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Original Article

Analysis of the prognostic factors of small cell carcinoma of the cervix

Renhua Na, Xiaoli Liu, Wei Zhong, Gulnar Kurban

The 1st Department of Gynecological Oncology, The Affiliated Cancer Hospital of Xinjiang Medical University, Urumqi 830011, China

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Abstract: Objective: This study is to investigate the prognostic factors of small cell carcinoma of the cervix (SCCC). Methods: This is a retrospective analysis. The clinical data of 21 patients with SCCC were analyzed to identify the prognostic factors of SCCC. Results: The age of the SCCC patients ranged from 30-60 years old, with a median age of 45 years. There were 9 cases with distant metastasis to the liver, lungs, brain, and bones. Five cases died, and only 8 cases had tumor-free survival. The 17 patients with complete follow-up data had a disease-free survival time of 3-87 months, and the median disease-free survival time was 27.0 months. The total survival time was 4-95 months, and the median total survival time was 27.0 months. The patients with age ≥ 45 and < 45 years old at first diagnosis had a median survival time of 18 months (95% CI: 9.2-26.8) and 44 months (95% CI: 16.3-71.7), respectively (P = 0.008). The patients with a tumor diameter ≤ 4 cm and > 4 cm had median survival time of 44 months (95% CI: 17.7-70.3) and 18 months (95% CI: 6.9-29.1), respectively (P = 0.014). Patients with pelvic lymph node metastasis and without pelvic lymph node metastasis had a median survival time of 8 months (95% CI: 0-21.7) and 35 months (95% CI: 17.5-52.5), respectively (P = 0.005). Conclusion: Age ≥ 45 years old at first diagnosis, tumor diameter > 4 cm, and pelvic lymph node metastasis might be adverse prognostic factors for SCCC.

Keywords: Cervical cancer, small cell carcinoma of the cervix, prognostic factors

Introduction

Cervical cancer is the most common gynecological malignant tumor seen in clinics and the cancer which most seriously threatens women's health and lives [1, 2]. Small cell [1] carcinoma of the cervix (SCCC) is a neuroendocrine tumor, a type which is rare in clinical practice [3]. SCCC has a similar stage distribution to squamous carcinoma and adenocarcinoma. However, SCCC has low morbidity compared with other types of cervical cancer [4, 5]. The reported incidence of SCCC varies from 0.6% to 18% [6]. Moreover, SCCC is highly invasive, so the prognosis of SCCC is relatively poor [6, 7]. Therefore, it is of great importance to identify the prognostic factors of SCCC.

The prognostic factors of SCCC are different among different studies. For, example, Lee *et al.* reported that stage was the only independent prognostic factor [8]. Wang *et al.* found that stage and lymph node metastasis were prognostic factors [9]. Age, stage, and race were identified as independent prognostic factors by Chen *et al.* [10]. Chemotherapy after radical surgery was also an independent prognostic factor [11].

This study retrospectively analyzed the clinical data and survival of SCCC patients from Xinjiang, China. The clinical features and prognosis of the SCCC patients were investigated and discussed.

Materials and methods

Clinical data of patients

A total of 21 cases of patients with SCCC from the Affiliated Cancer Hospital of Xinjiang Medical University during July, 2007 and June, 2015 were enrolled in this study. Their age ranged from 30 to 60 years old, with a median age of 45 years old and a mean age of 47 years old. The clinical data of the patients are listed in **Table 1**. Inclusion criteria: 1) patients with SCCC diagnosed by biopsy or postoperative

Table 1. Clinical characteristics of SCCC patients

Classification		N (%)
Age range (Years old)		
30-60		21
Age at first diagnosis (Years old)		
≥ 45		12 (57.1%)
< 45		9 (42.9%)
Ethnicity		
Han		13 (61.9%)
Minority		8 (38.1%)
Main clinical manifestations		
Vaginal bleeding		12 (57.1%)
Vaginal discharge		8 (38.1%)
Asymptomatic		1 (4.8%)
Menstrual status		
Menopause		8 (38.1%)
Premenopausal		13 (61.9%)
FIGO staging		
Stage I	IB1	3 (14.3%)
	IB2	1 (4.8%)
Stage II	IIA1	3 (14.3%)
	IIA2	3 (14.3%)
	IIB	6 (28.6%)
Stage IIIB		3 (14.3%)
Stage IV		2 (9.5%)
Tumor size		
≤ 4 cm		12 (57.1%)
> 4 cm		9 (42.9%)
Pathological type		
Small cell carcinoma		16 (76.2%)
Hybrid		5 (23.8%)
Treatment		
Surgery only		3 (14.3%)
Surgery + chemotherapy		3 (14.3%)
Surgery + radiotherapy + chemotherapy		10 (47.6%)
Radiotherapy + chemotherapy		5 (23.8%)

pathology examination; 2) patients with primary SCCC; 3) patients not treated before enrollment. Exclusion criteria: 1) patients complicated with other malignancies; 2) patients complicated with other life threatening diseases. Prior written and informed consent were obtained from every patient, and the study was approved by the ethics review board of the Affiliated Cancer Hospital of Xinjiang Medical University.

