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Differential clinical characteristics, treatment response and prognosis of locally advanced adenocarcinoma/adenosquamous carcinoma and squamous cell carcinoma of cervix treated with definitive radiotherapy

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Key words
Adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, cervix, radiotherapy

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Conflict of interest
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Abstract

Objective. To compare tumor characteristics and clinical outcome of patients with cervical locally advanced adenocarcinoma (AC)/adenosquamous carcinoma (ASC) and squamous cell carcinoma (SCC). *Design.* Retrospective study. *Setting.* National Taiwan University Hospital, Taipei, Taiwan. *Population.* All patients with cervical SCC (n = 35), AC or ASC (n = 194) with FIGO stage ≥IIB who received definitive radiotherapy or concurrent chemoradiotherapy (CCRT) from January 1995 to December 2009. *Method.* Medical and histopathological record review. *Main outcome measures.* Progression-free survival (PFS), local recurrence-free survival, distant metastasis-free survival, and overall survival (OS). *Results.* Compared with the SCC subgroup, patients with AC/ASC were significantly younger (p = 0.007), more of them without clinical symptoms were diagnosed by abnormal Pap smear findings (p = 0.043), and less responded to treatment (p = 0.018). After a median follow-up of 59.3 months, patients with AC/ASC had worse 5-year PFS (30.0% vs. 47.6%, p = 0.044), worse 5-year distant metastasis-free survival (41.5% vs. 69.9%, p = 0.005), and trends toward worse 5-year local recurrence-free survival (64.4% vs. 76.2%, p = 0.165) and worse 5-year OS (41.3% vs. 58.1%, p = 0.090) than patients with SCC. In univariate analysis, early FIGO stage and complete treatment response were significantly associated with PFS and OS. Histology of non-AC/ASC and Point A biologically equivalent doses in 2-Gy fractions >85 Gy were significantly associated with better PFS, and CCRT was significantly associated with better OS. In multivariate analysis, complete treatment response and early FIGO stage remained significant factors for predicting better PFS and OS. *Conclusions.* Cervical AC/ASC may be more aggressive than is SCC. For cervical AC/ASC, more comprehensively effective treatments are warranted.

Abbreviations: AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; EQD2, median biologically equivalent doses in

2-Gy fractions; FIGO, International Federation of Gynecology and Obstetrics; HDR, high dose rate; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SCC, squamous cell carcinoma.

Introduction

Adenocarcinoma (AC) and adenosquamous carcinoma (ASC) of the cervix are common histologic subtypes of non-squamous cell cervical cancer, accounting for 10–20% of cervical malignancies (1). Based on our recent study, cervical ASC could be categorized as one subtype of AC, since no difference was found in epidemiology, treatment modality or outcome (2). Compared with squamous cell carcinoma (SCC) of cervix, the relative proportion and the absolute incidence of AC and ASC has increased in the past two decades, since the incidence of cervical SCC has been declining after the wide implementation of Papanicolaou (Pap) smear screening for this disease (3,4). In clinical practice, patients with AC/ASC often received the same first-line treatment as those with SCC; however, the decision is often based on the results of studies in which the majority of patients had SCC (5,6). Nonetheless, it is worth investigating whether the same treatment strategy should be followed for patients with AC/ASC as for patients with SCC, especially in those with locally advanced disease, who are likely to have received definite radiotherapy (RT) with or without chemotherapy.

Our previous studies showed that in 300 patients with AC/ASC of the cervix (stage I–IV) who received surgery, RT, chemotherapy or combined modalities between 1977 and 1994, patients with AC/ASC were relatively younger at diagnosis and had a decreased survival rate compared with those with SCC in all stages (7,8). Even in early-stage disease, and in patients who had received RT alone, patients with AC/ASC had a worse prognosis than those with SCC (7,8). These findings suggest that the clinical behavior of the tumor and the effectiveness of RT may be different in AC/ASC vs. SCC (2). In addition to our previous study, increasing evidence has demonstrated that between AC/ASC and SCC cases there are differences in epidemiology, prognostic factors, response to similar treatment, and patterns of failure after first-line treatment (1,9). In a recent review of cervical AC by Gien et al. (1), the researchers showed a worse survival outcome for AC when comparing the survival outcome between stage IB and IIB in AC and SCC (1). However, the different response to RT and survival outcome between IIB and IVA AC/ASC and SCC is rarely studied.

