Small Cell Carcinoma as an Independent Prognostic Factor for Cervical Cancer Patients: A Population-Based Analysis

Wang Miao
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Wu Qiuji
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Congkuan Song
Wuhan University Second Clinical Hospital: Wuhan University Zhongnan Hospital
Liu Yixin
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Wang Xulong
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Zhang Boyu
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Qin Guizhen
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Zhang Jun
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy
Yongchang Wei (weiyongchang@whu.edu.cn)
Wuhan University Zhongnan Hospital Department of Chemotherapy and Radiation Therapy

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Abstract

Background: Small cell carcinoma (SmCC) of cervix was a rare neoplasm with little recognition. Population-based study describing difference in characteristics and outcomes between SmCC and squamous cell carcinoma (SCC), usual type, was limited. Here, we used the Surveillance, Epidemiology, and End Results (SEER) database to compare SmCC with SCC and investigated the prognostic values of the clinicopathological characteristics and survival outcomes in SmCC of cervix.

Methods: Patients diagnosed with cervical SmCC and SCC in SEER database from 2004-2015 were enrolled in analysis. Propensity-score matching analysis (PSM) was used to balance baseline characteristics between patients who were cervical SmCC and those who were cervical SCC. Cox regression models and Kaplan-Meier methods were conducted to analyze survival data before and after PSM. Stratified analyses were performed to investigate the risk of mortality at different stage.

Results: In total, 25345 patients including 287 cervical SmCC patients and 25058 cervical SCC patients were enrolled our analysis. Both histological subtypes were more common in unmarried women and in white populations. Compared with cervical SCC patients, cervical SmCC patients showed a higher rate of larger tumor size (tumor size ≥4 cm, 33.8% vs 51.9%, P<0.001), higher grade disease (grade III-IV, 32.2% vs 58.9%, P<0.001), regional lymph node involvement (22.5% vs 49.5%, P<0.001) and distant metastasis (10.3% vs 32.4%, P<0.001). Before PSM, multivariate regression model revealed that SmCC histology (P<0.001) and advanced FIGO stages (P<0.001) were principal prognostic factors of poor survival for cervical patients. After PSM, 1060 patients in SCC group were 4:1 matched with 278 patients in SmCC group. Multivariate regression model in PSM cohort showed histology and FIGO stage were crucial prognostic factors for survival. Kaplan-Meier survival curves clearly showed that cervical SmCC patients had worse survival than that of patients with SCC in all stages, stage I-II, III, IV before and after PSM analysis.

Conclusion: Compared to patients with cervical SCC, those with cervical SmCC showed a worse survival before and after adjustment baseline characteristic in all stages. SmCC was an independent poor prognostic factor in cervical cancer patients.

Background

Cervical cancer is the third most frequently diagnosed gynecologic cancer and the fourth leading cause of cancer death in women worldwide(1–3). Persistent high-risk human papillomavirus (HPV) infection has been identified as a prominent etiological factor for cervical cancer(4, 5). Early screening, improvement average socioeconomic levels and HPV vaccination injection have contributed to reduce of its prevalence and mortality in developed countries(6–8). However, in most developing countries, cervical cancer is still a severe public health problem and imposes serious threat to women's health(1, 2). Squamous cell carcinoma (SCC), the most common pathological type, accounts for 75% of all types of cervical cancer(9). Thus, therapeutic strategies for cervical cancer mainly focus on SCC of cervix. Among

cervical cancer pathology types, small cell carcinoma (SmCC) of cervix, first described by Regan et al. in 1957, was a rarely encountered neuroendocrinal tumor with less than 3% in all histological types(10–13). Compared to SCC, SmCC displays distinct clinicopathologic characteristics including a high degree of invasiveness, a high rate lymph-node and distant metastases, thus carrying an unfavorable prognosis according to existing studies(14–17). The rarity of the disease makes it exceedingly difficult to conduct randomized controlled clinical trials to guide therapy for cervical SmCC. Most studies were mere small case series and reports(18, 19).

Although SmCC of cervix is highly malignant and associated with dismal survival, it is often neglected as a result of its infrequent occurrence. There have been few studies describing the characteristics and survival of cervical SmCC. In addition, to our knowledge, there is no population-based study that compares the difference in clinicopathologic characteristics and survival outcomes between cervical SmCC and SCC.

Therefore, we investigated the clinicopathologic characteristics and survival outcomes between patients with cervical SmCC and SCC based on the data from Surveillance, Epidemiology, and End Results (SEER) database, with a hope to provide more information to clinicians on this rare malignancy.

Patients And Methods

Patient population

A retrospective research, based on data from SEER database, was conducted and SEER database is publicly available, covering approximately 28% of the US population. Informed consent was waived for use of the data from the SEER. The SEER * Stat 8.3.6 version was used to filter information and collect eligible patients for this research (https://seer.cancer. gov/data/). Adult patients (≥ 18 years of age) with a primary site ‘cervix uteri’ who were diagnosed from 2004 to 2015 were selected. Patients received a pathological diagnosis of SmCC (ICD-O-3 histology code: 8041/3: small cell carcinoma, NOS], 8042/3: oat cell carcinoma, 8043/3: small cell carcinoma, fusiform cell, 8044/3: small cell carcinoma, intermediate cell) and SCC (ICD-O-3 histology code: 8052/3, 8070/3-8078/3, 8083/3, 8084/3) were included in our analysis. Patients without survival data, more than one primary tumor, were excluded from the analysis.

