Analysis of Prognosis and Prognostic Factors of Cervical Adenocarcinoma and Adenosqumous Carcinoma of the Cervix

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OBJECTIVE   To analyze clinical characteristics and treatment methods of the patients with adenocarcinoma of the uterine cervix (AUC) and adenosquamous carcinoma of the cervix (ASCC). To compare the survival time of the patients in 2 groups and analyze the prognostic factors.

METHODS   Clinical data of both 123 patients with AUC and 32 patients with ASCC treated at the Cancer Hospital, Chinese Academy of Medical Science (CAMS) & Peking Union Medical College (PUMC), were retrospectively analyzed.

RESULTS   The median age of the AUC patients was 50 years, and that of the ASCC patients was 44, P = 0.019. Poorly-differentiated (grade 3) cases accounted for 59.5% of the total ASCC patients, while only 32.5% of the AUC patients were in grade 3, P = 0.002. In 123 AUC patients, relapse or failure of the treatment occurred in 63 of the patients (51.2%), and the median relapse time was 6 months (0-59 months). In 32 ASCC patients, relapse or failure of the treatment occurred in 8 of these patients (51.2%), with a median relapse time of 4.5 months (0-52 months). The overall 5-year survival rate of the AUC patients was 49.8%, which was significantly lower than that of the ASCC patients (74.1%), P = 0.015. The 5-year survival rates of the ASCC patients in Stage I-III were higher than that of the AUC patients with the same stages. However, statistical significant difference could only be found among the patients in Stage II, P = 0.006. The 5-year survival rates of the ASCC patients with various differential grade were higher than those of the AUC patients with the same differential grade, but statistical significant difference could only be found among the patients in the two groups with moderately differentiation, P = 0.039. It was found by Cox regression analysis that only clinical stage (P < 0.001) and histological type (P = 0.046) were the independent prognostic factors.

CONCLUSION   Clinical stage and histological type were the independent prognostic factors of the AUC and ASCC patients. The prognosis of ASCC patients is better than that of the AUC patients.

KEY WORDS: uterine cervix cancer, adenocarcinoma, adenosquamous carcinoma, survival, prognosis.

Introduction

Adenocarcinoma of the uterine cervix (AUC) is one of the most common subtypes in uterine cervix cancer (UCC), except squamous carcinoma of the cervix (SCC). The case of the UCC was relatively less in the past, so its proportion was small in the UCC, too. Based on

the literature and reports over the past few years, the incidence rate of the SCC has significantly fallen, and that of the AUC has been gradually increased. The rising of the incidence rate of the AUC patients resulted in an increasing proportion of the AUC in UCC, which reached 24% based on the report [1]. Adenosquamous Carcinoma of the Cervix (ASCC) is a rare subtype of the UCC. It is still remained unclear whether the specific disease is an independent prognostic factor, because firstly, the incidence of the ASCC was very low and most of the cases were reported as a case report in a small quantity, and secondly, in the previous studies, it was used to be put into the researches which analyze the AUC cases. It was shown in some researches that the prognosis of the ASCC was poor compared with that of the AUC cases, nevertheless the results of some other similar researches indicated that there were no significant differences in the prognosis between the two groups[2-7]. In our study, clinical data and case files of the AUC and ASCC patients from our hospital were retrospectively analyzed and the survivals and prognostic factors of both groups were compared.

Materials and Methods

Clinical data
From January 1994 to February 2006, a total of 32 ASCC patients and 123 AUC patients were treated in Cancer Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China. Retrospective analysis was conducted by reading all the case files. The follow-up data, ages, symptoms and signs, pathological grades and stages, as well as the treatments and survivals of the patients were recorded. The surgical pathological staging standard issued by the International Federation of Gynecology and Obstetrics (FIGO) in 1994 was used. The clinical staging was conducted by 2 or more surgeons with associate professorship or higher professional titles in our hospital, based on a preoperative gynecological examination and diagnostic image outcomes.

Statistical analysis
SPSS 13.0 was used for statistical analysis, Kaplan-Meier method used for computing the survival rate, χ^2 test for comparison of the rates and Cox regression model for analyzing the prognostic factors.

