage II (D) stage III (E) stage IV.

Discussion

The present study is the first to report the prognostic factors and outcomes of patients with cervical ADC or SCC who received definitive CCRT. We demonstrated that patients with ADC had a younger age, earlier disease stage, and higher income than did patients with SCC (**Table 1**). These results accord with those of studies that have demonstrated that ADC incidence is higher in women who are younger [13] and have higher incomes [23-25]. However, a larger number of patients with cervical ADC received definitive CCRT without intracavitary brachytherapy compared with SCC. This may be because patients with cervical ADC had poorer response rates from definitive CCRT and achieved response more slowly than did patients with SCC [8]. Therefore, performing intracavitary brachytherapy is more difficult in patients with cervical ADC than patients with SCC because the response to CCRT in patients with ADC is poorer [8].

Table 2 displays some of the poor prognostic factors for definitive CCRT in patients with CC, such as ADC pathologic type, advanced FIGO stage, high CCI score, old age, earlier year of diagnosis, and no intracavitary brachytherapy. Old age, advanced FIGO stage, earlier year of diagnosis, no intracavitary brachytherapy, and ADC have previously been reported as poor prognostic factors [13, 26-29]. However, high CCI scores had not previously been identified as a poor prognostic factor for patients with CC who have received CCRT. Furthermore, this is the first study to report lower OS in patients with cervical ADC than in patients with SCC following definitive CCRT at all FIGO stages after multivariate analysis (**Table 2** and **Figure 1**). In **Table 3**, we stratified stages I, II, III-IV, which revealed similar prognostic factors to those presented in **Table 2**. ADC and no intracavitary brachytherapy were independent poor prognostic factors for patients with stage I CC who received CCRT; ADC, no intracavitary brachytherapy, old age, and high CCI scores were independent poor prognostic factors for patients with stages II or III-IV CC who received CCRT. Old age and high CCI scores were not statistically significant factors for patients with stage I CC who received CCRT, possibly because of the small sample size in stage I (**Table 1**).

We further used a stratified Cox proportional hazard model to assess the risk of all-cause mortality, LRR, and DM among cervical patients with ADC or SCC who received definitive CCRT (**Table 4**). This study is the first to evaluate the OS outcomes of definitive CCRT in patients with cervical ADC and SCC, LRR, and DM. All-cause mortality was significantly higher in all stages (stage I, II, III, and IV) in patients with cervical ADC compared with patients with cervical SCC. Studies have reported that a higher DM in patients with cervical ADC who have received CCRT might be associated with poor survival [7, 30, 31], despite the differences in OS not reaching statistical significance. Furthermore, we demonstrated that the LRR after definitive CCRT was significantly higher in patients with ADC compared with patients with SCC; thus, both the DM rate and LRR were higher in patients with ADC. The higher LRR rate in patients with cervical ADC is compatible with the findings of a study that had a small sample size and inconsistent treatments [31]. Although a study indicated that the addition of CT to RT may reduce the treatment failure rate in patients with cervical ADC [16], our results demonstrated that CCRT could not overcome the high LRR and high DM rate in patients with cervical ADC. Our findings did not indicate a significant difference in LRR between patients with ADC and SCC in stages III-IV (**Table 4**), but the trend maintained an aHR of 1.47. This may be because the LRRs were high in both cervical SCC and ADC in the advanced stages III-IV [8], and thus a larger sample size might be necessary. Similarly, we did not observe significant differences in DM in stage I between patients with ADC and those with SCC, but the trend was present with an aHR of 1.50. The improved control of DM after CCRT between stage I ADC and SCC may have contributed to these results [16]; thus, a larger sample size in stage I may be necessary to verify differences. Overall, patients with cervical ADC who received definitive CCRT had lower OS, higher DM, and higher LRR compared with patients with cervical SCC who received definitive CCRT (**Table 4** and **Figure 1**). Therefore, improving local control modality and systemic treatments for reducing DM is crucial for cervical ADC. Conventional CCRT with a platinum-based CT regimen was insufficient for patients with cervical ADC; the five-year OS of stage IV patients with cervical

ADC who received definitive CCRT was only 9% in our study (Supplemental Table 2).