Given that patients with International Federation of Gynecology and Obstetrics (FIGO) ≥ stage IIB locally advanced cervical cancer, including SCC and AC/ASC subtypes, were treated with RT or concurrent chemoradiotherapy (CCRT) (10,11), in the present study, we sought to compare the tumor characteristics, treatment response, failure pattern and clinical outcome of these two subgroups of patients (stage IIB–IVA cervical cancer, AC/ASC compared with SCC) who received definitive RT or CCRT.

Material and methods

The study was approved by the Institutional Review Board of National Taiwan University Hospital (201202045RIC). Between 1995 and 2009, 229 women with FIGO stage IIB–IVA non-metastatic histologically proven cervical AC/ASC and SCC who received definitive RT or CCRT as primary treatment in our institution were included. The women were retrospectively evaluated for clinical characteristics, treatment parameters, treatment responses, and outcomes between histologic groups. The initial clinical symptoms, including no symptoms (diagnosed by abnormal cervical smear), bleeding, spotting/discharge, urinary symptoms or low abdominal pain, were coded for each patient. Since this study included patients who received definitive RT or CCRT, their actual initial tumor sizes or lymph node status was not available for the entire group.

External beam RT plus high dose rate (HDR) intracavitary brachytherapy was our standard protocol for locally advanced cervical cancer. Patients received 40–45 Gy whole-pelvis RT with 6- or 10-MV photon beams using either parallel-opposed anteroposterior or four-field box beams, with 1.8–2.0 Gy/fraction and five fractions weekly. An extended field to the para-aortic region to T12/L1 level at a dose of 40 Gy was not routinely given unless imaging suggested para-aortic lymphadenopathy. The parametria received a boost to ≤60 Gy using

Key Message

For patients with locally advanced cervical cancer, adenocarcinoma/adenosquamous carcinoma histology is associated with more radioresistance and more aggressive behavior than is seen with squamous cell carcinoma histology.

parallel-opposed anteroposterior fields with a 4-cm wide rectangular midline block. The intracavitary brachytherapy was given using a ^{192}Ir source. The dose to Point A was at the discretion of a radiation oncologist, using 5 Gy/fraction for five fractions, 6 Gy/fraction for four fractions or 7 Gy/fractions for three fractions, with one to two fractions weekly. The median biologically equivalent doses in 2-Gy fractions (EQD2) to Point A generated from the contribution of external beam RT and HDR ICRT was 80.0 Gy, with the α/β ratio for tumor effects assumed to be 10 Gy (12). For the three women who had had a previous hysterectomy due to benign disease, including adenomyosis or uterine fibroids (two in AC/ASC and one in SCC group), the vaginal cuff was boosted with an HDR dome cylinder limited to 10 Gy/fraction for two fractions prescribed to the vaginal surface.

In our institution, concurrent CCRT with weekly cisplatin at a dose of 30–45 mg/m^2 has been the major protocol drug for locally advanced cervical cancer. In the current study, the patients did not receive adjuvant chemotherapy.

All women were followed up every 3 months for the first 2 years, every 4 months for the third and fourth years, and then every 6 months until recurrence or death. The work-up during the follow-up period included pelvic examinations, tumor marker determination, cervical smears and imaging studies, if required. Incomplete treatment response was defined as persistent tumor at cervix after 3 months of all treatments, based on pelvic examinations, image studies or pathologic/cytologic evidence. Late toxicities were assessed at the time of each evaluation with the use of the Radiation Therapy Oncology Group late toxicity score. Local recurrence was defined as persistent tumor after treatment, recurrence in the primary tumor or lymph nodes below the aortic bifurcation; distant metastasis as disease recurrence outside the pelvis according to pathologic or radiologic evidence. Synchronous local and distant recurrence was defined as recurrence in which the interval between the two events was less than 1 month. First recurrence was defined only by the site of the first relapse, such as local, distant or synchronous. The survival data were confirmed with the Cancer Registry Medical Information Management Office in our hospital. Progression-free survival (PFS) was defined as the time in months from treatment completion to the date of recurrence, death or censoring, and overall survival (OS) as the time in months from treatment completion to the date of death, last follow-up or censoring.

