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Clinical analysis of 132 cases of cervical adenosquamous carcinoma and cervical adenocarcinoma

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[Abstract] Background and Objective: The incidence of cervical adenosquamous carcinoma is relatively low. This study was to analyze the clinicopathologic characteristics and prognostic factors of cervical adenosquamous carcinoma. **Methods:** Clinical data of 44 cervical adenosquamous carcinoma patients and 88 cervical adenocarcinoma patients (control), treated from January 2002 to December 2007, were compared by Chi-square test, Kaplan-Meier method, log-rank test and Cox regression model. **Results:** The proportion of large tumors (maximal diameter > 4 cm) was significantly higher in cervical adenosquamous carcinoma group than in cervical adenocarcinoma group (47.7% vs. 28.4%, $P < 0.05$); the proportion of poorly differentiated tumors was significantly higher in cervical adenosquamous carcinoma group than in cervical adenocarcinoma group (56.8% vs. 30.7%, $P < 0.05$). Univariate analysis showed that tumor size ($P = 0.011$), FIGO stage ($P = 0.013$), depth of stromal invasion ($P = 0.05$) and lymph node metastasis ($P = 0.017$) were correlated with prognosis, while multivariate analysis showed that FIGO stage and lymph node metastasis had great impact on prognosis. There was no significant difference of 2-year overall and disease-free survival rates between the two groups ($P > 0.05$). **Conclusions:** Cervical adenosquamous carcinoma is characterized by large tumor size and poor differentiation. FIGO stage and lymph node metastasis are significant prognostic factors. There is no difference in prognosis between cervical adenosquamous carcinoma and cervical adenocarcinoma.

Key words: Cervical neoplasm, adenosquamous carcinoma, clinicopathology, prognosis

Cervical adenosquamous carcinoma accounts for 8%–10% of cervical cancer, containing two components—squamous cell carcinoma and adenocacinoma. Both the proportions and differentiation of these two components may be different. The poorly differentiated carcinoma is easy to relapse and metastasize, with high degree of malignancy and poor prognosis.[1] The biological behaviors and response to treatment of cervical adenosquamous carcinoma are different from those of cervical adenocarcioma. The comparison of clinicopathologic characteristics and prognosis between adenosquamous carcinoma and adenocarcinoma has seldom been reported, and it still remains controversy at present.[2,3] Clinical data of 44 cervical adenosquamous carcinoma patients and 88 cervical adenocarcinoma patients were analyzed in this study to investigate the clinicopathologic characteristics, treatment modalities and prognosis of cervical adenosquamous carcinoma and provide a reference for clinical treatment.

Materials and Methods

Patients

Clinical data of cervical cancer patients, treated at Tongji Hospital and Union Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Zhongnan Hospital, Hubei Provincial People's Hospital Affiliated to Wuhan University, the Central Hospital of Wuhan, Business Staff Hospital of Wuhan form January 2002 to December 2007, were collected. The study population was patients of clinical stages I–IV according to classification system of International Federation of Gynecology and Obstetrics, 2000. The clinical information (clinical stage, pathologic characteristics, treatment methods and prognostic factors) of 44 adenosquamous carcinoma patients and 88 cervical adenocarcinoma patients (control) were compared. The clinical information of each patient was complete.

Clinical data

The median onset age was 43 (range, 26–68) in cervical adencarcinoma group and 43.5 (range, 28–62) in cervical

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adenosquamous carcinoma group. The average times of gravidity and parturition were 3.3 ± 2.1 (range, 0–14) and 1.8 ± 1.4 (range, 0–4) in cervical adenocarcinoma group, 3.4 ± 1.7 (range, 1–8) and 1.9 ± 1.1 (range, 1–6) in cervical adenosquamous group.