Methods

The study end point was overall survival (OS), which refers to the interval from initial diagnosis to death from any cause or to the last follow-up. Descriptive statistics were performed to summarize patients’ demographic and clinical characteristics among patients with cervical SmCC and SCC. Continuous variables were shown as mean ± SD and categorized variables were presented as frequency and their proportion. Two-sample t-tests were performed for continuous data and categorized data were analyzed by Chi-square tests. Survival data between the two different histology groups was analyzed by Kaplan-Meier methods and compared with log-rank tests. Comparative risk factors of OS were identified using

cox regression models. Stage-based stratified analyses were performed to evaluate the risk of mortality associated with cervical SCC or SmCC in each FIGO clinical stage. In order to accurately assess the importance of SmCC histology in prognosis of cervical cancer patients, propensity score matching (PSM) method was performed to adjust potential baseline confounding factors between two groups. Patients with cervical SmCC were matched with cervical SCC patients at a ratio of 1:4. After matching, patient clinical characteristics and survival outcomes between the two groups were re-analyzed within the matched cohort. A P value < 0.05 was considered statistically significant and all statistical tests were two-sided. All statistical analyses were conducted using the statistical software packages R version 3.6.2 (http://www.R-project.org, The R Foundation) and SPSS statistics version 23.0 (IBM SPSS Statistics, New York, United States).

Results

Patient characteristics

In total, 25345 cervical cancer patients in SEER database from 2004 to 2015 were enrolled in our analysis, including 287 cervical SmCC patients and 25058 cervical SCC patients. Baseline demographic and clinicopathologic characteristics among patients with cervical SCC and SmCC were summarized in Table 1.

Table 1
Baseline demographic and clinicopathologic characteristics for small cell and squamous cell carcinoma of cervix before and after propensity matching

Clinical parameter	Unmatched (complete) dataset			Matched (4: 1) dataset		
	squamous cell carcinoma (n = 25058)	Small cell carcinoma (n = 287)	P value	squamous cell carcinoma (n = 1060)	Small cell carcinoma (n = 278)	P value
Mean age (years, SD)	50.20 ± 14.91	47.80 ± 15.37	0.007	48.36 ± 15.26	48.10 ± 15.19	0.801
Marital status			0.272			0.503
Married	9796 (39.1%)	110 (38.3%)		403 (38.0%)	106 (38.1%)	
Single	13670 (54.6%)	165 (57.5%)		592 (55.8%)	160 (57.6%)	
Unknown	1592 (6.4%)	12 (4.2%)		65 (6.1%)	12 (4.3%)	
Race			0.476			0.384
Black	3988 (15.9%)	45 (15.7%)		185 (17.5%)	44 (15.8%)	
White	18318 (73.1%)	204 (71.1%)		760 (71.7%)	196 (70.5%)	
Other	2752 (11.0%)	38 (13.2%)		115 (10.8%)	38 (13.7%)	
Grade			**< 0.001**			0.521
Grade I-II	9659 (38.5%)	2 (0.7%)		16 (1.5%)	2 (0.7%)	
Grade III-IV	8064 (32.2%)	16 (58.9%)		610 (57.5%)	166 (59.3%)	
Unknown	7335 (29.3%)	116 (40.4%)		434 (40.9%)	112 (40.0%)	
FIGO Stage			**< 0.001**			0.717
I	11017 (44.0%)	67 (23.3%)		231 (21.8%)	66 (23.7%)	
II	3717 (14.8%)	14 (4.9%)		71 (6.7%)	14 (5.0%)	
III	5803 (23.2%)	87 (30.3%)		340 (32.1%)	86 (30.9%)	
IV	3133 (12.5%)	101 (35.2%)		363 (34.2%)	94 (33.8%)	

FIGO: Federation International of Gynecology and Obstetrics

Clinical parameter	Unmatched (complete) dataset			Matched (4: 1) dataset		
	squamous cell carcinoma (n = 25058)	Small cell carcinoma (n = 287)	P value	squamous cell carcinoma (n = 1060)	Small cell carcinoma (n = 278)	P value
Unknown	1388 (5.5%)	18 (6.3%)		55 (5.2%)	18 (6.5%)	
Tumor size			**< 0.001**			0.942
< 4 cm	8123 (32.4%)	58 (20.2%)		212 (20.1%)	55 (19.8%)	
≥ 4 cm	8465 (33.8%)	149 (51.9%)		569 (53.7%)	145 (52.2%)	
Unknown	8470 (33.8%)	80 (27.9%)		279 (26.3%)	78 (28.1%)	
Regional lymph node			**< 0.001**			0.992
Negative	17750 (70.8%)	114 (39.7%)		424 (40.0%)	112 (40.3%)	
Positive	5626 (22.5%)	142 (49.5%)		523 (49.3%)	136 (48.9%)	
Unknown	1682 (6.7%)	31 (10.8%)		113 (10.7%)	30 (10.8%)	
Distant metastasis			**< 0.001**			0.786
No	21542 (86.0%)	179 (62.4%)		673 (63.5%)	176 (63.3%)	
Yes	2587 (10.3%)	93 (32.4%)		340 (32.1%)	87 (31.3%)	
Unknown	929 (3.7%)	15 (5.2%)		47 (4.4%)	15 (5.4%)	
Primary surgery			**0.001**			0.988
None/unknown	12089 (48.3%)	167 (58.2%)		640 (60.3%)	164 (58.9%)	
Performed	12969 (51.7%)	120 (41.8%)		420 (39.6%)	114 (40.0%)	
Pelvic lymphadenectomy			**0.001**			0.630
Not performed	16996(67.8%)	185 (64.5%)		715 (67.5%)	183 (65.8%)	
Performed	7857(31.4%)	94 (32.8%)		327 (30.8%)	88 (31.7%)	

