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Original Article

Optimal treatments for cervical adenocarcinoma

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Abstract: To compare the effects of curative surgery and curative definitive concurrent chemoradiotherapy (CCRT) on cervical adenocarcinoma (AC) by conducting a national cohort study with a large sample size, we enrolled women with cervical AC and categorized them into two groups according to treatment modality to compare treatment outcomes: group 1, comprising patients who received curative surgery, and group 2, comprising patients who received curative definitive CCRT. Data of 1,621 patients with cervical AC were extracted from the Taiwan Cancer Registry database. Univariate and multivariate Cox regression analysis results indicated that high American Society of Anesthesiologists scores, advanced American Joint Committee on Cancer (AJCC) clinical stage, and curative definitive CCRT were significant independent poor prognostic factors. The adjusted hazard ratio (aHR; 95% confidence interval [CI]) for overall mortality in early invasive clinical stages (IB-IIA) was 1.27 (0.77-2.69) in group 2 compared with group 1, whereas that for overall mortality at AJCC clinical stage IIB was 2.46 (1.34-4.53) in group 2 compared with group 1. The aHR (95% CI) for overall mortality at advanced clinical stages (III and IV) was 1.47 (1.09-1.97) in group 2 compared with group 1. Curative surgery improves survival in cervical AC at advanced clinical stages. Either curative surgery or definitive CCRT is an option in the early invasive clinical stages of cervical AC.

Keywords: Cervical adenocarcinoma, surgery, CCRT, stages, survival

Introduction

Squamous cell carcinoma (SCC) is the most common histological type of cervical cancer. The second most common histological type is cervical adenocarcinoma (AC), which accounts for approximately 25% of all invasive cervical cancers diagnosed in the United States [1, 2]. The incidence of cervical AC has increased considerably over the past few decades [1, 2]. The incidence in Western countries is different from that in Eastern countries [1-3]. In Taiwan, cervical AC accounts for approximately 18.04% of cervical cancers, which is less than the incidence in Western countries, according to the Taiwan Cancer Registry database [3].

Previous studies predominantly enrolling patients with SCC have provided most of our knowledge about the treatment of cervical cancer; on average, AC has been reported to constitute 10% of cervical cancer cases [4-9]. Very few of these studies have reported separate outcomes for AC. Furthermore, prospective studies have not focused on the treatment of AC as the only histology. Consequently, our understanding of the natural history and optimal management of cervical AC is limited. Cervical AC and SCC share many similarities, and patients with both types of cancer have been reported to receive the same treatment at most institutions [4-9]. However, cervical AC and SCC also exhibit several differences in prognostic factors, epidemiology, and patterns of failure after primary treatment as well as possible responses to specific treatments [10]. Despite these differences, specific treatment strategies tailored to AC have yet to be developed.

Cervical AC constitutes only approximately 20%-25% of all cervical carcinomas [1, 2].

Therefore, specific level 1 evidence for guiding patient management is currently unavailable. Most trials have included cervical AC histological subtype, but the numbers are insufficient and can generate hypotheses from subset analyses. Consequently, our understanding of the natural history and optimal treatment of cervical AC is limited. Optimal treatment of cervical AC continues to be a subject of debate among practitioners: the debate is whether cervical AC should be considered to be different from SCC and which treatments would constitute its management. The purpose of the current study was to estimate the effects of two curative treatments, namely curative surgery and curative definitive concurrent chemoradiotherapy (CCRT), on cervical AC. This study focused on exploring well-known curative therapeutic decisions for the management of invasive early to locally advanced stages of cervical AC.

Patients and methods

Database

Using data from the Taiwan Cancer Registry database, we enrolled patients who had received diagnoses of cervical AC between January 1, 2006, and December 31, 2015. The follow-up duration was from the index date to December 31, 2015. Our protocols were reviewed and approved by the Institutional Review Board of Taipei Medical University. The Cancer Registry database of the Collaboration Center of Health Information Application contains detailed cancer-related information regarding clinical stages, radiotherapy (RT) doses and techniques, pathological types, and chemotherapy (CT) regimens [11-18].