Statistical analysis

Frequency distributions were compared using Pearson's chi-squared test, and mean values were compared using Student's *t*-test. Analysis was conducted using the follow-up data available on 30 June 2013. Kaplan–Meier life table analysis and the log-rank test were used to assess the survival rate and to differentiate according to the prognostic factors. All prognostic variables found to be significant in univariate analysis were included in the multivariate analysis using the Cox proportional hazards regression model. A *p*-value of $\leq$0.05 was considered significant.

Results

Between 1995 and 2009, 35 patients with FIGO stage IIB–IVA non-metastatic cervix AC/ASC and 194 patients with SCC receiving definitive RT or CCRT were included in the study. As shown in Table 1, compared with the SCC subgroup, patients with AC/ASC were significantly

Table 1. Characteristics of the study patients.

	AC/ASC		SCC		
	n = 35	%	*n* = 194	%	*p*-value
Age					
Mean (range)	56 (29–89)		63 (27–92)		0.007[a]
<40	4	11.4	10	5.2	0.010[b]
40–60	19	54.3	65	33.5	
≥60	12	34.3	119	61.3	
FIGO stage					
IIB	26	74.3	134	69.1	0.443[b]
IIIA IIIB	6	17.1	50	25.8	
IVA	3	8.6	10	5.2	
Major presenting symptoms					
None (diagnosed by abnormal Pap smear)	6	17.1	11	5.7	0.043[b]
Bleeding	20	57.1	118	60.8	
Spotting/ discharge	4	11.4	51	26.3	
Urinary symptoms	3	8.6	8	4.1	
Low abdominal pain	2	5.7	6	3.1	
Histology subtype					
AC	31	88.6			
ASC	4	11.4			
Gravidity					
Mean (range)	4 (0–12)		5 (0–12)		0.084[a]
<5	24	68.6	102	52.6	0.080[b]
≥5	11	31.4	92	47.4	

AC, adenocarcinoma; ASC, adenosquamous carcinoma; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

[a]Significance tested using Student's *t*-test.

[b]Significance tested using Pearson's chi-squared test.

younger ($p = 0.007$), and more of them were diagnosed by abnormal cervical smear without clinical symptoms ($p = 0.043$).

The treatment methods (Table 2) did not differ between histologic groups ($p = 0.675$). Of the 35 AC/ASC patients, 14 (40.0%) received RT and 21 (60.0%) CCRT. Of the 194 patients with SCC, 85 (43.8%) received RT and 109 (56.2%) CCRT. With regard to treatment response, 28.6% of patients with AC/ASC were found to have persistent tumor 3 months after completion of treatment, compared to only 12.9% of patients with SCC ($p = 0.018$). Of the 35 patients with persistent tumor, eight underwent salvage surgery (two with AC/ASC and six with SCC, $p = 0.799$). The late morbidities after RT (Table 2) were mainly in the gastrointestinal system.

Table 2. Treatment related parameters of the study patients receiving definitive radiotherapy.