FIGO: Federation International of Gynecology and Obstetrics

Clinical parameter	Unmatched (complete) dataset			Matched (4: 1) dataset		
	squamous cell carcinoma (n = 25058)	Small cell carcinoma (n = 287)	P value	squamous cell carcinoma (n = 1060)	Small cell carcinoma (n = 278)	P value
Unknown	205 (0.8%)	8 (2.8%)		18 (1.7%)	7 (2.5%)	
Radiotherapy			0.076			0.190
None/unknown	10425(41.6%)	104(36.2%)		736 (69.4%)	181 (65.1%)	
Performed	14633(58.4%)	183(63.8%)		324 (30.6%)	97 (34.9%)	
Chemotherapy			**< 0.001**			0.896
None/unknown	12629(50.4%)	58(20.2%)		845 (79.7%)	220 (79.1%)	
Performed	12429(49.6%)	229(79.8%)		215 (20.3%)	222 (20.9%)	
FIGO: Federation International of Gynecology and Obstetrics						

The mean age of onset in SmCC patients was younger than that in SCC patients (47.80 ± 15.37 vs 50.20 ± 14.91, P = 0.007). The majority in both SmCC and SCC groups were single women (54.6% and 57.5%, respectively) and white patients (73.1% and 71.1%, respectively). Grade III-IV diseases were more commonly seen in SmCC patients (32.2% vs 58.9%, P < 0.001). Cervical SmCC patients were prone to advanced stage compared with patients with cervical SCC (SCC vs SmCC: stage III: 23.2% vs 30.2%; stage IV: 12.4% vs 35.2%, P < 0.001). Specifically, a higher ratio of patients with larger tumor size (33.8% vs 51.9%, P < 0.001), regional lymph node metastasis (22.5% vs 49.5%, P < 0.001) and distant metastasis (10.3% vs 32.4%, P < 0.001) was found in SmCC group. In terms of cancer treatment, more patients with SCC received surgery (51.7% vs 41.8%, P = 0.001), while more patients with SmCC underwent pelvic lymphadenectomy (31.4% vs 32.8%, P = 0.001). In addition, more SmCC patients received chemotherapy compared with SCC patients (49.6% vs 79.8%, P < 0.001).

Survival analysis

Kaplan-Meier curves were performed to describe the survival data among patients with cervical SCC or SmCC at different stages (Fig. 1). Patients with cervical SCC showed better survival than that of patients with cervical SmCC regardless of stage (P < 0.001 for all stages by log-rank test). And the 5-year overall survival rates of SCC vs SmCC patients were 81.0% vs 56.0%, 51.0% vs 29.0%, 17% vs 11% for stage I-II, III and IV, respectively.

Prognostic analysis in cervical cancer patients

Cox regression models were performed to identify prognostic indictors for survival in cervical cancer patients (Table 2). SmCC pathology, older age, single women, black women, higher grade disease, advanced stage, no chemotherapy as well as no pelvic lymphadenectomy were significant independent poor prognostic factors for overall survival (OS). Notably, SmCC of cervix was associated with worse survival (adjusted HR = 2.02 [95% CI: 1.75–2.34], P < 0.001) compared to SCC of cervix. FIGO stage was a crucial prognostic indicator for survival (adjusted HR: 2.86 [95% CI: 2.61–3.12], 5.34[95% CI: 4.93–5.78], and 13.89 [95% CI: 12.83–15.04], for stage II, stage III and stage IV, respectively, compared to stage I).

Table 2
Cox regression models for overall survival among patients with cervical small cell or squamous cell carcinoma in unmatched cohort

Covariate, level	Crude HR (95% CI)	P value	Adjusted HR * (95% CI)	P value
Histology				
Squamous cell carcinoma	1		1	
Small cell carcinoma	2.90 (2.51–3.36)	**< 0.001**	2.02 (1.75–2.34)	**< 0.001**
Age (years)				
18–39	1		1	
40–59	1.80 (1.70–1.91)	**< 0.001**	1.28 (1.21–1.37)	**< 0.001**
≥ 60	3.19 (3.00-3.40)		1.94 (1.82–2.07)	**< 0.001**
Marital status				
Married	1			
Single	1.54 (1.47–1.61)	**< 0.001**	1.24 (1.18–1.30)	**< 0.001**
Unknown	1.18 (1.07–1.31)	**0.001**	1.10 (1.00- 1.22)	0.054
Race				
Black	1		1	
White	0.76 (0.72–0.81)	**< 0.001**	0.88 (0.83–0.93)	**0.01**
Other	0.62 (0.57–0.68)	**< 0.001**	0.69 (0.63–0.75)	**< 0.001**
Grade				
Grade I-II	1		1	
Grade III-IV	1.50 (1.43–1.58)	**< 0.001**	1.23 (1.17–1.30)	**< 0.001**
Unknown	1.02 (0.97–1.08)	0.458	0.91 (0.86–0.96)	**0.001**
FIGO Stage				
I	1		1	
II	3.22 (2.98–3.48)	**< 0.001**	2.86 (2.61–3.12)	**< 0.001**
III	4.98 (4.66–5.32)	**< 0.001**	5.34 (4.93–5.78)	**< 0.001**
IV	15.18 (14.19–16.25)	**< 0.001**	13.89 (12.83–15.04)	**< 0.001**
Unknown	4.72 (4.28–5.20)	**< 0.001**	3.49 (3.15–3.85)	**< 0.001**