Selection of study participants

The diagnoses of the enrolled patients were determined using their pathological data, and patients who had received new diagnoses of cervical AC were confirmed to have no other cancers or distant metastasis. Patients were included if they had received cervical AC diagnoses, were aged ≥ 18 years, and had stage IB1-IVA invasive AC (without metastasis) according to the American Joint Committee on Cancer (AJCC) Seventh Edition. Patients who had a history of cancer before cervical AC diagnosis, distant metastasis (stage IVB), unclear staging, mucinous, endometrioid, adenosquamous, and non-AC histology were excluded. In addition, we excluded patients with cervical AC who had not received curative-intent surgery (radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection) or curative-intent definitive CCRT (≥ 45 Gy to the whole pelvis and ≥ 20 Gy high dose rate (HDR) intracavity (IC) brachytherapy to point A), had received RT alone, or did not commence therapy within 12 weeks of diagnosis. Finally, we enrolled women with cervical AC and categorized them into the following groups according to treatment modality for comparing treatment outcomes: group 1, comprising patients who had received curative surgery, and group 2, comprising patients who had received curative definitive CCRT. Patients who had received adjuvant therapy after curative surgery, such as adjuvant RT, adjuvant CCRT, and adjuvant CT, were included in group 1. Patients who had received definitive CCRT with or without surgery were included in group 2. To minimize immortal time bias, the index date was set as the date of the start of therapy in both treatment groups. To ensure that the CCRT group did not include patients with poor performance related to their inoperable status, we selected only patients with an American Society of Anesthesiologists (ASA) physical status score of 1, which indicates a healthy performance status and tolerance of curative surgery (**Table 1**). Table S1 presents the initial selection of cervical AC patients with any ASA physical status score.

Exposure assessment

Comorbidities were also scored using the Charlson comorbidity index (CCI) [19, 20]. Only comorbidities that were observed 6 months before the index date were included; comorbid conditions were identified and included according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for the first admission or three or more repeated main diagnosis codes for visits to outpatient departments. The ASA physical status classification system is a promising tool for improving the classification of prognostic comorbidity in surgical cancer patients and may be used as an alternative to the CCI scores [21, 22]; therefore, we also used ASA physical status score as a prognostic factor in our assessment of patients with cervical AC

Table 1. Characteristics of women with cervical adenocarcinoma who received curative surgery or definitive CCRT (All patients had ASA physical status scores of ≥ 1, indicating tolerance toward curative surgery)

	Curative Surgery n = 849 (%)		Curative definitive CCRT n = 228 (%)		*P* value
Age Group					< 0.001
Age < 65 y	822	96.82%	208	91.23%	
Age ≥ 65 y	27	3.18%	20	8.77%	
Income					0.267
< NTD 22,000/month	544	64.08%	162	71.05%	
NTD 22,000-36,000/month	163	19.20%	34	14.91%	
NTD 36,000-48,000/month	75	8.83%	17	7.46%	
≥ NTD 48,000/month	67	7.89%	15	6.58%	
Region of residence					0.824
Rural	226	26.62%	63	27.63%	
Urban	623	73.38%	165	72.37%	
CCI Scores					< 0.001
CCI = 0	178	20.97%	29	12.72%	
CCI ≥ 1	671	79.03%	199	87.28%	
AJCC Stages					< 0.001
IB1-IIA	587	69.14%	26	11.40%	
IIB	66	7.77%	55	24.12%	
III	133	15.67%	62	27.19%	
IVA	63	7.42%	85	37.28%	
Death					< 0.001
No	681	80.21%	110	48.25%	
Yes	168	19.79%	118	51.75%	
Follow-up (years) (median, IQR)	(4.43, 5.22)		(1.79, 3.42)		< 0.001
RT Dose (Gy) (median, IQR)	NA		(50.40, 11.73)		< 0.001
Brachytherapy Dose (Gy) (median, IQR)	NA		(25, 9.0)		< 0.001
Cisplatin Cumulative Dose (mg/m^2) (median, IQR)	NA		(600, 240)		< 0.001

RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IQR, interquartile range; NTD, New Taiwan dollar; Gy, gray; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

to avoid including relatively unhealthy patients (ASA physical status scores of > 1) in the CCRT group.

Statistical analysis

The time-dependent Cox proportional hazards model was used to calculate the hazard ratios (HRs) for determining whether factors, such as curative therapy, age, CCI score, income, ASA physical status score, AJCC clinical stage, and region of residence, were significant independent predictors of death (Table S2). The independent predictors were controlled in the analysis, and the endpoint was mortality in the different treatment groups, with group 1 (curative surgery) serving as the control group. The cumulative incidence of death was estimated using time-dependent Cox proportional hazards model curves for overall survival (OS) in patients who received different treatments and at different stages. After adjustment for confounding factors, the time-dependent Cox proportional hazards model was also used to model the time between the index date and all-cause mortality in patients who received the aforementioned treatments. In the multivariate analysis, HRs were adjusted for curative therapy, age, CCI score, income, ASA physical status score, AJCC clinical stage, and region of residence. Because ASA physical status score, AJCC clinic stage, and curative therapeutic modality were statistically significant independent predictors of death (Table S2), we excluded