	AC/ASC		SCC		
	n = 35	%	*n* = 194	%	*p*-value
Treatment method					
RT	14	40.0	85	43.8	0.675[c]
CCRT	21	60.0	109	56.2	
CCRT weekly chemotherapy cycles	*n* = 21		*n* = 109		
Mean	5		5		0.546[a]
<5	4	19.0	42	38.5	0.087[c]
≥5	17	81.0	67	61.5	
Brachytherapy technique in definitive treatment					
No brachytherapy	2	5.7	16	8.2	0.041[c]
Vaginal cuff brachytherapy	2	5.7	1	0.5	
Intracavitary brachytherapy	31	88.6	177	91.2	
Point A EQD2 (EBRT + HDR brachytherapy)					
≥85 Gy	10	28.6	80	41.2	0.086[c]
75–85 Gy	22	62.9	83	42.8	
<75 Gy	3	8.6	31	16.0	
RT duration					
Mean (days)	57		59		0.520[a]
≤8 weeks	15	44.4	76	39.2	0.682[c]
>8 weeks	20	55.6	118	60.8	
Treatment response					
Complete	25	71.4	169	87.1	0.018[c]
Incomplete[b]	10	28.6	25	12.9	
Treatment-related late complications					
Grade 3 radiation proctitis	6	17.1	17	8.8	0.727[c]
Grade 3 radiation cystitis	0	0.0	7	3.6	
Grade 4 RV/VV fistula	2	5.7	11	5.7	
Grade 4 Hip AVN	0	0.0	2	1.0	

AC, adenocarcinoma; ASC, adenosquamous carcinoma; AVN, avascular necrosis; CCRT, concurrent chemoradiotherapy; EBRT, external beam radiotherapy; EQD2, biologically equivalent doses in 2-Gy fractions; HDR, high dose rate; RT, radiotherapy; RV, recto-vaginal; SCC, squamous cell carcinoma; VV, vesico-vaginal.

[a]Significance tested using Student's *t*-test.

[b]Incomplete: persistent cervical tumor after 3 months of treatment.

[c]Significance tested using Pearson's chi-squared test.

The median follow-up time was 59.3 months. The median PFS and 5-year PFS rates for AC/ASC patients and SCC patients were 29.5 months and 30.0%, and 57.8 months and 47.6%, respectively ($p = 0.044$, Figure 1A). The median OS and 5-year OS rates for AC/ASC patients and SCC patients were 52.7 months and 41.3%, and 73.6 months and 58.1%, respectively ($p = 0.090$, Figure 1B).

As shown in Table 3, the pattern of first recurrence did not differ between histologic groups. The 5-year local recurrence-free survival rates for AC/ASC and SCC patients were 64.4 and 76.2%, respectively ($p = 0.165$, Figure 1C). The 5-year distant metastasis-free survival rates for AC/ASC and SCC patients were 41.5 and 69.9%, respectively ($p = 0.005$, Figure 1D). As shown in Table 4, when compared with SCC patients, patients in the AC/ASC group experienced more distant metastasis (51.4% vs. 26.8%, $p = 0.004$). Furthermore, the PFS and OS of these patients were stratified according to FIGO stage. In FIGO stage IIB patients, the 5-year PFS and OS for patients with AC/ASC were 34.6 and 50.6%, and with SCC 53.3 and 63.1% ($p = 0.150$ and $p = 0.373$, respectively). In FIGO stage III or IVA patients, the 5-year PFS and OS for patients with AC/ASC was 14.8 and 13.3%, and with SCC 34.6 and 46.8% ($p = 0.135$ and $p = 0.013$, respectively).

On univariate analysis of all patients (Table 5), FIGO stage and treatment response were found to be significantly associated with both PFS and OS. Histology and Point A EQD2 were significantly associated with PFS, and concurrent chemotherapy was significantly associated with OS. After multivariate analysis (Table 6), incomplete treatment response and FIGO stage III or IVA remained significant factors for predicting worse PFS and OS, and RT alone remained a significant factor for predicting worse OS.

Discussion

We have demonstrated that patients with locally advanced AC/ASC (most with AC) were younger and more likely to have had increased radioresistance of the tumors, and they also had worse PFS and somewhat worse OS than did those with SCC. These findings suggest that the underlying biological properties are responsible for the different clinical behavior of AC/ASC and SCC. In addition, incomplete response to RT or CCRT and FIGO stage III or IVA are important factors for predicting worse OS in patients with AC/ASC. These results are line