HR: hazard ratio; 95% CI□95% confidence interval

Covariate, level	Crude HR (95% CI)	P value	Adjusted HR * (95% CI)	P value
Surgery				
None/unknown	1		1	
Performed	0.92 (0.88–0.96)	**< 0.001**	0.99(0.95–1.04)	0.991
Pelvic lymphadenectomy				
Not performed			1	
Performed	0.35 (0.33–0.37)	**< 0.001**	0.45 (0.42–0.48)	**< 0.001**
Unknown	1.38 (1.13–1.66)	**0.001**	1.13 (0.93–1.37)	0.232
Radiotherapy				
None/unknown	1		1	
Performed	2.39 (2.27–2.51)	**< 0.001**	1.03 (0.96–1.10)	0.425
Chemotherapy				
None/unknown	1		1	
Performed	1.98 (1.89–2.08)	**< 0.001**	0.66 (0.62–0.70)	**< 0.001**
HR: hazard ratio; 95% CI□95% confidence interval				

Table 3
Multivariate cox regression analysis for overall survival, stratified by disease stage in unmatched cohort

Covariate, level	Stage I-II		Stage III		Stage IV	
	Adjusted HR	P value	Adjusted HR	P value	Adjusted HR	P value
Histology						
squamous cell carcinoma	1		**1**		**1**	
Small cell carcinoma	2.43 (1.68,3.51)	**< 0.001**	1.86 (1.42, 2.44)	**< 0.001**	1.38 (1.11, 1.72)	**0.004**
Age						
18–39	1		**1**		**1**	
40–59	1.42 (1.27,1.59)	**< 0.001**	1.15 (1.03, 1.28)	**0.010**	0.94 (0.83, 1.05)	0.255
≥ 60	2.78 (2.48,3.12)	**< 0.001**	1.57(1.40, 1.76)	**< 0.001**	1.04 (0.92, 1.17)	0.564
Marital status						
Married	1		**1**		**1**	
Single	1.42 (1.30,1.55)	**< 0.001**	1.21 (1.11,1.32)	**< 0.001**	1.02 (0.94, 1.11)	0.648
Unknown	1.34 (1.12,1.61)	**0.001**	1.05 (0.85,1.29)	0.650	0.93(0.77, 1.13)	0.469
Race						
Black	1		**1**		**1**	
White	0.82 (0.75,0.91)	**< 0.001**	0.92 (0.83, 1.02)	0.11 2	0.87 (0.79, 0.97)	**0.008**
Other	0.66 (0.56,0.77)	**< 0.001**	0.70 (0.60, 0.82)	**< 0.001**	0.74 (0.63, 0.88)	**< 0.001**
Grade						
Grade I-II	1		**1**		**1**	
Grade III-IV	1.34 (1.22,1.47)	**< 0.001**	1.11 (1.02, 1.22)	**0.017**	1.11 (1.01, 1.22)	**0.037**
Unknown	0.90 (0.82,1.00)	0.056	1.07 (0.97, 1.19)	0.182	0.94 (0.85, 1.04)	0.250

HR: hazard ratio; 95% CI：95% confidence interval

Covariate, level	Stage I-II		Stage III		Stage IV	
	Adjusted HR	P value	Adjusted HR	P value	Adjusted HR	P value
Surgery						
None/unknown	1		**1**		**1**	
Performed	1.00 (0.93,1.08)	0.972	1.03 (0.95, 1.11)	0.445	0.94 (0.87, 1.02)	0.154
Pelvic lymphadenectomy						
Not performed	1		**1**		**1**	
Performed	0.53 (0.48,0.59)	**< 0.001**	0.39 (0.35, 0.43)	**< 0.001**	0.46 (0.41, 0.52)	**< 0.001**
Unknown	2.38 (1.49,3.79)	**< 0.001**	1.06 (0.65, 1.74)	0.807	0.97 (0.66, 1.43)	0.897
Radiotherapy						
None/unknown	1		**1**		**1**	
Performed	2.45 (2.17,2.77)	**< 0.001**	0.54 (0.47, 0.62)	**< 0.001**	0.69 (0.63, 0.75)	**< 0.001**
Chemotherapy						
None/unknown	1		**1**		**1**	
Performed	0.98 (0.88,1.08)	0.662	0.66 (0.60, 0.74)	**< 0.001**	0.45 (0.41, 0.50)	**< 0.001**
HR: hazard ratio; 95% CI□95% confidence interval						

Next, we queried if different stages showed varied risk of mortality among patients with SmCC and SCC of cervix. Stratified cox regression models by stage were conducted. Interestingly, after adjustment for age, race, marital status, grade and treatment, SmCC pathology was still related to worse OS at stage I-II, III and IV with the adjusted HR being 2.43 (95% CI: 1.68–3.51, P < 0.001), 1.86 (95% CI: 1.42–2.44, P < 0.001) and 1.38 (95% CI: 1.11–1.72, P = 0.004) compared with SCC. Pelvic lymphadenectomy and radiotherapy improved survival in both SCC and SmCC patients, regardless of disease stages. Cancer grade was still an independent prognostic indicator of survival at different stages. Additionally, black women and older age were significant poor prognostic factors in stage I-II and stage III.