Table 2. Cox proportional hazards regression analysis of the risk of death among women with stage IB1-IIA cervical adenocarcinomas who received different curative therapy (All patients had ASA physical status scores of > 1, indicating tolerance toward curative surgery)

	Crude HR (95% CI)		Adjusted HR* (95% CI)		*P* value
Therapeutic modality (REF: Curative Surgery)					
Curative Definitive CCRT	2.45	(0.88, 3.83)	1.27	(0.77, 2.69)	0.239
Age (REF: < 65 y)					
Age ≥ 65 y	2.07	(0.74, 5.75)	1.63	(0.55, 4.82)	0.377
Income (REF: < NTD 22,000/month)					
NTD 22,000-36,000/month	0.65	(0.29, 1.46)	0.68	(0.3, 1.54)	0.357
NTD 36,000-48,000/month	0.26	(0.04, 1.89)	0.29	(0.04, 2.12)	0.221
≥ NTD 48,000/month	1.00	(0.36, 2.81)	1.14	(0.4, 3.24)	0.808
Region of residence (REF: rural)					
Urban	0.75	(0.41, 1.36)	0.76	(0.41, 1.4)	0.373
CCI Scores (REF: = 0)					
≥ 1	0.96	(0.49, 1.89)	0.85	(0.42, 1.7)	0.641

*All the aforementioned variables were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; REF, reference; NTD, New Taiwan dollar; CI, confidence interval; HR, Hazard Ratio; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

Table 3. Cox proportional hazards regression analysis of the risk of death among women with stage IIB cervical adenocarcinoma who received different curative therapy (all patients had ASA physical status scores of > 1, indicating tolerance toward curative surgery)

	Crude HR (95% CI)		Adjusted HR* (95% CI)		*P* value
Therapeutic Modality (REF: Curative Surgery)					
Curative Definitive CCRT	1.98	(1.15, 3.4)	2.46	(1.34, 4.53)	0.003
Age (REF: < 65 y)					
Age ≥ 65 y	1.45	(0.11, 1.84)	1.12	(0.08, 1.35)	0.122
Income (REF: < NTD 22,000/month)					
NTD 22,000-36,000/month	0.92	(0.47, 1.81)	1.24	(0.6, 2.55)	0.568
NTD 36,000-48,000/month	0.67	(0.21, 2.19)	0.86	(0.25, 2.94)	0.810
≥ NTD 48,000/month	1.12	(0.4, 3.15)	1.77	(0.59, 5.27)	0.306
Region of residence (REF: Rural)					
Urban	0.95	(0.52, 1.74)	1.02	(0.54, 1.94)	0.951
CCI Scores (REF: = 0)					
≥ 1	0.81	(0.44, 1.49)	0.76	(0.4, 1.42)	0.387

*All the aforementioned variables were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; REF, reference; NTD, New Taiwan Dollar; CI, confidence interval; HR, Hazard Ratio; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

patients with ASA physical status scores of > 1 from the study (**Table 1**). Stratified analyses of AJCC clinical stages in patients with cervical AC were performed using the Cox proportional hazards model to evaluate the risk of death associated with different curative treatments (**Tables 2**-**4**). All analyses were performed using SAS software (version 9.3; SAS, Cary, NC, USA). A two-tailed *P* value of < .05 was considered statistically significant.

The cumulative incidence of death was estimated using the inverse probability of treatment weighting (IPTW)-adjusted Kaplan-Meier method, and differences between the two treatment modalities were determined using the Cox model test (**Figures 1** and S1). After adjustment for confounding factors, the Cox proportional hazards method was used to model the time from the index date to death in patients receiving different curative-intent treatments. In the

Table 4. Cox proportional hazards regression analysis of the risk of death among women with stage III -IVA cervical adenocarcinoma who received different curative therapies (All patients had ASA physical status scores of > 1, indicating tolerance toward curative surgery)

