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ORIGINAL RESEARCH

Prognostic Factors and Local Treatment Modalities of Small-Cell Carcinoma of the Cervix: An Analysis According to the International Federation of Gynecology and Obstetrics Stage

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Purpose: Small-cell carcinoma of the cervix (SCCC) is a rare type of cervical cancer. This study aimed to investigate the clinicopathological characteristics and survival as well as the optimal local treatment modalities for SCCC.

Patients and Methods: We retrospectively evaluated the data of patients diagnosed with SCCC between 1988 and 2015 in our institution – those included in the Surveillance, Epidemiology, and End Results (SEER) database and those in the Periodical Database. Kaplan–Meier method and Cox regression proportional hazard methods were used to evaluate overall survival (OS). A nomogram that could predict OS was constructed based on the Cox proportional hazard model.

Results: In total, 695 patients were included in this study. The 5-year overall survival in FIGO stage I-IIA and IIB-IV patients was 45.7% and 14.4%, respectively (P <0.01). Univariate and multivariate analyses showed that lymph node status (P <0.01) and cancer-directed surgery (P <0.01) were independent prognostic factors for FIGO I-IIA stage patients, and age (P <0.05), tumor size (P <0.01), chemotherapy (P <0.01) and radiation (P <0.01) were independent prognostic factors for FIGO stage IIB-IV patients.

Conclusion: Better prognosis was associated with negative lymph node status, no lymphatic vasculature, surgery, and early-stage patients. Furthermore, our data showed that the prognosis and treatment pattern varied depending on the FIGO stage, and that optimal treatment modalities included radical surgery for early-stage SCCC and chemoradiotherapy for advanced-stage SCCC. It is helpful to assess the individual prognosis of SCCC patients and choose personalized treatment modalities.

Keywords: treatment modalities, prognosis, C-index, COX risk regression model, nomogram

Introduction

Small-cell carcinoma of the cervix (SCCC) is a rare type of cervical cancer, accounting for less than 0.8% of all carcinomas affecting the female cervix.[1–4] The mean age of onset is 47 years (range, 32–65 years), and SCCC patients are at least 20 years old.[2] There have been several terms used to refer to SCCC due to its low incidence, including small cell neuroendocrine tumors, small cell undifferentiated carcinoma, argyrophilic cell carcinoma, and endocrine intermediate cell carcinoma.[5,6] It was not until 2007 when the term small-cell carcinoma was used in the General Rules of Clinical and

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Pathological Management of the Uterine Cervix that SCCC was classified as an independent disease because of its distinct clinicopathologic characteristics, deteriorating clinical progression, and markedly poor prognosis.[2,7,8] SCCC is known to have a predilection for lymph node (LN) involvement during the early stages of the disease, leading to poor prognosis. Due to the high invasiveness of the disease and its characteristic recurrence within 2 years, modern treatment is less effective.[9–11] Given the poor prognosis due to rapid clinical progression, this study aimed to identify prognostic factors that can positively influence survival and optimal local treatment modalities in SCCC. Towards this goal, we pooled cases from our institution, the Periodical Database, and the Surveillance, Epidemiology, and End Results (SEER) database for survival analysis.[12,13]

Patients and Methods

Patients and Data Collection

This was a retrospective pooled analysis of the data of patients pathologically diagnosed with SCCC between 1988 and 2015 in the SEER database (Surveillance Research Program, National Cancer Institute SEER*Stat software, Version 8.2.1),[12,13] between 1995 and 2015 in the Periodical Database, and between 2007 and 2015 at the Shanghai East Hospital, Shanghai, China. Pathological diagnosis was based on the primary site using the International Classification of Disease for Oncology (3rd Edition). The inclusion criteria were: (1) a definite diagnosis of SCCC as the primary malignancy via biopsy or postoperative pathology and (2) availability of clinical data such as pathological type, International Federation of Gynecology and Obstetrics (FIGO) stage, LN status, specific treatment method, follow-up time, and survival status. The exclusion criteria were: (1) the presence of concurrent primary tumors in other locations or other life-threatening diseases, (2) lack of a concrete treatment plan, and (3) lack of information on follow-up, survival status, and other information or loss to follow-up. Baseline variables collected were age, marital status, and clinicopathologic variables such as tumor grade, tumor size, FIGO stage, LN status, lymphovascular space invasion (LVSI), depth of stromal invasion, and treatment methods were also collected.