Propensity score matched analysis

In order to minimize potential influence of baseline confounding factors and accurately assess the importance of SmCC histology in prognosis of cervical cancer patients, propensity score matched (PSM)

analysis was performed. After PSM, 278 cervical SCC patients and 1060 cervical SmCC patients were included in further analysis. Patient characteristics after PSM were showed in Table 1 and all confounding factors were well matched **(**Fig. 2**)**. In PSM cohort, cox regression analysis showed that SmCC pathology was an independent indictor for unfavorable survival (adjust HR = 1.87, 95% CI: 1.57–2.23, P < 0.001) **(Supplemental Table 1)** and FIGO stage also showed great impact on survival (P < 0.001) and the adjust HR was increased with advancement from stages II through IV (adjust HR after PSM were 2.21, 3.46, 8.17 for stage I-II, III, IV compared to stage I). These results were similar to the results in the unmatched cohort. Besides, the stratified cox regression analysis for OS after PSM **(Supplemental Table 2)**, revealed that cervical SmCC patients had worse OS compared to cervical SCC patients in stage I-II (adjust HR = 1.68,95% CI: 1.05–2.68, P = 0.031), III (adjust HR = 2.11, 95% CI: 1.52–2.94, P < 0.001) and IV (adjust HR = 1.33, 95% CI: 1.03–1.72, P = 0.030). Patients with SCC exhibit better OS than that of patients with SmCC in all stages, stage I-II, III and IV (Fig. 3).

Discussion

The aim of the present study was to investigate clinical features and outcomes among patients with cervical SmCC to ensure that doctors and patients clearly understand the different clinical and survival features for cervical SmCC. As far as we know, this was first population-data study to compared SmCC and SCC according to specified inclusion criteria.

In our study, we found the average morbidity age of the two malignances was similar, but cervical SmCC patients were somewhat a little younger. Both pathological types are more likely to occur in single women and in white patients. This could be explained by the fact that socioeconomic psychological factors and genetic diversity might play an important role in tumorigenesis and tumor progression(20–22). Several previous studies did demonstrate that marital status and ethnicities were important etiological and prognostic factors in several solid tumors, including cervical cancer (23–26). Similarly, in our study better survival was seen in married patients and in white women.

Significant differences between patients with cervical SmCC versus SCC were also observed in our study. Patients with SmCC of cervix were much more likely than patients with SCC of cervix to present with larger tumor size, local lymph node involvement, distant metastasis and advanced disease stage, all of which might contribute to poorer survival in SmCC patients. These observations were in accordance with previous studies showing that FIGO stage, tumor size, distant metastases were important clinicopathological characteristics that dictated the survival of patients with cervical SmCC (27–29). Moreover, cox regression models in our study indicated that pathology SmCC and higher stage primarily led to poor prognosis of patients with cervical cancer. In addition, stratified analyses by stages showed that SmCC was an independent prognosis factor for poor survival in stage I-II, III and IV patients.

More importantly, to balance the confounding factors, we conducted a PSM study to match confounding factors between patients with cervical SmCC and SCC. Multivariate regression analysis in matched cohorts suggested that SmCC histology and FIGO stage were crucial indictors for poor survival. Kaplan-

Meier curves clearly displayed that OS was lower in stages I-II, III, and IV in patients with cervical SmCC compared to patients with the same stage of cervical SCC. Furthermore, stratified analyses by stage in matched cohorts yielded similar results, indicating that SmCC pathology was the main influencing factor for poor survival. These findings suggested that cervical SmCC itself was highly malignant, undifferentiated, and aggressive, associated with poorer prognosis. Consistently, precious studies had proved that SmCC of cervix was associated with a dismal survival(9, 30). However, in our study we offered a relatively large sample size of patients with SmCC and PSM and stratified analyses were performed to more convincingly illustrate this fact.