Treatment methods

Among the patients of FIGO stages IB–IIA, those with tumor diameter less than 4 cm underwent radical hysterectomy and pelvic lymphadenectomy, those with tumor diameter more than 4 cm were usually treated with neo-adjuvant chemotherapy and (or) radiotherapy at first, and underwent radical hysterectomy and pelvic lymphadenectomy after local tumor shrank. The patients of FIGO stages IIB-IIIA were usually treated with neo- adjuvant chemotherapy and (or) after-loading therapy firstly, and underwent radical surgery after local tumor shrank. Those patients of FIGO stages IIB-IIIA who had unresectable tumor and those had tumors beyond stage IIIA received curative radiotherapy. Postoperative adjuvant radiotherapy (external irradiation of 40 Gy) and (or) chemotherapy was given to the patients with high risk factors such as tumor diameter more than 4 cm, lymph node metastasis, parametrial involvement and positive vaginal margins. At present, combined chemotherapy, such as TP, CP, DF and PFM regimens, was mainly used.

Follow-up

The patients were followed up mainly by telephone or letter since the time of diagnosis. The median follow-up period was 32 months (range, 12–93 months). Patients lost of follow-up were considered as censored data.

Statistical analysis

SPSS13.0 software was used for statistical analyses. Enumeration data were analyzed by Chi-square test. Survival was analyzed by Kaplan-Meier method. Intergroup comparison was performed by log-rank test. Multivariable analysis was conducted using Cox regression model. Statistical significance was defined as $P \leqslant 0.05$.

Results

Clinicopathologic characteristics

The proportion of bulky tumor (maximal diameter of more than 4 cm) was significantly lower in cervical adenocarcinomas than in cervical adenosqumous carcinomas ($P < 0.05$); the proportions of FIGO stages IIB-IV tumor and poorly differentiated tumor were significantly lower in adenocarcinomas than in adenosquamous carcinomas ($P < 0.05$) (Table 1).

Parametrial involvement was noted in 12.5% of adenocarcinoma patients and 18.2% of adenosquamous carcinoma patients ($P > 0.05$). Lymph node metastasis was found in 27.3% of adenocarcinoma patients and 31.8% of adenosquamous carcinoma patients ($P > 0.05$). Among the 79 adenocarcinoma patients who underwent surgical operation, 70 (88.6%) underwent radical hysterectomy plus pelvic lymphadenectomy, and 9 (11.4%) underwent other surgical operations (radical hysterectomy plus unilateral oophorectomy, contralateral ovarian transposition and pelvic lymphadenectomy, radical hysterectomy plus bilateral salpingo-oophorectomy and pelvic lymphadenectomy); among the 40 adenosquamous carcinoma patients who underwent surgical operation, 37 (92.1%) underwent radical hysterectomy plus pelvic lymphadenectomy, and 3 (7.9%) underwent other surgical operations. No significant difference was noted between the two groups ($P > 0.05$) (Table 1).

Table 1 The comparison of clinical characteristics between cervical adenocarcinoma and cervical adenosquamous carcinoma

Characteristic	Cervical adenocarcinoma [patient No. (%)]	Cervical adenosquamous carcinoma [patient No. (%)]	*P*
Total	88	44	
Tumor size			0.045
⩽4 cm	63(71.6)	23(52.3)	
>4 cm	25(28.4)	21(47.7)	
FIGO stage			0.430
Ia–IIa	69(78.4)	31(70.5)	
IIb–IV	19(21.6)	13(29.5)	
Differentiation			0.007
Well-moderate	61(69.3)	19(43.2)	
Poor	27(30.7)	25(56.8)	
Depth of stromal invasion			0.496
⩽1/2 layer	51(58.0)	22(50.0)	
>1/2 layer	37(42.0)	22(50.0)	
Parametrial involvement			0.539
Negative	77(87.5)	36(81.8)	
Positive	11(12.5)	8(18.2)	
Depth of muscular invasion			0.848
⩽1/2 layer	72(81.8)	33(75.0)	
>1/2 layer	16(18.2)	11(25.0)	
Lymph node metastasis			0.734
Negative	64(72.7)	30(68.2)	
Positive	24(27.3)	14(31.8)	
Vaginal margins			0.312
Negative	79(89.8)	36(81.8)	
Positive	9(10.2)	8(18.2)	

Prognostic factors

Univariate analysis showed that tumor size, FIGO stage, stromal invasion and lymph node metastasis were significant factors for both disease-free and overall survival ($P < 0.05$), while age, degree of differentiation, parametrial involvement, ovary reservation and preoperative or postoperative adjuvant therapy had no effect on overall survival (OS) and disease-free survival (DFS) (Table 2, Figures 1 and 2).