To balance the confounding factors, we conducted a PSM study, the results of which are displayed in Supplemental Table 3 and demonstrate that the confounding factors were well matched between patients with cervical ADC and SCC who received CCRT. The results of Cox proportional hazards regression analysis for the PSM cohort also demonstrated lower OS, higher DM, and higher LRR in all FIGO stages (Supplemental Table 4). OS was lower in stages I, II, III, and IV in patients with cervical ADC compared with patients with the same stage of cervical SCC (Supplemental Table 4 and Supplemental Figure 1). Patients with cervical ADC who received definitive CCRT had a higher LRR rate in stages I and II compared with patients with cervical SCC who received CCRT. Moreover, in stages II and III-IV, the DM rate was higher in patients with cervical ADC who received CCRT than in patients with cervical SCC who received CCRT. Our results demonstrated that current definitive CCRT was insufficient for patients with cervical ADC and resulted in a low OS, high DM, and high LRR. The 5-year OS of patients with cervical ADC who received CCRT was extremely poor (Supplemental Table 2). Based on the inconsistent outcomes after CCRT in patients with cervical SCC and ADC, we suggest more aggressive treatments for better local control and less distant failure to improve survival. Carbon-ion RT or high dose intracavitary brachytherapy could be considered for patients with cervical ADC because of their greater affordance of local control, and trials for patients with cervical ADC should be performed [32-34]. However, cervical ADC is similarly sensitive to CT, at least for advanced diseases [6, 35]. The use of neoadjuvant CT may be beneficial in selected women [36, 37]. Novel systemic regimens with paclitaxel, cisplatin, carboplatin, bevacizumab, etoposide, or mitomycin could be considered in future clinical trials because they may reduce high distant failure rates in patients with cervical ADC [38, 39].

The main strength of our study is that it is the largest cohort study to estimate the outcomes, including OS, LRR, and DM, of definitive CCRT with platinum-based CT for patients with cervical SCC and ADC. Furthermore, the treatment was highly homogenous because we only used definitive CCRT. PSMs were also performed before and after to eliminate possible confounding factors (Supplemental Table 3), preserve clinical characteristics in patients with ADC and SCC (**Table 1**), and evaluate the outcomes of definitive CCRT in patients with cervical SCC and ADC (**Table 4** and Supplemental Table 4). Our findings demonstrated that patients with cervical ADC had lower OS, higher LRR, and higher DM than did patients with cervical SCC following conventional definitive CCRT. These findings indicate that physicians should consider that standard CCRT following NCCN guidelines is insufficient and results in poor survival outcomes among patients with cervical ADC (Supplemental Table 2, and **Figure 1**). The study outcomes indicate that increasing local control and reducing DM are crucial for patients with cervical ADC and can be achieved using charged-particle [32] and novel systemic regimens [39], respectively. Definitive CCRT may be suitable for patients with cervical SCC but insufficient for patients with cervical ADC (Supplemental Table 2). These findings could also be considered in future clinical practice and randomized controlled studies.

This study had some limitations. First, because all patients with cervical ADC were enrolled from an Asian population, the corresponding ethnic susceptibility remains unclear; therefore, caution should be exercised when extrapolating these results to non-Asian populations. However, differences in outcomes of definitive CCRT for CC between Asian and non-Asian populations have not been reported. Second, the diagnoses of all comorbid conditions were based on ICD-9-CM codes. However, the Taiwan Cancer Registry Administration randomly reviews charts and interviews patients to verify the accuracy of diagnoses, and hospitals with outlier chargers or practices may be audited and subsequently heavily penalized if malpractice or discrepancies are identified. Third, to prevent the creation of several subgroups, various adjuvant treatments after curative definitive CCRT were not categorized separately during the analyses. Subsequently, the effects of different adjuvant treatments after CCRT remain unclear. Therefore, a large-scale randomized trial comparing carefully selected patients undergoing suitable treatments is essential to obtain crucial information regarding population specificity and disease occurrence. 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.

Conclusions

Definitive CCRT resulted in lower OS, higher LRR, and higher DM rates in patients with cervical ADC than in patients with cervical SCC. Improving local control and DM are crucial for the treatment of patients with cervical ADC, and thus standard CCRT might be insufficient for patients with cervical ADC.

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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, locoreional 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 Classification of Diseases, Ninth Revision, Clinical Modification; PSM, Propensity scores matched.