However, the mechanism was not yet clear due to its rarity. Some studies showed that most patients with SmCC of cervix were etiologically associated with high-risk HPV, especially HPV 18, and that HPV infection was involved at an early stage of oncogenesis in SmCC of cervix(31–33). Moreover, SmCC of cervix are characterized by high mitosis, massive necrosis and common lymph-vascular involvement(34). Besides, existing studies have demonstrated that additional driven events also involved in the progression of SmCC of cervix. For example, loss of heterozygosity has been reported to be a driven event in SmCC of cervix(35). Besides, there were studies showing that recurrent mutations involving *PIK3CA, KRAS*, and *TP53* genes in SmCC of cervix. And in SmCC of cervix genetic alterations involving the *MAPK*, *PI3K/AKT/mTOR*, and *TP53/BRCA* pathways were found in a recent study(36). These findings may have implications to targeted therapy for the rare disease, offering the potential individualized management for this aggressive tumor. There was study suggesting that cervical SmCC showed a higher expression of the synaptophysin than that in lung SmCC, while a higher expression *TTF-1* in tumor cell nuclei was observed in lung SmCC. Both pulmonary and cervical SmCC had similar immunoreactive staining for *CD56* and *chromogranin A*(37). These results were useful for early diagnosis. But we did not know much about the mechanism of cervical SmCC and more efforts were needed to explore the mechanism for this aggressive tumor.

The optimal therapeutic strategies for cervical SmCC were not clear due to lack of standardized guidelines for treatment. Treatment options for cervical SmCC were according to the data for treating small carcinoma of lung because SmCC of the cervix share similar histological and clinical characteristics with small cell lung cancer.(38) Accepted treatment modalities included surgery, radiotherapy and chemotherapy. Surgery is mainly used to diagnosis or a resection to early stage disease(39). For limited stage disease, radiotherapy is an important approach and it is usually given with concurrent etoposide/cisplatinum(40). Platinum-based combination chemotherapy was the standard primary approach for advanced stage disease, which could achieve a high response rates of 50–79% but also developed recurrent or progressive chemoresistant disease.(41) Future prospective studies designed to explore the treatment for cervical SmCC were necessary.

As a retrospective study based on SEER databases, there were limitations existing. Firstly, information of detailed treatment regimens was insufficient in SEER databases, which may lead to different survival. Secondly, Selection bias may exist, which is inevitable for clinical observational studies even when PSM was used. But our analysis also had some strengths. Firstly, we collected 278 cases with cervical SmCC

from 2004 to 2015, which offered a relatively large sample size to perform accurate and multiple forms of analysis. Secondly, PSM analysis and stratified analyses were used to analyze potential confounding factors.

Conclusion

SmCC of cervix conferred a poorer survival than SCC of cervix in all stages, even after adjustment clinical characteristics and cancer treatment by PSM. SmCC of cervix was a crucial independent prognostic factor for patients with cervical cancer.

Abbreviations

SmCC: small cell carcinoma; SCC: squamous cell carcinoma; SEER: Surveillance, Epidemiology, and End Results; PSM: Propensity-score matching; OS: overall survival; HR: hazard ratio； 95% CI：95% confidence interval; HPV: human papillomavirus; FIGO: federation International of Gynecology and Obstetrics

Declarations

Ethics approval and consent to participate: the patient information in the SEER database is deidentified and publicly available, our study was exempt from Institutional Review Board approval.

Consent for publication: Not applicable

Availability of data and materials

The data in the current study are available in the Surveillance, Epidemiology, and End Results (SEER) database, (https://seer.cancer. gov/data/)

Conflict of interest: The authors declare no competing interests.

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Author contribution

All authors were integral for the study and contributed to the research as noted below. Wang Miao: Data collection and data analysis, and writing of the manuscript; Wu Qiuji: Design and data analysis, and writing of the manuscript; Song Congkuan: Data analysis and data collection; Liu Yixin and Wang Xulong: Data collection and data analysis; Zhang Boyu: Writing of the manuscript; Qin Guizhen: data analysis and writing of the manuscript; Zhang Jun: Critical review of the manuscript; Wei Yongchang: Design, administrative support, resources, funding support and critical revision of the manuscript.