Staging and Tumor Grading

In all patients, the staging was according to the 2014 FIGO clinical staging system for carcinoma of the uterine cervix (there was no difference in the classification of early and late patients by the FIGO stage before 2014 and the FIGO stage in 2014).[14] Tumor grade was used to indicate the size of tumor tissue atypia, which reflects the morphological difference between tumor tissue and normal tissue cells in tissue structure and cell morphology. Grade I referred to well-differentiated; Grade II, moderately-differentiated; Grade III, poorly-differentiated; and Grade IV, undifferentiated (i.e., highly malignant tumors which do not show a tendency to differentiate).[15,16]

Statistical Analysis

Qualitative data were analyzed using the chi-square test. Univariate and multivariate Cox regression analyses were used to identify the independent prognostic factors for overall survival (OS). Kaplan-Meier survival analyses were used to evaluate OS. A nomogram was developed from the results of the Cox regression analysis, and it was used to predict the 3- and 5-year overall survival by representing the sum of points for each variable.[17] The internal validation of the model was performed using a 1000 bootstrap resample. The C-index, which denotes the proportion of pairs, measured on a scale of 0.5 (no better than chance) to 1 (perfect discrimination), was calculated to verify the nomogram's predictive accuracy, with the responder having a higher predicted probability of response than the non-responder. The larger the C-index value, the more accurate the prediction. If the C-index of a nomogram is 0.85, it can discern a patient with an event from a patient without an event with 85% accuracy. Simply, it was used to quantify the degree of consistency between prediction probability and the actual chance of having the event of interest.[18–20] Calibration plots were presented to compare the nomogram-predicted and observed 3-5-year prognosis visually. All statistical analyses were performed using SPSS statistical software package version 25.0 (SPSS Inc., Chicago, IL) and R project V.3.5.1 (http://www.r-project.org/). *P*-values <0.05 were considered statistically significant.

Results

Clinicopathological Patient Characteristics and Treatments

From the SEER database,[12,13] 7 of the 592 patients identified were excluded due to unclear treatment methods. From the Chinese Periodical Database, 260 of the 353 patients identified were excluded due to lack of information. From our institution, 5 of the 22 patients identified were excluded due to loss to follow-up (n=4) and concurrent ovarian borderline mucinous cystadenoma (n=1). Eventually, 695

patients were included in this study. The demographic and clinicopathologic characteristics and treatment of the patients are shown in Table 1. Of the 644 patients with available FIGO stage information, 330 (51.2%) had early-stage diseases (FIGO stage I-IIA), while 314 (48.8%) had advanced-stage diseases (FIGO stage IIB-IV). Of the 455 patients with available information on tumor size, 302 (69.1%) had tumors measuring ≥ 4 cm. Of the patients with known LN status, 78 (38.2%) and 126 (61.8%) of the early-stage patients had positive and negative LNs, respectively. Meanwhile, 57 (76.0%) and 18 (24.0%) of the advanced-stage patients had positive and negative LNs, respectively (P<0.01). Concerning LVSI, 27 (42.2%) of the patients with early-stage and 12 (57.1%) of the patients with advanced-stage disease had LVSI (P = 0.233). Concerning stromal invasion, 41 (63.1%) and 20 (87.0%) of the early-stage and advanced-stage patients, respectively, had invasion greater than one-half of the stromal layer (P <0.05). Concerning primary treatment, 226 (68.5%), 99 (30.0%), and 5 (1.5%) of the early-stage patients underwent surgery, chemoradiation, and chemotherapy alone, respectively. Meanwhile, primary treatment modalities in the advanced-stage patients were more diverse, with 70 (22.2%), 15 (4.8%), 6 (1.9%), 149 (47.5%), and 74 (23.6%) patients undergoing surgery, chemoradiation, radiation, chemotherapy alone, and other or no treatment, respectively (P <0.01) (Table SI).

Prognostic Factors and Local Treatment Modalities of All Patients

The 1-, 3-, and 5-year OS in the whole cohort were 63.3%, 36.9%, and 30.2%, respectively. The 3- and 5-year OS in the early-stage patients were 53.8% and 46.0%, whereas those in the advanced-stage patients were 21.1% and 15.9%, respectively (P <0.01) (Figure 1). Univariate analysis showed that age (P <0.01), FIGO stage (P <0.01), whether radiation was performed (P <0.01), LN involvement (P <0.01), undergoing primary surgery (P <0.01), and LVSI (P = 0.024) correlated with OS. In contrast, the depth of stromal invasion, tumor size, chemotherapy, and tumor grade did not correlate (P >0.05). The 5-year OS and univariate Cox regression model are summarized in Figure 2. In multivariate Cox regression model with adjustment for potential confounders, LN status (HR 2.193, 95% confidence interval CI 1.487–3.235, P <0.01), cancer-directed surgery (CDS) (HR 1.784, 95% CI 1.146–2.776, P <0.01), and FIGO stage (HR 1.297,

Table 1 Demographic and Clinicopathological Characteristics and Treatment of the Patients

Variables	n (%)
Year of Diagnosis	
1988–1994	77 (14.4)
1995–2001	90 (16.8)
2002–2008	183 (34.3)
2009–2015	184 (34.5)
Unknown	161
Age at Diagnosis	
<50	361 (57.4)
≥50	268 (42.6)
Unknown	66
Marital Status	
Married	230 (44.2)
Single	290 (55.8)
Unknown	175
FIGO Stage	
I-IIA	330 (51.2)
IIB-IV	314 (48.8)
Unknown	51
FIGO Stage (Detailed)	
I	264 (41.5)
II	158 (24.5)
III	124 (19.3)
IV	98 (14.7)
Unknown	51
Grade	
I–II	5 (1.4)
III–IV	357 (98.6)
Unknown	333
Tumor Size (cm) (n=437)	
<4	135 (30.9)
≥4	302 (69.1)
Unknown	258
Lymph Node Involvement (n=279)	
Positive	135 (48.4)
Negative	144 (51.6)
Unknown	416
LVSI (n=85)	
Positive	39 (45.9)
Negative	46 (54.1)
Unknown	610
Stromal Invasion (n=88)	
<1/2	27 (30.7)
≥1/2	61 (69.3)
Unknown	607

(*Continued*)

Table 1 (Continued).