Results

Clinical data
The clinical features of all the patients in the study are shown in Table 1. In the AUC patient group, the median age was 50 which was older than 44 of the median age in ASCC patient group, $P = 0.019$. The mean value of tumor diameter for patients of 2 groups were 4.3 cm and

4.8 cm, respectively, and there was no significant difference in diameter, $P = 0.132$. In 123 AUC patients, there were 30 in Stage I (24.4%), 38 in Stage II (30.9%), 50 in Stage III (40.6%) and 5 in Stage IV (4.0%). In 32 ASCC patients, the number of the cases in the Stage I-IV was 8 (25.0%), 13 (40.6%), 8 (25.0%) and 3 (9.4%), respectively. There were no significant differences in distribution of the clinical stages between the two groups, $P = 0.748$. In the ASCC group, 59.5% of the patients had poorly differentiated tumor, while in the of the AUC group, only 32.5% of the patients had poorly differentiated cancer, $P = 0.002$.

Table 1. Clinical features of the AUC and ASCC patients.

Characteristics	No. of patients (%)		P
	AUC	ASCC	
Age, years (median)	50	44	0.019
Tumor size, cm (mean)	4.3	4.8	0.132
Tumor stages	123	32	0.748
IA	2 (1.6)	0 (0.0)	
IB	28 (22.8)	8 (25.0)	
IIA	8 (6.5)	5 (15.6)	
IIB	30 (24.4)	8 (25.0)	
IIIA	2 (1.6)	0 (0.0)	
IIIB	48 (39.0)	8 (25.0)	
IVA	2 (1.6)	1 (3.1)	
IVB	3 (2.4)	2 (6.3)	
Histological grade	123	32	0.002
1	33 (26.8)	2 (6.25)	
2	50 (40.7)	11 (34.4)	
3	40 (32.5)	19 (59.4)	

Treatment methods
In all patients with Stage IA to Stage IIA of 2 groups, radical correction ± postoperative adjunctive therapy (POAT) was conducted in 94.7% of the AUC patients and 92.3% of the ASCC patients, respectively, $P = 0.557$. In the patients with Stage IIB to Stage IIIB of 2 groups, 38.8% of the AUC patients underwent simple radiotherapy (SRT) and another 61.2% of the AUC patients received synchronized chemo-radiotherapy (SCRT), and the 5-year survival rate of the 2 treatment methods was 37.4% and 37.2%, respectively, which were no significant differences between the 2 treatment methods, $P = 0.888$. And in the patients with Stage IIB to Stage IIIB of the ASCC group, the ratio of the patients who underwent SRT reached 43.8% and another 56.2% of the patients received SCRT, and the 5-year survival rate of the 2 treatment methods was 85.7% and 58.3%, respectively, which failed to reach a statistically significant difference, $P = 0.164$. The rate of the patients receiving SRT in the AUC patient group was not significantly different from that of the patients in the ASCC

group and the rates of the patients in the two groups, that received SCRT were not significantly different, $P = 0.712$. The Stage IV patients in both groups underwent a palliative chemotherapy (PCT) ± radiotherapy (Table 2).

Table 2. Treatment methods of the AUC and ASCC patients.

Clinical stage	Treatment method	No. of Patients (%)		P
		AUC	ASCC	
IA-IIA	Surgery ± POAT	36 (94.7)	12 (92.3)	0.577
	Radiotherapy	0 (0.0)	1 (7.7)	
	SCRT	2 (5.3)	0 (0.0)	
IIB-IIIB	Radiotherapy	31 (38.8)	7 (43.8)	0.712
	SCRT	49 (61.2)	9 (56.2)	
IV	PCT ± Radiotherapy	5 (100.0)	3 (100.0)	-

Relapse and prognosis
During the follow-up, relapse or failure of tumor management occurred in 63 of the 123 AUC patients (51.2%), with a median relapse time of 6 months (0-59 months). Among 57 of the 63 patients (90.5%), the relapse or failure of the treatment occurred within 2 years after the initial treatment was conducted. The relapse or failure was found in 8 of the 32 ASCC patients (25.0%), with a median relapse time of 4.5 months (0-52 months). Among 6 of the 8 patients (75.0%), the recurrence or failure of tumor management occurred within 2 years after the initial treatment.