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Supplemental Table 1. Elixhauser comorbidities in patients with cervical squamous cell carcinoma and adenocarcinoma who received definitive concurrent chemoradiotherapy

Variable	*Total (N = 3258)*	*SCC (N = 2927)*	*Adenocarcinoma (N = 331)*	*P value*
	n (%)	*n (%)*	*n (%)*	
Congestive heart failure	73 (2.2)	68 (2.3)	5 (1.5)	.3437
Cardiac arrhythmia	71 (2.2)	66 (2.3)	5 (1.5)	.3794
Valvular disease	34 (1.0)	34 (1.2)	0	.0487
Pulmonary disease	104 (3.2)	92 (3.1)	12 (3.6)	.6362
Peripheral vascular disorders	25 (0.8)	-	-	.3061
Hypertension	857 (26.3)	784 (26.8)	73 (22.1)	.0639
Paralysis	7 (0.2)	7 (0.2)	0	.3731
Other neurological disorders	27 (0.8)	24 (0.8)	3 (0.9)	.8695
Diabetes	407 (12.5)	357 (12.2)	50 (15.1)	.1292
Hypothyroidism	15 (0.5)	-	-	.6834
Renal failure	67 (2.1)	59 (2.0)	8 (2.4)	.6259
Liver disease	40 (1.2)	35 (1.2)	5 (1.5)	.6220
Peptic ulcer disease (excluding bleeding)	115 (3.5)	105 (3.6)	10 (3.0)	.5968
Rheumatoid arthritis/collagen vascular diseases	58 (1.8)	51 (1.7)	7 (2.1)	.6272
Coagulopathy	7 (0.2)	-	-	.7176
Fluid and electrolyte disorders	34 (1.0)	29 (1.0)	5 (1.5)	.3777
Blood loss anemia	34 (1.0)	-	-	.4066
Deficiency anemia	39 (1.2)	35 (1.2)	4 (1.2)	.9839
Alcohol abuse	7 (0.2)	7 (0.2)	0	.3731
Depression	66 (2.0)	56 (1.9)	10 (3.0)	.1751

Supplemental Table 2. Survival rates of all-cause mortality determined using the Kaplan-Meier method

	Patient no.	Event no. (%)	Survival rate			Survival time (months)	
			1 y	3 y	5 y	Median	95% CI
All patients							
SCC	2927	1081 (36.9)	0.91	0.72	0.66	.	-
adenocarcinoma	331	183 (55.3)	0.78	0.52	0.43	40.72	(33.67, 57.74)
Stage I							
SCC	438	100 (22.8)	0.97	0.85	0.80	.	-
adenocarcinoma	68	27 (39.7)	0.97	0.73	0.61	114.13	(47.21, -)
Stage II							
SCC	1426	420 (29.5)	0.95	0.80	0.74	237.00	-
adenocarcinoma	149	71 (47.7)	0.83	0.59	0.50	63.97	(39.05, -)
Stage III							
SCC	699	326 (46.6)	0.90	0.63	0.55	80.52	(64.10, 102.39)
adenocarcinoma	65	43 (66.2)	0.68	0.41	0.33	25.67	(14.39, 40.13)
Stage IV							
SCC	364	235 (64.6)	0.72	0.43	0.33	23.82	(20.00, 32.39)
adenocarcinoma	49	42 (85.7)	0.51	0.18	0.09	12.10	(10.23, 17.28)

Supplemental Table 3. Characteristics of patients in propensity score-matched cohorts for cervical squamous cell carcinoma and adenocarcinoma who received definitive concurrent chemoradiotherapy