	Crude HR (95% CI)		Adjusted HR* (95% CI)		*P* value
Therapeutic Modality (REF: Curative Surgery)					
Curative Definitive CCRT	1.51	(1.13, 2.01)	1.47	(1.09, 1.97)	0.011
Age (REF: < 65 y)					
Age ≥ 65 y	1.62	(0.79, 3.13)	1.24	(0.82, 2.46)	0.222
Income (REF: < NTD 22,000/month)					
NTD 22,000-36,000/month	1.06	(0.71, 1.59)	1.16	(0.77, 1.74)	0.484
NTD 36,000-48,000/month	1.13	(0.68, 1.87)	1.17	(0.7, 1.95)	0.552
≥ NTD 48,000/month	0.83	(0.41, 1.7)	0.86	(0.42, 1.77)	0.685
Region of residence (REF: Rural)					
Urban	0.95	(0.69, 1.31)	0.91	(0.65, 1.26)	0.564
CCI Scores (REF: = 0)					
≥ 1	1.17	(0.79, 1.76)	1.14	(0.76, 1.71)	0.530

*All the aforementioned variables were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; REF, reference; NTD, New Taiwan dollar; CI, confidence interval; HR, Hazard Ratio; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

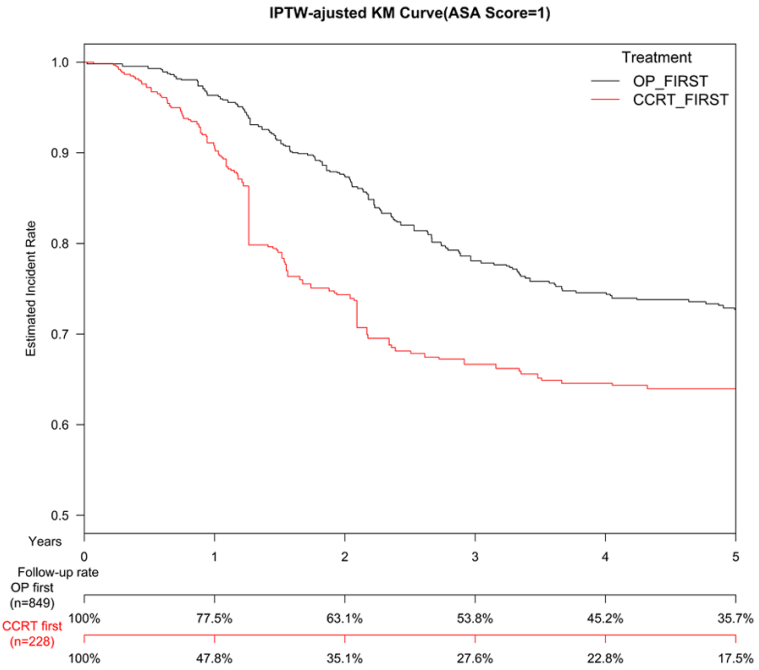

Figure 1. Cox proportional hazards model curves for overall survival of patients with cervical adenocarcinoma who underwent different curative treatments in all stages, as obtained using the inverse probability of treatment weighting-adjusted Kaplan-Meier method (adjusted for age, income, region of residence, Charlson comorbidity index score, and American Joint Committee on Cancer stage). (All patients had an American Society of Anesthesiologists physical status score of 1, indicaitng tolerance of curative surgery). Note: *P* value of the Cox model test for cumulative incidence of death in the two groups was 0.004.

multivariate analysis, the HRs were adjusted for age, CCI score, income, ASA physical status score, AJCC clinical stage, and residential region. A two-tailed *P* value of < .05 was considered statistically significant.

Results

First, data of 1,621 patients with cervical AC were extracted from the Taiwan Cancer Registry database (Table S1). After the exclusion of patients with ASA physical status scores of > 1, 1,077 patients with cervical AC remained (**Table 1**). Among the remaining patients, 849 and 228 received curative surgery (group 1) and curative definitive CCRT (group 2), respectively. In groups 1 and 2, the mean ages of the patients were 57.28 and 58.39 years, respectively, and the median follow-up durations were 4.430, and 1.79 years, respectively. The 2-year OS rates in groups 1 and 2 were 86.11% and 73.13%, respectively. Group 2 had a higher proportion of elderly patients with cervical AC than did group 1. Furthermore, the AJCC clinical stages in group 2 (stages IIB-IV) were

more advanced than those in group 1 (stages IB-IIA). The CCI scores in group 2 were higher than those in group 1. In group 2, the median total dose and fraction size of RT were 50.40 and 1.8 Gy per fraction to the whole pelvis and HDR IC brachytherapy 25 Gy to point A (**Table 1**). The median cumulative cisplatin dose was 600 mg/m^2 in group 2. The groups did not differ significantly in region of residence and income.