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Figures

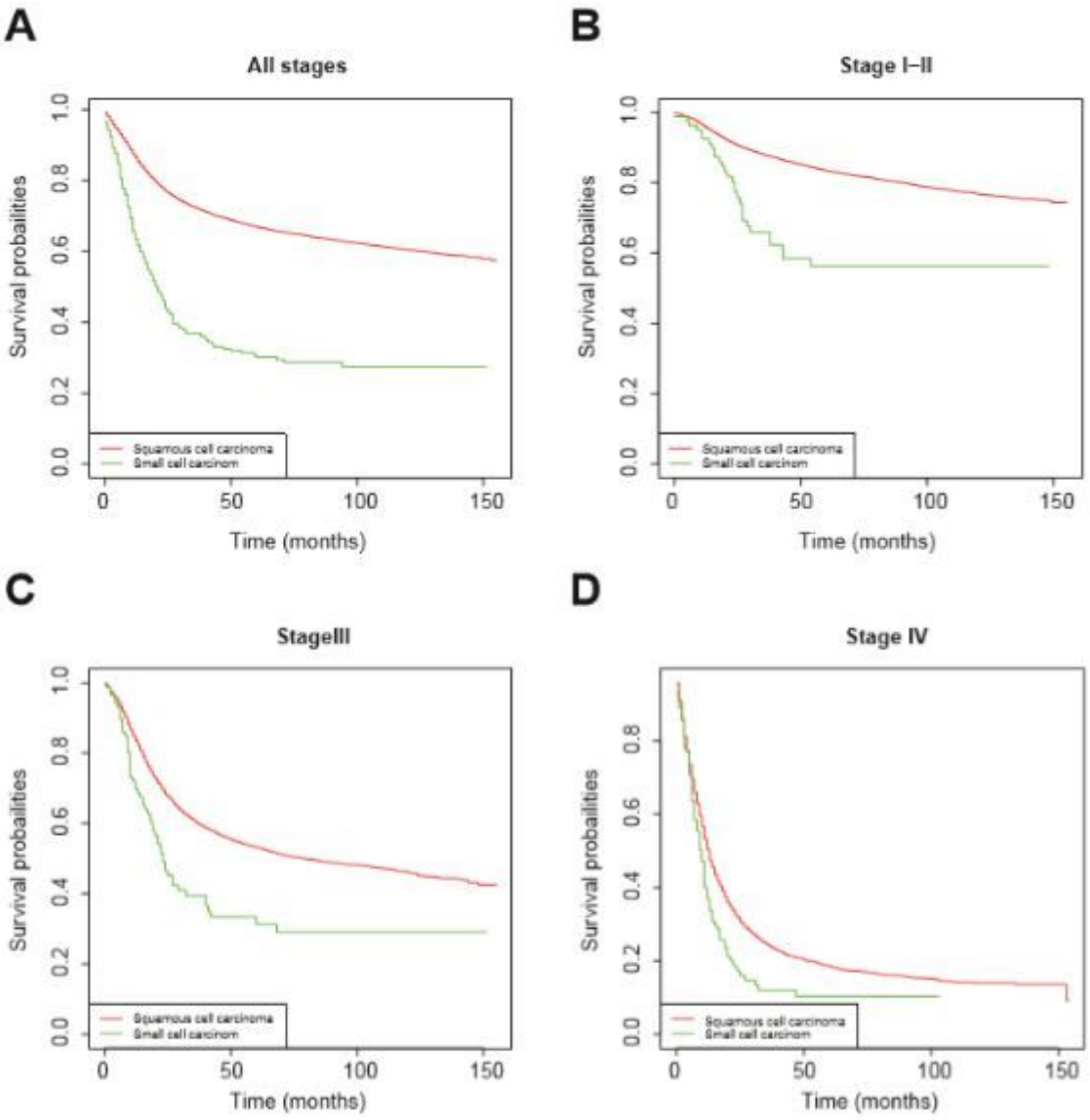

Figure 1

Survival curves of OS among patients with cervical SCC and SmCC at (A) all stages, (B) stage I-II, (C) stage III, (D) stage IV. Abbreviation: OS: overall survival; SCC: squamous cell carcinoma; SmCC: small cell carcinoma