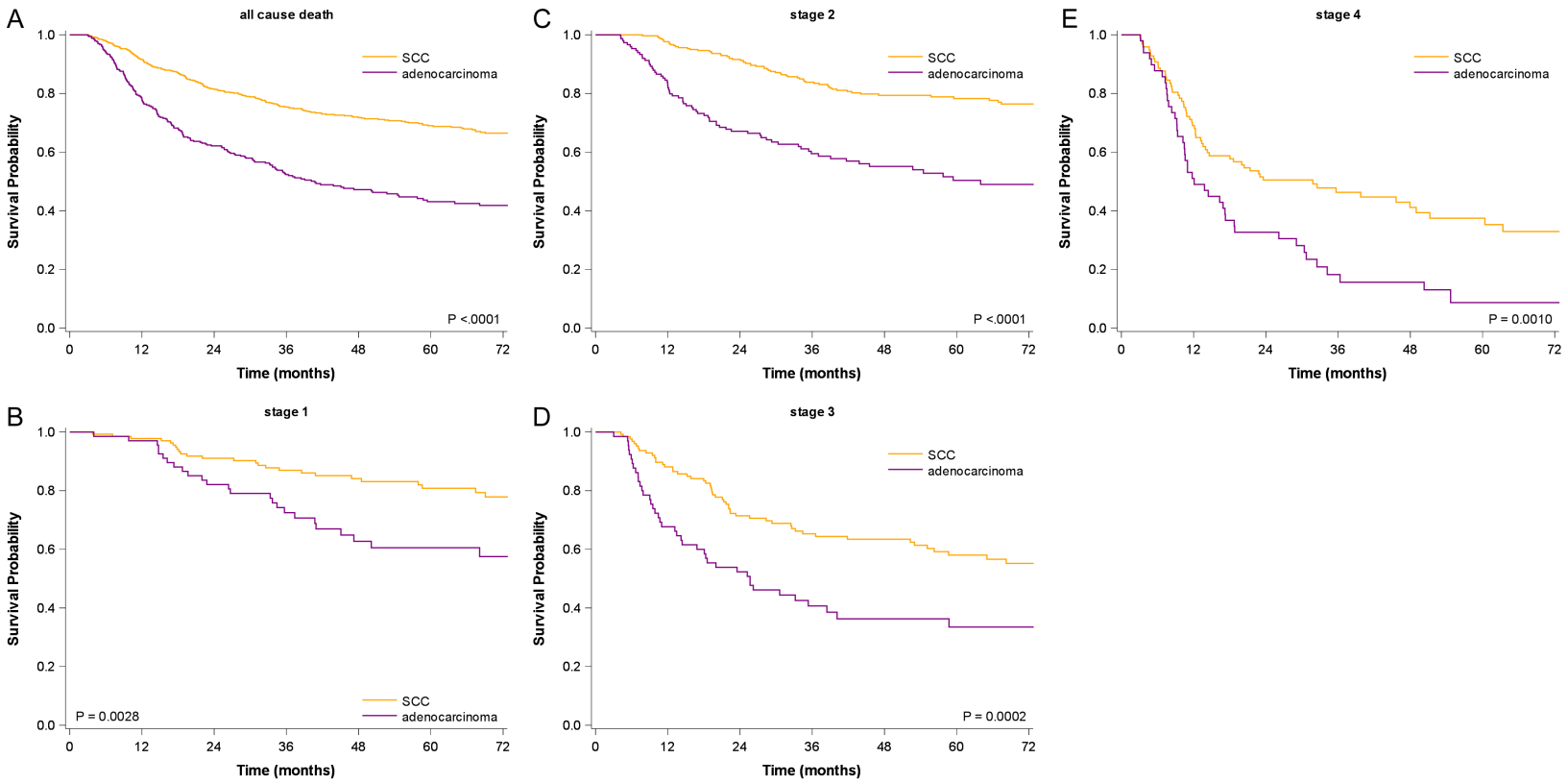
		SCC (N = 655)	*Adenocarcinoma (N = 330)*	*P value*
		n (%)	*n (%)*	
Age, years	0-49	216 (33.0)	110 (33.3)	1.000
	50-59	222 (33.9)	111 (33.6)	
	60-69	125 (19.1)	63 (19.1)	
	≥ 70	92 (14.0)	46 (13.9)	
FIGO stage	1	134 (20.5)	67 (20.3)	1.000
	2	298 (45.5)	149 (45.2)	
	3	126 (19.2)	65 (19.7)	
	4	97 (14.8)	49 (14.8)	
Year of diagnosis	2007-2009	203 (31.0)	104 (31.5)	.4292
	2010-2012	204 (31.1)	94 (28.5)	
	2013-2015	248 (37.9)	132 (40.0)	
RT cumulative dose	< 50 Gy	276 (42.1)	142 (43.0)	.7502
	≥ 50 Gy	379 (57.9)	188 (57.0)	
Platinum cumulative dose	< 500 mg	315 (48.1)	158 (47.9)	.9641
	≥ 500 mg	340 (51.9)	172 (52.1)	
IC Brachytherapy dose	No IC Brachytherapy	115 (17.6)	69 (20.9)	.3535
	< 2500 cGy	238 (36.3)	114 (34.5)	
	≥ 2500 cGy	302 (46.1)	147 (44.5)	
CCI scores	0	500 (76.3)	244 (73.9)	.4451
	1	88 (13.4)	53 (16.1)	
	≥ 2	67 (10.2)	33 (10.0)	
Income	< 18,000 NTD	167 (25.5)	84 (25.5)	.1689
	18,000-22,500 NTD	204 (31.1)	95 (28.8)	
	22,500-30,000 NTD	77 (11.8)	51 (15.5)	
	≥ 30,000 NTD	207 (31.6)	100 (30.3)	
Hospital type	Medical center	499 (76.2)	248 (75.2)	.6792
	others	156 (23.8)	82 (24.8)	
Hospital location	North	304 (46.4)	153 (46.4)	.9941
	Middle	170 (26.0)	87 (26.4)	
	South/East	181 (27.6)	90 (27.3)	