Univariate and multivariate Cox regression analysis indicated that high ASA physical status scores (> 1), high AJCC clinical stages (IIB-IV), and curative definitive CCRT were significant independent poor prognostic factors (Table S2). After multivariate analysis, curative definitive CCRT (adjust HR [aHR]: 1.44; 95% confidence interval [CI]: 1.21-1.86) was a significant independent poor prognostic factor for OS. An ASA physical status score of > 1 (aHR: 2.94; 95% CI: 1.47-4.28) was also a significant independent prognostic factor for OS ($P < .01$; Table S2). AJCC clinical stage was also a crucial independent prognostic factor. Furthermore, the aHRs increased with advancement from stage IIB to stage IVA (aHRs: 5.98, 6.94, and 18.54 for stages IIB, III, and IVA, respectively; Table S2). We divided the cohort into separate models for all patients with an ASA physical status score of 1, as defined by different AJCC clinical stages. A stratified Cox proportional hazards model was used to analyze the mortality risk associated with different treatment modalities at various AJCC clinical stages (**Tables 2**-**4**). After adjustment, the aHR (95% CIs) for overall mortality at early invasive clinical stages (IB-IIA) was 1.27 (0.77-2.69) in group 2 compared with group 1. Furthermore, the aHR (95% CI) for overall mortality at the AJCC clinical stage IIB was 2.46 (1.34-4.53) in group 2 compared with group 1 (**Table 3**). The aHR (95% CIs) for overall mortality at advanced clinical stages (III-IVA) was 1.47 (1.09-1.97) in group 2 compared with group 1 (**Table 4**).

The estimates of the cumulative incidence of mortality in the patients with cervical AC (all patients exhibited ASA physical status scores of 1 and could tolerate curative surgery), obtained using the IPTW-adjusted Kaplan-Meier method, were then used to determine the risk of death associated with the different curative treatments (**Figure 1**). To investigate the risk of death after the different curative treatments, group 1 was used as the control. After IPTW adjustments for age, income, region of residence, CCI score, and AJCC stage, the *P* value obtained from the Cox model test for the cumulative incidence of death in the two groups was .004 (**Figure 1**). Irrespective of their ASA physical status scores, we also estimated the cumulative incidence of death in women with cervical AC who received curative surgery or definitive CCRT by using the IPTW-adjusted Kaplan-Meier method adjusted for age, income, region of residence, CCI score, ASA physical status score, and AJCC stage (Figure S1). The *P* value obtained from the Cox model test for the cumulative incidence of major heart events in the two groups was < .001.

Discussion

The major clinical prognostic factors for cervical AC are the same as those reported in previous studies for SCC, including tumor extension, nodal status, tumor size, and AJCC clinical stage [23-25]. Whether histological type is an independent prognostic factor in cervical cancer remains controversial [7, 8, 26-30]. After adjustment for clinical stage, some series have supported the prognostic equivalence of cervical AC and SCC; however, most studies have shown that AC is associated with worse prognosis than SCC [7, 8, 26-30]. One of the largest studies, which included 24,562 patients with cervical cancer from the Surveillance, Epidemiology, and End Results database, showed a higher risk of death in women with AC who presented with early-stage cervical cancer (stages IB1-IIA) compared with those with SCC (odds ratio [OR] 1.39, 95% CI 1.23-1.56) as well as a higher risk of death in women with AC who presented with advanced stages of the disease (stages IIB-IVA) (OR 1.21, 95% CI 1.10-1.32) compared with those with SCC [30]. The relatively poor outcomes reported in many series have been attributed to several factors, including a higher rate of distant metastases in AC than in SCC [9, 31-33]. The use of cervical SCC treatments for cervical AC might be controversial, but sufficient evidence on optimal treatments for cervical AC at different clinical stages is currently unavailable. Assessing the major clinical prognostic factors in our current multivariate analysis with Cox regression showed that ASA physical status score, AJCC

stage, and different curative treatments were independent factors for risk of death in patients with cervical AC (Table S2). Our study is the first to prove that the AJCC clinic staging system seventh edition can offer satisfactory survival prediction not only in patients with cervical SCC but also in those with cervical AC. Our results also reveal that ASA physical status score is a more valuable tool than the CCI for improving the classification of prognostic comorbidities in cervical AC patients receiving curative treatments; therefore, ASA physical status score may be used as an alternative to the CCI (Table S2). As presented in **Tables 2**-**4**, at different disease stages, a relatively high CCI score was not an independent prognostic factor for OS. An explanation for this finding might be that we selected patients with cervical AC with an ASA physical status score of 1, indicating that they could tolerate curative surgery as well as the toxicity from curative treatments. Our study is the first to demonstrate that different curative therapeutic decisions would exert major effects on the OS of patients with cervical AC.