The 5-year overall survival rate was 49.8% in the AUC patients, obviously lower than 74.1% of the rate in the ASCC patients, $P = 0.015$. The 5-year survival rates of the ASCC patients with Stage I and Stage III were all higher than that of the AUC patients with the same stages, when compared the patients with the same stages in two different groups. However, statistically significant difference between the 5-year survival rates of the two groups of the patients with Stage II can only be found, $P = 0.006$. It was found that, when the patients with the same histological grades but in the two different groups were compared (Table 3), the 5-year survival rates of the ASCC patients with various histological grades were all higher than those of the AUC patients with the same grades. Nevertheless, statistically significant difference of the 5-year survival rate can only be found between the two groups of patients with moderately differentiation, $P = 0.039$.

After analyzing the age, tumor size, staging, histological grades and pathological classifications such as adenocarcinoma and adenosquamous carcinoma of the patients in two groups using Cox regression model, we found that only clinical stage ($P < 0.001$) and pathological classification ($P = 0.046$) were the independent prognostic factors. It meant that the higher the clinical stage was, the poorer the prognosis would be. The prognosis of the AUC patients was poorer than that of the ASCC patients.

Discussion

Comparison of the survivals between the AUC and ASCC patients with various stages
With regard to the prognosis of ASCC patients in early stages, some authors believed that it is similar to the prognosis of AUC patients. However, some findings even indicated that the former was poorer than the latter[3-5]. Jayanthi et al.[8] have compared 39 low-risk patients with ASCC in Stage IB1 and 139 low-risk patients with AUC in Stage IB1. Their findings have shown that the relapse rates of the two groups were 18% and 4%, respectively, $P < 0.01$. The 5-year disease-free rate was 79% and 99%, respectively, $P < 0.01$, and the 5-year survival rate was 88% and 99%, respectively, $P < 0.01$. The prognosis of AUC group was obviously better than the ASCC group. Therefore, the authors believed that ASCC is an independent risk factor for Stage-IB1 UCC patients, which should be taken into consideration while decide if a postoperative supplementary treatment is

Table 3. Survivals of the patients with different stages and histological grades.

	AUC		ASCC		
	Median survival time (month)	Five-year survival rate (%)	Median survival time (month)	Five-year survival rate (%)	P
Clincial stage					
I	48.5	89.4	40.5	100.0	0.393
II	37.5	47.9	65.0	90.0	0.006
III	33.5	32.8	48.5	56.3	0.191
IV	15.0	1/5	10.0	0/3	-
Histological grade					
1	41.0	53.0	107.5	2/2	0.264
2	37.0	48.5	47.0	90.9	0.039
3	26.0	47.7	51.0	62.2	0.193

offered. However, John et al.[9] found that, after summarizing many previous findings, the 5-year survival rate of the AUC patients, AUC + ASCC patients and ASCC patients, who were all in Stage I was 80%, 80% and 69%, respectively, so the ASCC was not an independent risk factor for UCC patients in Stage I. In our study, the 5-year survival rate of the AUC and ASCC patients in Stage I was 89.4% and 100% respectively, which meant that the survival rate of ASCC patients was slightly higher than that of the AUC patients. But, there was no significant difference between 2 groups, $P = 0.393$, and this was in accordance with the result shown in John's report.

The results shown in John's review indicated that based on findings from most of the studies, the survival rate of ASCC patients was obviously decreased as the stages were increased[9]. Comprehensive research findings indicated that the 5-year survival rate of AUC patients in Stage II and III was 59% and 14%, respectively, and that of AUC + ASCC patients in Stage II and III was 48% and 17%, respectively , while that of ASCC patients in Stage II and III was 27% and 0%, respectively. The 5-year survival rates shown in latter group was significantly lower than those of the former two groups, i.e. the prognosis of advanced ASCC patients was apparently poorer than that of advanced AUC patients. Therefore, the authors believed that in view of advanced ASCC patients, more active treatment should be considered besides standard SCRT, such as augmentation of radiation dose and searching for more sensitive chemotherapeutic agents etc., so as to attain a better therapeutic efficacy. However, it needs further investigation.