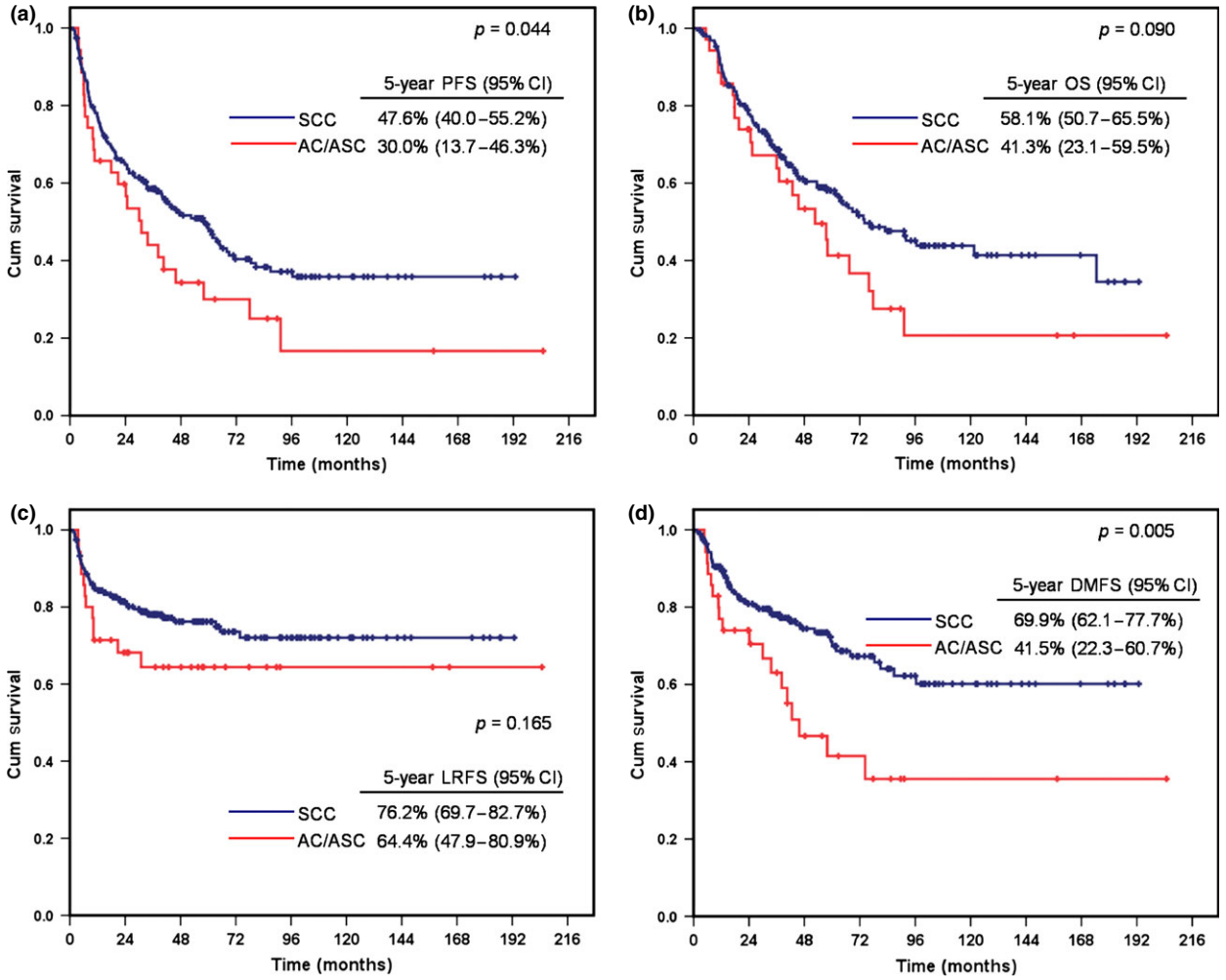

Figure 1. Long-term outcome of patients with locally advanced adenocarcinoma (AC)/adenosquamous carcinoma (ASC) (n = 35) and squamous cell carcinoma (SCC) of cervix (n = 194). (a) Progression-free survival (PFS), p = 0.044. (b) Overall survival (OS), p = 0.090. (c) Local recurrence-free survival (LRFS), p = 0.165. (d) Distant metastasis-free survival (DMFS), p = 0.005.