Treatment methods

SCCC is mainly treated by surgery, and adjuvant radiotherapy and chemotherapy. The chemotherapy regimens used in this study were etoposide + cisplatin, ifosfamide + etoposide + cisplatin, cisplatin + bleomycin + vincristine, paclitaxel + platinum, and bleomycin + etoposide + cisplatin. The chemotherapy lasted 4 to 6 courses, with 21 days in each course. The radiotherapy used pelvic external irradiation and intracavitary brachytherapy.

Data collection

The clinical data, such as age, ethnicity, main clinical manifestations, menstrual status, FIGO staging, tumor size, pathological type, and treatment methods, was collected and analyzed.

Follow-up

Patients were followed up for 84 months. Follow-up was performed mainly by telephone and clinic reexamination. The patients' survival, recurrence, and metastasis of SCCC were recorded.

Statistical analysis

The statistical analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL, USA). Survival analysis was performed using the Kaplan-Meier method, a non-parametric method used to estimate the probability of survival past given time points. The difference in survival was analyzed using a log-rank test. A multivariate survival analysis of the prognostic factors was performed using Cox regression. $P < 0.05$ was considered statistically significant.

Results

Analysis of the prognostic factors

To determine the prognostic factors of SCCC, a multivariate survival analysis was conducted using Cox regression (**Table 2**). The results showed that the factors of age, tumor size, and pelvic lymph node metastasis had a significant impact on the prognosis of SCCC. The other factors, such as ethnicity, FIGO staging, depth of cervical matrix infiltration, vascular invasion, surgical approach, and neoadjuvant chemotherapy, had no obvious impact on the prognosis of SCCC. Thus, patients who are younger (< 45 years old), who have smaller tumors (≤ 4

Table 2. Analysis of prognostic factors and survival conditions

Prognostic factors		Survival (Survival No./Total No.)	Median survival time (month)	95% CI	*P* value
Age (years old)	≥ 45	6/9	18.0	9.2-26.8	0.008
	< 45	6/8	44.0	16.3-71.7	
Ethnicity	Han	8/11	29.0	16.1-41.9	0.623
	Minority	4/6	18.0	0-39.6	
FIGO staging	IB-IIB	9/13	24.0	11.1-36.9	0.742
	IIIB-IV	3/4	29.0	3.5-54.5	
Tumor size	≤ 4 cm	7/9	44.0	17.7-70.3	0.014
	> 4 cm	5/8	18.0	6.9-29.1	
Pathological type	Simple	8/12	29.0	10.6-47.4	0.988
	Hybrid	4/5	24.0	21.9-26.1	
Interstitial infiltration depth	≥ 1/2 muscle layer	7/11	34.8	18.2-51.4	0.677
	< 1/2 muscle layer	2/2	26.5	9.8-43.2	
Vascular infiltration	Yes	3/7	18.0	2.6-33.4	0.105
	No	6/6	35.0	11.0-59.0	
Pelvic lymph node metastasis	Positive	2/4	8.0	0-21.7	0.005
	Negative	7/9	35.0	17.5-52.5	
Surgical approach	Laparotomy	4/6	18.0	2.0-34.0	0.520
	Laparoscopy	5/7	29.0	13.6-44.4	
Neoadjuvant chemotherapy	Yes	4/5	23.0	12.3-33.7	0.147
	No	5/8	35.0	0-86.3	

cm), and who have negative lymph node metastasis tend to have a better prognosis.

Patients who are older, who have larger tumors, or who have positive lymph node metastasis have a shorter survival time

There were four patients with whom we lost follow-up, including 1 case of Stage IIA1, 2 cases of Stage IIB and 1 case of Stage IV. For the remaining 17 cases, there were 8 cases with tumor-free survival and 9 cases with distant metastasis, including 5 cases of liver metastasis, 2 cases of lung metastasis, 1 case of brain metastasis, and 1 case of bone metastasis. Five patients died, and the individual survival time for them was 4, 8, 11, 12, and 24 months, respectively. For the 17 cases with complete follow-up information, the disease-free survival time was 3-87 months, and the median disease-free survival time was 27 months. The overall survival time (OS) was 4-95 months, and the median OS was 27 months (**Figure 1**).