Most of the data that guide the treatment of cervical cancer have been obtained from randomized trials in which the majority of patients had SCC, with patients with AC constituting only 10% of the cases, on average [4-9]. None of these trials have reported separate outcomes for AC, and no prospective study has focused on the treatment of AC as the sole histology. Consequently, treatment for AC follows the principles established for cervical SCC at most institutions. However, data from some of these randomized trials that have reported subgroup analysis according to cell type have suggested that treatments might have different effects on recurrence rates and survival [4, 5]. A second US Intergroup trial compared CCRT versus RT alone in 243 patients (50 patients with AC) with resected clinical stage IA2, IB, or IIA cervical cancer [5]. In a subgroup analysis, patients with AC exhibited worse prognosis than did those with SCC when treated with RT alone; this difference was not observed in patients who received CT in addition to RT [5]. The findings are consistent with our findings presented in **Table 2**; the risk of death in patients with early-stage cervical AC who received curative definitive CCRT was not significantly different from that in those who received curative surgery. Another trial included patients with stage IB-IIA cervical cancer, who were randomly assigned to surgery (n = 172) or radical RT (n = 171); 46 patients had AC [4]. In the entire cohort, the 5-year OS did not differ between the surgery and RT arms; however, among the patients with AC, surgery appeared to be significantly more advantageous than RT alone (5-year OS 70% versus 59%) [4]. These data indicate a high possibility that responses to specific components of a treatment can differ between patients with AC and those with SCC [4, 5]. The use of RT a part of treatment modalities for disease management may be effective in achieving local control in early-stage cervical AC. Nevertheless, even with adequate pelvic control in cervical AC treated with RT, distant relapse rates are relatively high. This thus raises the question of whether distant relapse could be prevented through the routine use of systemic CT. However, previous studies have not compared survival outcomes in curative surgery with those in curative definitive CCRT in cervical AC. Accordingly, our study is the first and the largest to demonstrate that OS did not differ between the curative surgery and curative definitive CCRT groups in patients with stage IB to IIA cervical AC (**Table 2**). In addition, our study including all patients with cervical AC hypothesis creation are different from previous studies with unplanned subset analyses of small groups of patients, and nonhypothesis generating [4, 5]. Our findings show that CCRT with cisplatin-based CT was also a feasible curative treatment in the early stages of cervical AC compared with curative surgery. As mentioned, because patients with AC treated with RT alone may exhibit poorer outcomes compared with patients with SCC, relative radioresistance and high distant relapse rates might be overcome through the use of concurrent cisplatin-based CT. Consequently, when RT is administered for treating early-stage cervical AC, we suggest concurrent cisplatin-based CT with RT instead of RT alone.

For women with locoregionally advanced cervical SCC, primary RT has been the treatment of choice at most institutions, although practices vary. Guidelines from the National Comprehensive Cancer Network suggest either initial curative surgery or initial curative definitive CCRT for such patients [34]. However, in previous studies, patients with advanced-stage (IIB-IVA) SCC have initially been treated with

CCRT [5, 35, 36]. One of the main arguments against a primary surgical approach for such patients is the high potential for multimodality therapy, given that the majority of women have high-risk or intermediate-risk disease for which adjuvant CCRT is recommended [5, 35, 36]. Multiple randomized phase III trials, which have predominantly enrolled patients with SCC, and a meta-analysis have confirmed the survival benefit of adding cisplatin-based concurrent CT to RT for primary treatment of locally advanced cervical cancer [5, 37]. CCRT appears to be a reasonable treatment for AC, according to previous studies on AC that have predominantly enrolled patients with SCC [5, 35-37]. Nevertheless, AC-specific phase III trials are not feasibly due to the low incidence of glandular disease. Moreover, the poor prognosis of all histological types of advanced disease, particularly stage III-IV disease, emphasizes the need for novel approaches [38, 39]. In our multivariate analysis, patients with stage IIB-IVA cervical AC who were treated with CCRT first exhibited poorer OS than did those who were treated with surgery first (**Tables 3** and **4**). This is the first study to demonstrate that curative surgery at advanced stages of cervical AC is associated with superior OS compared with CCRT. The less promising outcomes observed for CCRT might be because advanced-stage (IIB-IVA) cervical AC tumors exhibit considerably high radioresistance, large sizes, extensive metastases, and high depths of invasion, which could not be overcome by even curative definitive CCRT with concurrent cisplatin-based CT. Performing surgery first can remove large volumes of radioresistant AC tumors, resulting in superior OS compared with definitive CCRT.