Table 3. First recurrence patterns of the study patients.

	AC/ASC		SCC		
	n = 35	%	n = 194	%	p-value[a]
Local recurrence	7	20.0	35	18.0	0.188
Distant recurrence	9	25.7	35	18.0	
Synchronous (<1 month) local and distant failure	4	11.4	9	4.6	

AC, adenocarcinoma; ASC, adenosquamous carcinoma; SCC, squamous cell carcinoma.
[a]Significance tested using Pearson's chi-squared test.

with the recent review by Gien et al. (1). In their analyses, AC was associated with significantly lower survival rates than SCC in the same advanced stage, and AC showed differences in response to RT and chemotherapy regimens, a higher incidence of local recurrence, lymph nodes metastases, and distant metastases when compared with SCC.

The epidemiologic factors associated with cervical AC are different from those associated with SCC (1,9,13). For example, in an early study of cervical AC, Miller et al. (13) reported an increasing percentage of cervical AC (including ASC), from 16% in 1964 to 24% in 1989 for women younger than 35 years. Around 39% of them had the disease diagnosed by cytopathologic examination (13). These findings were supported by our current observations that patients with locally advanced AC/ASC of the cervix were, on average, 6 years younger than those with SCC, and more were diagnosed by abnormal cervical smears without clinical symptoms.

Table 4. Total recurrence during follow-up period and locations of the study patients.

	AC/ASC		SCC		
	n = 35	%	*n* = 194	%	*p*-value[a]
Total local recurrence					0.163
No LR	23	65.7	149	76.8	
LR	12	34.3	45	23.2	
Persistence of disease	10		25		
Cervix	1		12		
Pelvis beyond cervix	1		8		
Total distant metastasis					0.004
No DM	17	48.6	142	73.2	
DM	18	51.4	52	26.8	
Lung	4		15		
Para-aortic lymph node	4		19		
Neck lymph node	5		9		
Liver	6		5		
Bone	2		9		
Cancerous peritonitis	9		3		

AC, adenocarcinoma; ASC, adenosquamous carcinoma; DM, distant metastasis; LR, local recurrence; SCC, squamous cell carcinoma.
[a]Significance tested using Pearson's chi-squared test.

Table 5. Univariate analysis of risk factors on progression-free and overall survival of the study patients.

		p-value[a]	
	n	5-year PFS (%)	5-year OS (%)
Histology		*0.044*	*0.090*
AC/ASC	35	30.0	41.3
SCC	194	47.6	58.1
Age		*0.757*	*0.654*
<40	14	46.9	51.9
40–60	84	40.2	58.3
≥60	131	47.4	53.6
FIGO stage		*0.003*	*0.003*
IIB	160	50.1	60.9
III IVA	69	32.2	42.3
Concurrent chemotherapy		*0.060*	*0.011*
Yes (CCRT)	130	48.0	61.6
No (RT only)	99	40.7	46.9
Point A EQD2 (EBRT + HDR brachytherapy)		*0.013*	*0.053*
≥85 Gy	90	51.9	60.4
75–85 Gy	105	44.4	54.4
<75 Gy	34	29.8	45.3
RT duration		*0.182*	*0.078*
≤8 weeks	91	39.4	51.5
>8 weeks	138	48.9	58.2
Treatment response		*<0.001*	*<0.001*
Complete	194	53.0	64.7
Incomplete[b]	35	0	4.7

AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; EBRT, external beam radiotherapy; EQD2, biologically equivalent doses in 2-Gy fractions; HDR, high dose rate; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy; SCC, squamous cell carcinoma.
[a]Significance tested using Kaplan–Meier life table analysis and the log-rank test.
[b]Incomplete: persistent cervical tumor after 3 months of treatment.