Patients whose age at first diagnosis was ≥ 45 years old had a significantly shorter median survival time (18 months) than those whose age was < 45 years old (44 months) ($P < 0.05$) (**Figure 2**). This suggests that age at first diagnosis ≥ 45 years old is an adverse prognostic factor of SCCC.

Patients with a tumor diameter ≤ 4 cm had a significantly longer median survival time (44 months) than those with a tumor diameter > 4 cm (18 months) ($P < 0.05$) (**Figure 3**), which indicates that tumor diameter > 4 cm is an adverse prognostic factor for SCCC.

Patients with pelvic lymph node metastasis had a significantly shorter median survival time (8 months) than those without pelvic lymph node metastases (35 months) ($P < 0.05$) (**Figure 4**), suggesting that pelvic lymph node metastasis is an adverse prognostic factor for SCCC.

These results showed that older patients (≥ 45 years old), larger tumor size (> 4 cm), and positive lymph node metastasis had a relatively shorter survival, implying that these are adverse prognostic factors for SCCC.

Discussion

Most studies have shown that the onset age of SCCC ranges from 20 to 83 years old, with

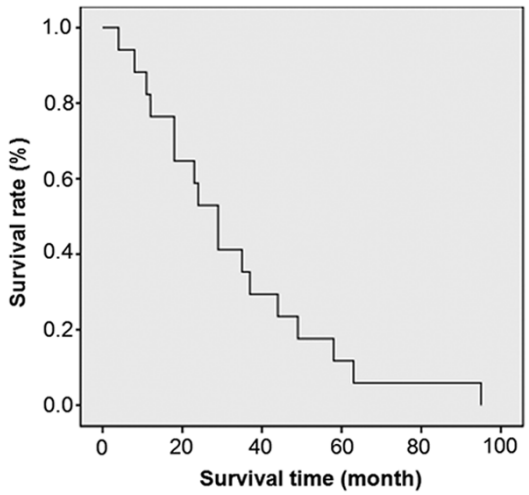

Figure 1. The survival curve of the 17 patients of SCCC. The overall survival time was analyzed. The survival analysis was performed using the Kaplan-Meier method.

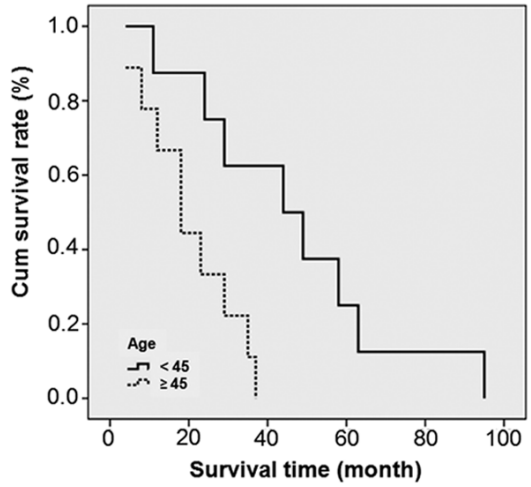

Figure 2. The survival curves of the patients with an initial diagnosed age ≥ 45 years old or < 45 years old. The survival analysis was performed using the Kaplan-Meier method and the difference in survival was analyzed using a log-rank test.

an average of 47 years old [12, 13]. Consistently, in this study, the ages of patients at their first diagnosis were 30-60 years old, with median and average ages of 45 and 47 years old. It is reported that patients with SCCC show neuroendocrine symptoms. For example, Kim *et al.* [14] and Santhosh *et al.* [15] both reported on the antidiuretic hormone secretion abnormalities of SCCC patients. In this study, only one patient was asymptomatic, while the rest suffered from abnormal vaginal bleeding and discharge. No neuroendocrine abnormalities were observed.

In extrapulmonary small cell carcinoma, the most common metastatic sites are the liver, lymph nodes, lungs, and bones [16]. Scutiero *et al.* [17] found that SCCC was usually transferred to the liver, lungs, bones, chest, and brain through the blood vessels, and to the pelvic lymph nodes, abdominal aortic lymph nodes, and supraclavicular lymph nodes through the lymphatic vessels. In this study, there were 9 cases of distant metastasis, and the metastasis sites were the liver (n = 5), the lungs (n = 2), the brain (n = 1), and the bones (n = 1). This suggests that the liver is also a common site of metastasis in SCCC.