Cox regression multivariate analysis showed that FIGO stage and lymph node metastasis were independent factors affecting both OS and DFS. The later the FIGO stage, the worse the prognosis; the earlier the lymph node metastasis, the worse the prognosis (Table 3).

Table 2 Univariate prognosis analysis of 44 cases of cervical adenosquamous carcinoma

Characteristic	Overall survival			Disease-free survival		
	Median survival (months)	2-year survival rate (%)	*P*	Median survival (months)	2-year survival rate (%)	*P*
Age (years)			0.240			0.104
<40	45.0	80.0		45.0	76.7	
≥40	28.0	71.4		25.0	60.0	
Tumor size			0.040			0.011
≤4 cm	35.0	85.7		35.0	85.7	
>4 cm	33.5	65.3		32.5	50.0	
FIGO stage			0.034			0.013
IA–IIA	37.0	88.9		37.0	85.7	
IIB–IV	35.0	33.3		35.0	33.3	
Differentiation			0.489			0.887
Well-moderate	33.5	60.0		33.5	75.0	
Poor	30.5	57.1		29.5	66.7	
Depth of stromal invasion			0.044			0.050
≤1/2 layer	31.5	83.3		31.5	83.3	
>1/2 layer	29.0	50.0		29.0	60.0	
Parametrial involvement			0.429			0.074
Negative	31.5	80.7		31.5	71.3	
Positive	28.5	50.5		29.0	43.3	
Lymph node metastasis			0.042			0.017
Negative	31.5	80.0		31.5	83.3	
Positive	28.5	42.9		28.5	60.0	
Ovarian preservation			0.176			0.236
No	25.0	57.1		25.0	75.0	
Yes	42.0	60.0		42.0	66.7	
Adjuvant treatment			0.563			0.334
No	24.0	60.0		26.5	66.7	
Yes	26.5	57.1		24.0	80.3	

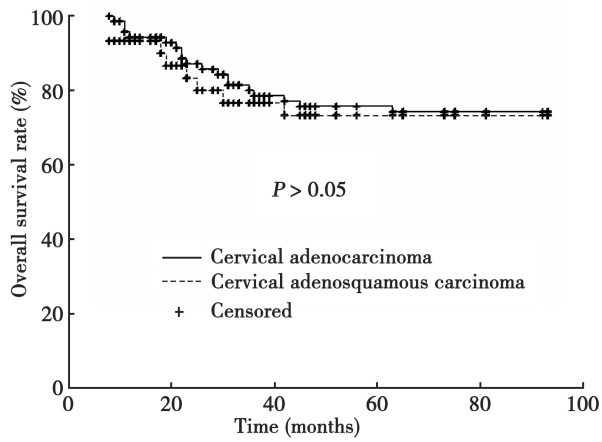

Figure 1 Overall survival curves of cervical adenocarcinoma and cervical adenosquamous carcinoma patients

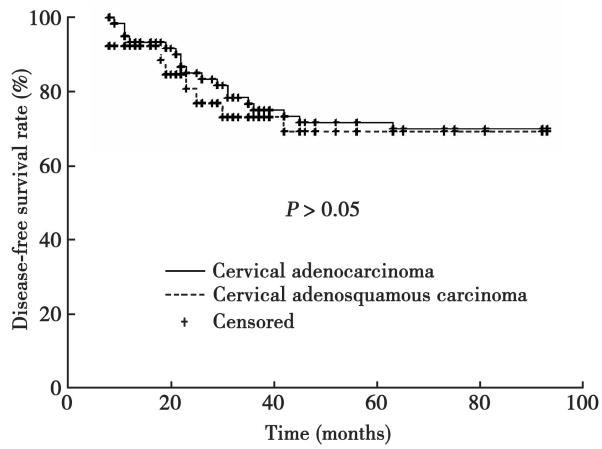

Figure 2 Disease-free survival curves of cervical adenocarcinoma and cervical adenosquamous carcinoma patients