As illustrated in **Figure 1**, after adjustments for age, income, region of residence, CCI score, and AJCC stage, women with cervical AC who received curative surgery exhibited superior OS compared with those who received curative definitive CCRT. This is the first study to reveal that surgery might be associated with superior OS in cervical AC, particularly that at locoregionally advanced stages (stages IIV-IV), compared with definitive CCRT (**Tables 3** and **4**). For therapeutic decisions of curative treatments in the early invasive stage of cervical AC (Stage IB-IIB), curative definitive CCRT and curative surgery did not differ significantly (**Table 2**).

The strength of our study is that it is the first to compare curative surgery and curative definitive CCRT in order to estimate the optimal curative therapy for cervical AC with stratified analysis of different clinical stages. Furthermore, among existing studies, the current study has the largest sample size, most homogenous histology, highest curative therapeutic consistency for cervical AC. AC-specific phase III trials are not feasible because of the low incidence of cervical AC. The study outcomes support the importance of curative surgery in cervical AC at advanced clinical stages. Definitive CCRT might be an option in early invasive clinical stages (IB-IIA) of cervical AC. These findings could also be considered in future clinical practices and randomized controlled studies.

This study has some limitations. First, the toxicity induced by the two curative treatments could not be determined; therefore, the treatment-related mortality estimates may have been biased. However, a previous study demonstrated more complications and higher toxicity in curative surgery compared with CCRT at advanced stages [35]. In the current study, the benefits of an improved survival rate engendered by curative surgery at advanced stages could only be underestimated. Second, because all patients with cervical AC were enrolled from an Asian population, the corresponding ethnic susceptibility remains unclear; hence, our results should be cautiously extrapolated to non-Asian populations. Third, there was no HPV typing performed in this study but there is a large number of AC with HPV and precious study showed no survival differences in various HPV typing in cervical AC [40]. Fourth, there was no next generation sequencing or molecular biomarkers in the study lacking the landscape of genetic alterations in cervical AC, because there was no genetic funding in TCRD. Fifth, 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 chargers or practices may be audited and subsequently be heavily penalized if malpractice or discrepancies are identified. Sixth, to prevent the creation of several subgroups, various adjuvant treatments after curative surgery or curative definitive CCRT were not categorized separately during the

analyses. Thus, the effects of different adjuvant treatments remain unclear. 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.

Conclusions

Curative surgery improves survival in cervical AC at advanced clinical stages. Curative surgery or definitive CCRT might be an option in early invasive clinical stages of cervical AC.

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Disclosure of conflict of interest

None.

Abbreviations

RT, radiotherapy; CT, chemotherapy; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CCRT, concurrent chemoradiotherapy; AJCC, American Joint Committee on Cancer; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index; AC, adenocarcinoma; SCC, squamous cell carcinoma; OS, overall survival; CCRT, concurrent chemoradiotherapy; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; Gy, gray; US, United States; HDR, high dose rate; IC, intracavity; IPTW, inverse probability of treatment weighting; OR, odds ratio.

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Table S1. Characteristics of patients with cervical adenocarcinoma who received curative surgery or definitive CCRT

	Curative Surgery n = 1,226 (%)		Curative definitive CCRT n = 395 (%)		*P* value
Age Group					< 0.001
Age < 65 y	1131	92.25%	305	77.22%	
Age ≥ 65 y	95	7.75%	90	22.78%	
Income					0.035
< NTD 22,000/month	790	64.44%	286	72.41%	
NTD 22,000-36,000/month	233	19.00%	57	14.43%	
NTD 36,000-48,000/month	108	8.81%	29	7.34%	
≥ NTD 48,000/month	95	7.75%	23	5.82%	
Region of residence					0.951
Rural	333	27.16%	106	26.84%	
Urban	893	72.84%	289	73.16%	
CCI Scores					< 0.001
CCI < 0	206	16.80%	34	8.61%	
CCI ≥ 1	1020	83.20%	361	91.39%	
ASA Scores					< 0.001
ASA ≤ 1	849	69.25%	228	57.72%	
ASA > 1	377	30.75%	167	42.28%	
AJCC Stages					< 0.001
IB1-IIA	832	67.86%	54	13.67%	
IIB	108	8.81%	108	27.34%	
III	194	15.82%	91	23.04%	
IVA	92	7.50%	142	35.95%	
Death					< 0.001
No	965	78.71%	180	45.57%	
Yes	261	21.29%	215	54.43%	
Follow-up (Years) (median, IQR)	(4.18, 5.04)		(1.65, 2.79)		< 0.001
RT dose (Gy) (median, IQR)	NA		(52.20, 13.30)		< 0.001
Brachytherapy dose (Gy) (median, IQR)	NA		(25, 9.0)		< 0.001
Cisplatin Cumulative dose (mg/m^2) (median, IQR)	NA		(550, 250)		< 0.001

RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IQR, interquartile range; NTD, New Taiwan dollar; Gy, gray; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

Table S2. Cox proportional hazards regression analysis of the risk of death among the patients with cervical adenocarcinomas and received different curative therapies

	Crude HR (95% CI)		Adjusted HR* (95% CI)		*P*-value
Therapeutic modality (REF: Curative surgery)					
Curative definitive CCRT	2.38	(2.04, 3.05)	1.44	(1.21, 1.86)	< 0.001
Age (REF: < 65 y)					
Age ≥ 65 y	1.29	(0.77, 2.17)	1.20	(0.7, 2.05)	0.512
Income (REF: < NTD 22,000/month)					
NTD 22,000-36,000/month	0.84	(0.61, 1.16)	0.94	(0.68, 1.3)	0.713
NTD 36,000-48,000/month	0.91	(0.58, 1.42)	0.95	(0.6, 1.5)	0.836
≥ NTD 48,000/month	0.76	(0.46, 1.26)	0.97	(0.58, 1.63)	0.918
Regions of residence (REF: rural)					
Urban	0.95	(0.73, 1.23)	0.90	(0.69, 1.17)	0.415
CCI Scores (REF: CCI = 0)					
≥ 1	1.15	(0.85, 1.55)	0.94	(0.7, 1.28)	0.710
ASA Scores (REF: ASA = 1)					
> 1	3.13	(1.94, 3.35)	2.94	(1.47, 4.28)	< 0.001
AJCC Stages (REF: IB1-IIA)					
IIB	7.14	(4.84, 10.54)	6.11	(4.07, 9.18)	< 0.001
III	7.80	(5.47, 11.13)	6.94	(4.8, 10.04)	< 0.001
IVA	21.52	(15.16, 30.56)	18.54	(12.77, 26.91)	< 0.001

*All the aforementioned variables were used in the multivariate analysis. CCRT, concurrent chemoradiotherapy; REF, reference; NTD, New Taiwan dollar; CI, confidence interval; HR, Hazard Ratio; ASA, American Society of Anesthesiologists; CCI, Charlson Comorbidity Index; AJCC, The American Joint Committee on Cancer; NA, not available.

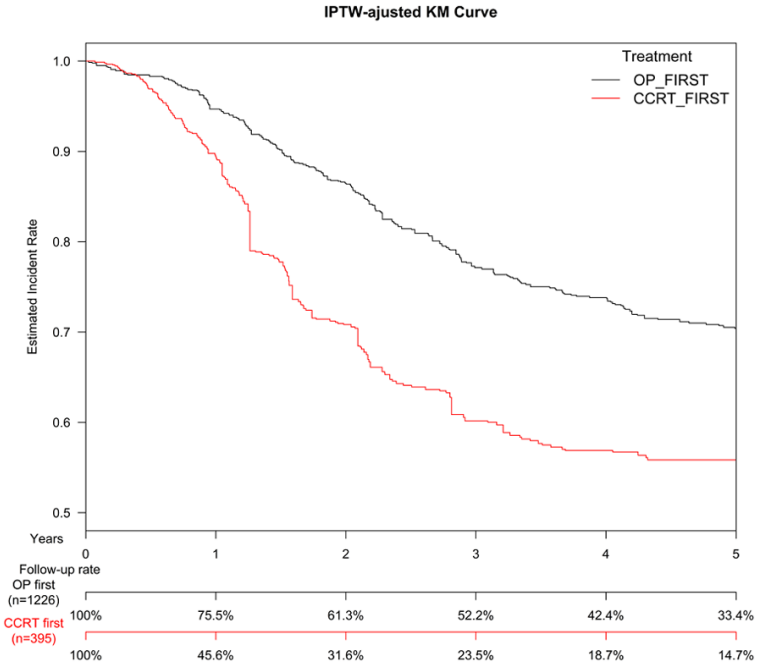

Figure S1. Cox proportional hazards model curves for overall survival of cervical adenocarcinoma patients who underwent different curative treatments in all stages, as obtained using the inverse probability of treatment weighting-adjusted Kaplan-Meier method. (adjusted for age, income, regions, CCI scores, ASA scores, and AJCC stages). Note: *P* value of Cox model test for cumulative incidence of major heart events in the two groups was < 0.001.