In our study, the 5-year survival rate of AUC patients in Stage II and III was 47.9% and 32.8%, respectively, which are similar to the results of the previous reports[9,10]. The 5-year survival rate of the ASCC patients in Stage II and III was 90.0% and 56.3%, respectively, which were obviously higher than the results from the previous reports[9,10]. All these survival rates of the ASCC patients were higher than those of the AUC patients with the same stages, nevertheless, the statistically significant difference was only found in 2 groups of the patients with Stage II, $P = 0.039$. It is known to all that comparing with the SCC, AUC has less sensitivity to radiotherapy, and its prognosis of AUC patients is poorer[11]. The ASCC contains the elements of squamous carcinoma (SqCa) and adenocarcinoma (ACA) at the same time, and the ratio between ACA and SqCa may be varied in different ASCC patients. It remains unclear whether the element of SqCa in ASCC is relatively sensitive to radiotherapy, thus enhancing the sensitivity of ASCC to radiotherapy, then improving the survival rate of the Stage II and III patients. The result of our study indicated that since most of the ASCC and AUC patients in Stage-I underwent surgery, their prognoses were similar, and for most of the Stage II and III patients in 2 groups, who received radiation therapy, the prognosis of

ASCC patients was better than that of the AUC patients. Further investigations are expected for authentication of all outcomes above.

In our group, the 5-year survival rate of AUC and ASCC patients in Stage IV was 20.0% (1/5) and 0.0% (0/3), respectively, which are in accordance with the results in the previous reports[9,10,12]. So, the therapeutic tool of better efficacy is not available for these patients at present, and their prognosis is very poor.

Analysis of the prognostic factors

The result of the Cox regression analysis in our group showed that only the clinical stage, $P < 0.001$, and pathological classification were the independent prognostic factor, $P = 0.046$, i.e., the higher the clinical stage was, the poorer the prognosis would be, and this was in accordance with the result of previous reports[10]. Moreover, the prognosis of AUC patients was poorer than that of the ASCC patients, and the 5-year overall survival rate was 49.8% in the AUC patients, obviously lower than that of the ASCC patients (i.e. 74.1%), $P = 0.015$, and this is somewhat different to the results in the previous report and literature[9].

According to the analysis of some possible influencing factors in our study, the authors found that there were no significant difference in the distribution of clinical stages, tumor size and treatment methods between the patients of the two groups, but there was significant difference in distribution of the median age and histological grades only. The median age of AUC patients was 50 and that of the ASCC patients was 44 which was less than that of the AUC patients and the age of the patients didn't reach the advanced age. No death cases caused by advanced age or other senile diseases were found during the follow-up. The results of the Cox regression analysis showed that the age of the patients has no significant impact on the overall survival rate. As for the histological grades, the proportion of the well-differentiated cancer cells was higher in the AUC patients than that in the ASCC patients, and the proportion of the poorly differentiated was lower in the AUC group than that in the ASCC group. The 5-year survival rates of patients in the two groups were both gradually decreased with the histological grades increased (Table 3), so the high proportion of the well-differentiated cancer cells should result in the 5-year survival rate of the AUC patients relatively increased, and in our study, however, the survival rate was still lower in the AUC group than that in the ASCC group.

Besides, it was found that, after respective analysis of the patients with various histological grades, the 5-year survival rates of the ASCC patients with different histological differentiations were all higher than those in the AUC patients with the same histological differentiation (Table 3). Nevertheless, there was only a statistically significant difference between the two groups of patients with moderate differentiation, $P = 0.039$. All the results

from analyzing the histological grades shown in the previous reports demonstrated that the higher the degree of histological differentiation was, the higher the 5-year survival rate would be. However, the result of a multi-factorial analysis showed that histological grade is not the independent prognostic factor of the AUC and ASCC patients[13,14], which is in accordance with the results of our study.

It can be judged from our results that the prognosis of ASCC patients is better than that of the AUC patients, the clinical stage and pathological classification are the independent prognostic factor of AUC and ASCC patients. Anyhow, further collection of data and information and prospective clinical research are needed for verification of the final conclusion.

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