The prognostic factors of SCCC are complex and diverse, but due to differences in the number of cases and regions, different scholars come to different conclusions. For example, Suthida *et al.* [18, 19] found that for cases with early stage SCCC, surgery combined with adjuvant chemotherapy had a better prognosis than surgery alone, and surgery combined with radiotherapy, and surgery combined with both radiotherapy and chemotherapy, so they believed that chemotherapy could improve the survival time of early-stage SCCC and surgery combined with chemotherapy was an effective treatment modality. Cohen *et al.* [7] found that in FIGO-I-IIA patients who received radical hysterectomy had a significantly improved 5-year survival rate compared with those without surgery, and inferred that surgery was an active treatment of early SCCC, which is in agreement with the conclusion of a study by Tian *et al.* [20]. However, another study showed that for the FIGO I-IIB patients, the patients who received initial surgery had a tendency to relapse compared to the non-surgical patients [9]. Chen *et al.* [21] retrospectively studied the treatment method of 110 cases of stage I-II SCCC patients and found that the 5-year survival rate was 78% for the patients who received initial treatment with radiotherapy combined with 5 cycles of platinum chemotherapy, while the survival rate of the patients who received initial surgical treatment was 46%. In this study, we found that the factors for a poor prognosis of SCCC were older age (≥ 45 years old), larger tumor size (> 4 cm), and positive lymph node metastasis. However, the factors of FIGO staging, surgical approach, and neoadjuvant

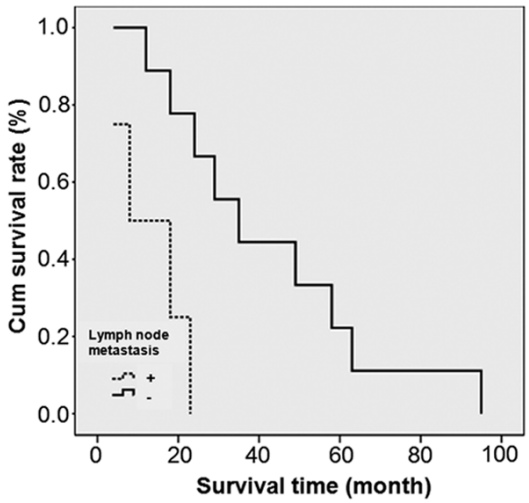

Figure 3. The survival curves of patients with a tumor size ≤ 4 cm or > 4 cm. The survival analysis was performed using the Kaplan-Meier method and the difference in survival was analyzed using a log-rank test.

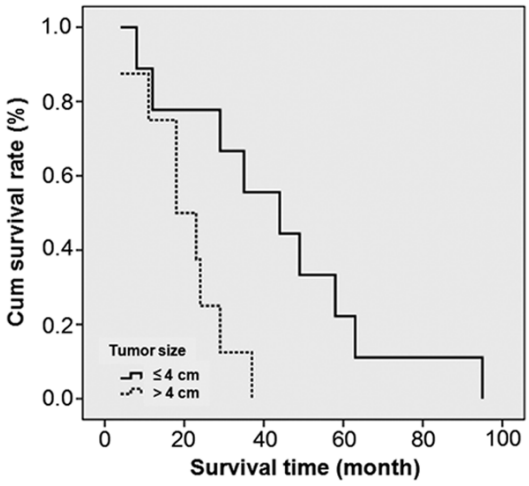

Figure 4. The survival curves of patients with (+) or without (-) lymph node metastasis. The survival analysis was performed using the Kaplan-Meier method and the difference in survival was analyzed using a log-rank test.

chemotherapy were not independent prognostic factors for SCCC. This inconsistency with previous studies still needs further investigation.

In this study, most patients died within two years after onset. Among the 17 patients with complete follow-up data, the longest survival time was 95 months, and the patient was still alive at the end of the follow-up period. However, the overall prognosis of SCCC was poor. Chan *et al.* [22] reported that the 5-year survival rate of SCCC was 30-46% for the early stage and 0-15% for the advanced stage. Kuji *et al.* [11] studied the clinical data of 52 cases of SCCC and found that the 4-year overall survival rates of Stage IB1, IB2, IIB, IIIB, and IVB were 63%, 67%, 30%, 29%, and 25%, respectively. The above results indicate that the prognosis gets worse with the progression of SCCC.

This study has some limitations. First, this was a study based on a single center. Second, the sample size was relatively small.

In conclusion, our findings demonstrate that older age (≥ 45 years old), larger tumor size (> 4 cm) and positive lymph node metastasis are poor prognostic factors of SCCC. Due to the uniqueness and rareness of SCCC, there is currently no prospective case-control study and there is no uniform standard in its treatment and prognosis. Future studies are warranted to further reveal the prognostic factors of SCCC, to prolong the survival and to improve the quality of life of SCCC patients.

Disclosure of conflict of interest

None.

Address correspondence to: Gulnar Kurban, The 1st Department of Gynecological Oncology, The Affiliated Cancer Hospital of Xinjiang Medical University, No. 789, Su Zhou East Road, Xin Shi District, Urumqi 830011, China. Tel: 86-15099181109; Fax: 86-0991-7968088; E-mail: 15099181109@163.com

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