Gy, gray; SCC, squamous cell carcinoma; ADC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; mg, milligrams; HR, hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; IC, intracavitary; aHR, adjusted hazard ratio.

Supplemental Table 4. Results of Cox proportional hazards regression analysis of propensity score-matched cohorts and the risk of all-cause mortality, locoregional recurrence, and distant metastasis among patients with cervical adenocarcinoma or squamous cell carcinoma who received definitive concurrent chemoradiotherapy

FIGO stage	Event	Pathologic type	Patient no.	Event no. (%)	Adjusted HR* (95% CI)	*P* value
All patients	All-cause mortality	SCC	655	211 (32.2)	ref.	< .0001
		adenocarcinoma	330	183 (55.5)	2.39 (1.95-2.92)	
	Locoregional recurrence	SCC	655	80 (12.2)	ref.	.0004
		adenocarcinoma	330	58 (17.6)	1.86 (1.32-2.61)	
	Distant metastasis	SCC	655	97 (14.8)	ref.	< .0001
		adenocarcinoma	330	75 (22.7)	2.00 (1.47-2.71)	
Stage I	All-cause mortality	SCC	134	29 (21.6)	ref.	.0009
		adenocarcinoma	67	27 (40.3)	2.56 (1.47-4.48)	
	Locoregional recurrence	SCC	134	12 (9.0)	ref.	.0066
		adenocarcinoma	67	14 (20.9)	3.19 (1.38-7.36)	
	Distant metastasis	SCC	134	16 (11.9)	ref.	.3605
		adenocarcinoma	67	11 (16.4)	1.46 (0.65-3.32)	
Stage II	All-cause mortality	SCC	298	69 (23.2)	ref.	< .0001
		adenocarcinoma	149	71 (47.7)	2.91 (2.07-4.08)	
	Locoregional recurrence	SCC	298	44 (14.8)	ref.	.0378
		adenocarcinoma	149	29 (19.5)	1.66 (1.03-2.67)	
	Distant metastasis	SCC	298	37 (12.4)	ref.	< .0001
		adenocarcinoma	149	36 (24.2)	2.62 (1.64-4.18)	
Stage III-IV	All-cause mortality	SCC	223	113 (50.7)	ref.	< .0001
		adenocarcinoma	114	85 (74.6)	2.06 (1.54-2.76)	
	Locoregional recurrence	SCC	223	24 (10.8)	ref.	.0892
		adenocarcinoma	114	15 (13.2)	1.80 (0.91-3.55)	
	Distant metastasis	SCC	223	44 (19.7)	ref.	.0220
		adenocarcinoma	114	28 (24.6)	1.79 (1.09-2.95)	

*Propensity scores were estimated using a logistic regression model with the variables of age, FIGO stage, year of diagnosis, RT cumulative dose, platinum cumulative dose, IC Brachytherapy dose, CCI score, income, hospital type, and hospital location. *Patients were 1:2 matched with the same stage, age group, and caliper (logit PS) within 0.5. Gy, gray; SCC, squamous cell carcinoma; ADC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiotherapy; CCI, Charlson comorbidity index; mg, milligrams; HR, hazard ratio; CI, confidence interval; NTD, New Taiwan dollar; IC, intracavitary; aHR, adjusted hazard ratio.



Supplemental Figure 1. Survival curves for all-cause mortality determined using the Kaplan-Meier method for propensity score-matched cohort at (A) stage I-IV (B) stage I (C) stage II (D) stage III (E) stage IV.