Prognosis and recurrence

Of the 8 cervical adenosquamous carcinoma patients who had metastasis, 4 had bone metastasis, 2 had pelvic cavity metastasis, and 2 had lung metastasis; of the 18 cervical adenocarcinoma patients who had tumor recurrence or metastasis, 8 had pelvic cavity metastasis, 2 had lung metastasis, 3 had liver and lung metastasis, and 3 had local recurrence. The recurrence and metastasis rates of adenosquamous carcinoma and adenocarcinoma were 22.2% and 25.7%, respectively ($P > 0.05$). According to the results of

Table 3 Multivariate prognosis analysis of 44 cases of cervical adenosquamous carcinoma

Variable	B	SE	Wald	RR	*P*	95% CI
Age	0.016	0.098	0.027	0.984	0.869	0.041–18.424
Tumor size	0.299	1.410	0.017	1.348	0.897	0.023–13.525
FIGO stage	1.448	2.297	1.015	4.141	0.032	0.261–65.696
Depth of stromal invasion	0.346	1.852	0.035	0.707	0.852	0.033–80.391
Lymph node metastasis	1.921	1.293	2.207	6.825	0.017	0.542–86.756

RR, relative risk; CI, confidence interval.

prognostic analysis, patients were divided into high-risk group (tumor diameter of more than 4 cm, depth of stromal invasion of more than 1/2 layer, lymph node metastasis) and low-risk group (tumor diameter of no more than 4 cm, depth of stromal invasion of no more than 1/2 layer, no lymph node metastasis). No significant differences were observed in the DFS between adenocarcinoma group and adenosquamous carcinoma group ($P > 0.05$), in recurrence rate between adjuvant therapy group and non-adjuvant therapy group as well as between low-risk group and high-risk group ($P > 0.05$) (Table 4).

Table 4 The comparison of prognosis between cervical adenocarcinoma and cervical adenosquamous carcinoma

Item	Cervical adenocarcinoma [Patient No. (%)]	Cervical adenosquamous carcinoma [Patient No. (%)]	*P* (Fisher)
Total	70	36	
Recurrence	18(25.7)	8(22.2)	
Time to recurrence (months)			0.325
Median	16.5	13.0	
Range	2–42	3–23	
Recurrence-free survival (months)			0.819
Mean	31.5	30.1	
Range	9–93	8–56	
No adjuvant treatment	32(45.7)	16(44.4)	0.701
Recurrence	6(18.8)	2(12.5)	
Adjuvant treatment	38(54.2)	18(50.0)	1.000
Recurrence	12(31.6)	6(33.3)	
Low-risk group	58(82.9)	26(72.2)	0.565
Recurrence	13(22.4)	4(15.4)	
High-risk group	12(17.1)	10(27.8)	1.000
Recurrence	5(41.7)	4(40.0)	

As stratified by age, FIGO stage, tumor diameter, infiltration depth, lymph node metastasis, ovarian reservation and preoperative or postoperative radiotherapy and chemotherapy, no significant differences in 2-year OS and DFS rates were observed between adenocarcinoma and adenosquamous carcinoma groups ($P > 0.05$), suggesting that there was no statistical difference in prognosis between the two groups.

Discussion

Cervical cancer is one of the most common gynecologic malignancies. Cervical adenosquamous carcinoma accounts for 3%–5% of cervical cancer. It comes into being that the reserve cells develop into gland cells and squamous cells at the same time and it contains two components--adenocarcinoma and squamous cell carcinoma.[4] It has been reported that pathologic types had no significant effect on prognosis,[5] while Farley *et al.*[2] considered that adenosquamous carcinoma was an independent prognostic factor, especially for advanced stage patients. It is necessary to analyze clinicopathologic characteristics and prognosis of cervical adensquamous carcinoma as a separate pathologic type.