When comparing the survival rates by histologic subtype and by stage, several studies have suggested that patients with certain histologic subtypes of AC, including ASC, had a worse prognosis than did those with SCC (2,14–16). Our present study demonstrated that in the modern era of improving radiation techniques and the use of HDR brachytherapy, patients with AC/ASC had a worse 5-year survival when compared with patients with a similar stage of SCC. In accordance with the previous reports that patients with stage IIB–IVA had a 5-year OS ranging from 31 to 38%, our study still demonstrated that patients with stage IIB/III/IV AC/ASC receiving definitive RT or CCRT had a 5-year OS of 41.3%, which was not less than previously reported (14–17).

In the present study, more SCC patients had received Point A dose > 85 Gy than AC/ASC patients did (41.2 vs 28.6%, $p = 0.086$). It could be argued that insufficient brachytherapy dose may decrease the local control and affect clinical outcomes for AC/ASC patients. However, nearly one-third of AC/ASC patients (28.6%) had persistent tumor at the cervix 3 months after completing RT. Our findings are in accordance with a recent observation that 40% of 148 AC/ASC patients (77% advanced stage) had residual tumors after definitive RT (the median biologically equivalent dose to Point A: 90 Gy, α/β ratio: 10 Gy) (17). Importantly, poor tumor regression after RT has been recognized as an important poor prognostic factor for relapse-free survival (17). In addition, Moyses et al. (18) showed a higher incidence of residual tumor for AC/ASC (91%) than for SCC (48%) after preoperative RT for stage IB cervical cancer. Poujade et al. (19) also showed that 67% of stage IB2–IIIB cervical AC patients had a pathologic residual tumor after neoadjuvant CCRT (19). These findings suggested that cervical AC/ASC is more radioresistant than SCC. Because cervical AC/ASC showed little regression to RT, salvage surgery may be an alternative treatment strategy for patients who have responded poorly to RT or CCRT.

Although several randomized trials have shown the efficacy of concurrent CCRT in improving local control and survival for patients with high-risk and locally advanced cervical cancer (11), the efficacy of cisplatin-based chemotherapy on AC/ASC remains unclear because these randomized trials have included only a minority of

Table 6. Multivariate analysis of risk factors on progression-free and overall survival of the study patients (n = 229).

	Progression-free survival			Overall survival		
	HR	95% CI	p-value[b]	HR	95% CI	p-value[b]
AC/ASC vs. SCC	1.13	0.72–1.78	0.600	1.20	0.73–1.95	0.476
FIGO stage IIB vs. III or IVA	0.82	0.68–0.98	0.027	0.76	0.62–0.92	0.006
CCRT vs. RT alone	0.84	0.71–1.01	0.065	0.77	0.63–0.94	0.009
Point A EQD2 ≥ 85 vs. <85 Gy	0.97	0.80–1.19	0.790	0.92	0.74–1.15	0.446
Treatment response complete vs. incomplete[a]	0.24	0.19–0.31	<0.001	0.38	0.30–0.48	<0.001

AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBRT, external beam radiotherapy; EQD2, biologically equivalent doses in 2-Gy fractions; HDR, high dose rate; RT, radiotherapy; SCC, squamous cell carcinoma.
[a]Incomplete: persistent cervical tumor after 3 months of treatment.
[b]Significance tested using the Cox proportional hazards regression model.

patients with AC/ASC, ranging from 10 to 20%. The addition of chemotherapy to RT was thought to improve the survival of patients with AC/ASC by increasing radiosensitivities and inhibiting micrometastases. Our present study demonstrated that a greater percentage of AC/ASC patients receiving CCRT (76.2%) had a complete response, compared with those receiving RT (64.3%); however, the greater benefit of CCRT was not apparent when evaluating local or distant PFS, and OS of our patients.

Our study excluded patients with FIGO stage I–IIA disease because treatment outcomes for these patients may be influenced by factors related to surgery. The present study presented different clinical manifestations and treatment outcomes between AC/ASC and SCC; nevertheless, the small number of patients, single center experience, and 14 years of retrospective inclusion could limit the present conclusions.

Based on the results of previously published retrospective studies and reviewed results, and on the results of our study, AC/ASC of the cervix is more radioresistant and behaves more aggressively than does SCC of the cervix, even with combined RT and chemotherapy. For this subgroup of cervical cancer, more comprehensive effective treatment is warranted.

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