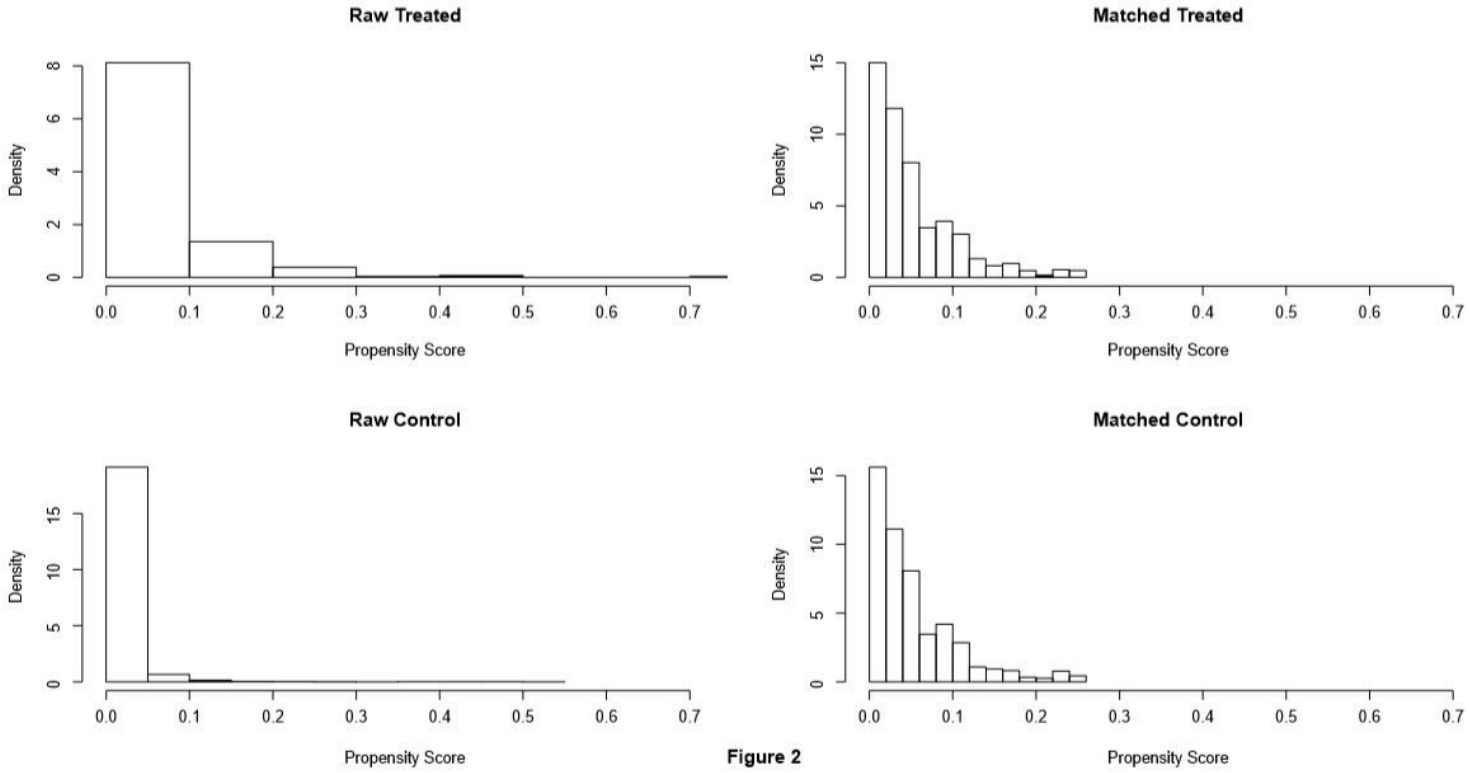

Figure 2

Propensity score matching for cervical SCC and SmCC. Abbreviation: SCC: squamous cell carcinoma; SmCC: small cell carcinoma

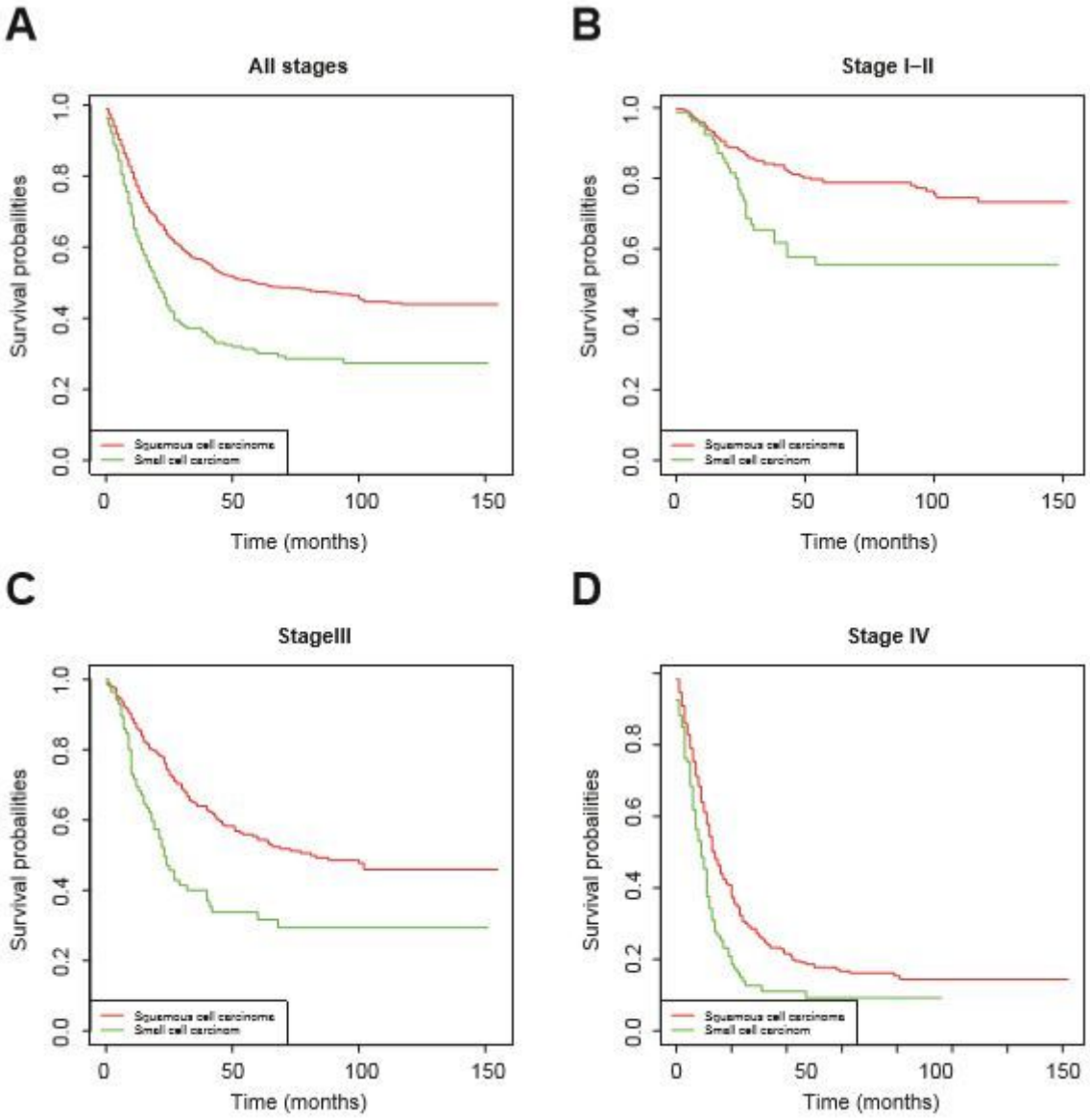

Figure 3

Survival curves of OS among patients with cervical SCC and SmCC at (A) all stages, (B) stage I-II, (C) stage III, (D) stage IV in PSM cohort. Abbreviation: OS: overall survival; SCC: squamous cell carcinoma; SmCC: small cell carcinoma; PSM: propensity score matching

Supplementary Files

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