The incidence of cervical adenosquamous carcinoma is lower than those of other types of cervical cancer, but it is inconsistent in the literature. Yasuda *et al.*[6] reported that adenosquamous carcinoma accounted for 5%–10% of cervical cancer, Takac *et al.*[7] reported 5.3%, Le *et al.*[4] reported 3%-5%. In this study, cervical adenosquamous carcinoma accounted for 2.4% of cervical cancer and its incidence was low.

We compared the clinicopathologic characteristics of adenocarcinoma and adenosquamous carcinoma, and found that tumor size and histological grade were statistically different. It was consistent with the literature.[5] Wang *et al.*[8] discovered that poorly differentiated tumor and lymph node metastasis were more common in cervical adenosquamous carcinoma and its histological behavior was more aggressive than cervical adenocarcinoma. Yasuda *et al.*[6] compared 28 cases of stage IB1 adenosquamous carcinoma with stage IB1 adenocarcinoma and squamous cell carcinoma, and found that lymph node metastasis rates were 21.4%, 13.6% and l5.8%, respectively, indicating that adenosquamous carcinoma was more aggressive. Among the 44 cases of adenosquamous carcinoma in our study, 25 (56.8%) were poorly differentiated, and 14 (31.8%) were with lymph node metastasis. It confirmed the above conclusion.

It is mostly reported that the later the FIGO stage of cervical cancer, the broader the surrounding invasion and the greater the risk of lymph node metastasis; the larger the tumor diameter, the greater the risk of parametrial invasion; the deeper the tumor invasion, the greater the risk of lymph node metastasis.[9,10] These are significant prognostic factors of cervical adenosquamous carcinoma. Our univariate analysis showed that FIGO stage, tumor size, lymph node metastasis and depth of stromal invasion

had dramatic impact on prognosis of cervical adenosquamous carcinoma, which was consistent with the literature.[9] Our multivariate analysis showed that FIGO stage and lymph node metastasis were important factors for prognosis of adenosquamous carcinoma, which was in accordance with the results of Li *et al.*[11]

It is still disputed that whether different pathologic types affect prognosis. Farley *et al.*[2] pointed out that the 5-year survival rate of cervical adenosquamous carcinoma patients was much lower than that of adenocarcinoma patients, but the difference only exist among advanced stage patients, not among stage I patients. Lea *et al.*[12] found that the patients with stage IB1 adenosquamous carcinoma were easy to have tumor relapse with a low survival rate. Cai *et al.*[13] also discovered that the prognosis of adenosquamous carcinoma patients was poor. In contrast, Irie *et al.*[3] reported that there was no difference in survival rates between them. In our study, the prognosis of adenosquamous carcinoma and adenocarcinoma patients were similar, which may lie in the following reasons: (1) the follow-up time was short, (2) the sample size was small, especially that of advanced tumor, which could not reflect the clinical stage distribution characteristic of adenosquamous carcinoma.

dos-Reis *et al.*[5] and Lai *et al.*[14] reported that there was no significant difference in recurrence rate between adenosquamous carcinoma and adenocarcinoma as well as squamous carcinoma. There was no statistical difference in recurrence rate and time-to-recurrence between adenosquamous carcinoma and adenocarcinoma in our study. It may be associated with higher proportion of early stage patients.

In conclusion, cervical adenosquamous carcinoma, with a low incidence, is characterized by large tumor size, poor differentiation and high invasion. FIGO stage and lymph node metastasis are significant prognostic factors. According to our results, the prognosis of adenosquamous carcinoma and adenocarcinoma are similar, therefore, comprehensive treatment based on radical surgery is still the main treatment at present. For those patients with large tumor and can not tolerate operation, radiotherapy and chemotherapy should be performed firstly, operation would be performed later when appropriate.

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