Variables	n (%)
CDS (n=644)	
Yes	296 (46.0)
No	348 (54.0)
Unknown	51
Chemotherapy (n=644)	
Yes	477 (74.1)
No	167 (25.9)
Unknown	51
Radiotherapy (n=644)	
Yes	217 (33.7)
No	427 (66.3)
Unknown	51
Radiotherapy Record (n=217)	
Beam radiation	135 (62.8)
Radioactive implants	13 (6.0)
Beam + implants or isotopes	67(31.2)
Unknown	2
Treatment Method (n=644)	
CDS	64 (9.9)
Chemotherapy	154 (23.9)
Radiotherapy	6 (0.9)
Surgery+ Chemotherapy	135 (21.0)
Surgery+ Radiotherapy	23 (3.6)
Chemoradiation	114 (17.7)
Surgery+ Chemoradiation	74 (11.5)
No treatment	74 (11.5)
Unknown	51

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; CDS, cancer-directed surgery; LVSI, lymphovascular space invasion.

95% CI 1.055–1.594, P <0.01) were independent prognostic factors for OS (Figure 3). Consequently, we analyzed data on the LVSI and stromal invasion group, and found that LVSI (HR 2.842, 95% CI 1.064–7.590, P <0.05) was also an independent prognostic factor (Table SII).

Prognostic Factors and Local Treatment Modalities According to FIGO Stage

We performed a further stratified analysis according to the FIGO stage and found that there were significant differences in treatment patterns and prognostic factors according to the stage. For stages I-IIA patients, univariate analysis showed that age ≥50 years (27.7% vs 55.1%, HR 2.254, 95% CI 1.633–3.110, P = 0.000), no CDS (54.8% vs 28.6%, HR 2.267, 95% CI 1.594–2.999, P <0.01), use of radiotherapy (primary, adjuvant, or concurrent with chemotherapy; 51.1% vs 40.1%, HR 0.683, 95% CI 0.497–0.938, P = 0.001) and LN metastasis (30.2% vs 60.3%, HR 2.368, 95% CI 1.531–3.661, P = 0.001) were associated with worse prognosis. Multivariate analysis showed that CDS (HR 3.678, 95% CI 1.535–8.810, P <0.01) and LN status (HR 2.021, 95% CI 1.263–3.232, P <0.01) were independent prognostic factors.

In stages IIB-IV patients, univariate analysis showed that age ≥50 years (10.8% vs 22.0%, HR 1.656, 95% CI 1.282–-2.139, P = 0.000), tumor size ≥4 cm (18.2% vs 36.9%, HR 1.960, 95% CI 1.105–3.478, P = 0.021), no CDS (11.8% vs 29.3%, HR 1.982, 95% CI 1.431–2.746, P = 0.000), no chemotherapy (primary, adjuvant, or concurrent with radiation; 12.5% vs 18.1%, HR 2.683, 95% CI 1.957–3.678, P = 0.000), and no radiotherapy (primary, adjuvant, or with concurrent chemotherapy; 12.9% vs 30.3%, HR 1.550, 95% CI 1.101–2.182, P = 0.012) were associated with poor prognosis. However, LN status was not (P = 0.156), possibly because the majority of patients (76%) in the advanced stage already had LN metastasis. In the multivariate Cox regression model with adjustment for confounders, age ≥50 years (HR 1.435, 95% CI 1.014–2.030, P <0.05), tumor size ≥4 cm (HR 2.081, 95% CI 1.101–3.935, P <0.05), no chemotherapy (HR 2.268, 95% CI 1.487–3.454, P <0.01), and no radiation (HR 1.632, 95% CI 1.027–2.959, P <0.05) were significantly correlated with a worse prognosis. However, there was no significant difference in the prognosis of patients who underwent surgery and those who did not (P >0.05; Table 2, Figure 4).

Nomogram for Different FIGO Stages

We created prognostic nomograms for different FIGO stages that could predict OS based on the Cox proportional hazard model. The prognostic factors, after a stepwise forward selection in the COX regression analysis, were subsequently included in the nomogram construction. To use the nomogram, the variable value attributed to an individual patient is located on each variable axis, and a line is drawn upwards to determine the number of points received for each variable value. To determine the 3-5-year overall survival probability, a line is drawn downwards from the total points axis to the survival axis, where the total points represent the sum of points of each variable. We internally validated the model by conducting a 1000 bootstrap resample, while the C-index was calculated to validate the discrimination power for OS of multiple factors.

Age, LN status, CDS, chemotherapy, and radiation were subsequently included in the nomogram construction for FIGO stage I-IIA patients (Figure 5A). As indicated in the nomogram, CDS and LN status were prominent contributors

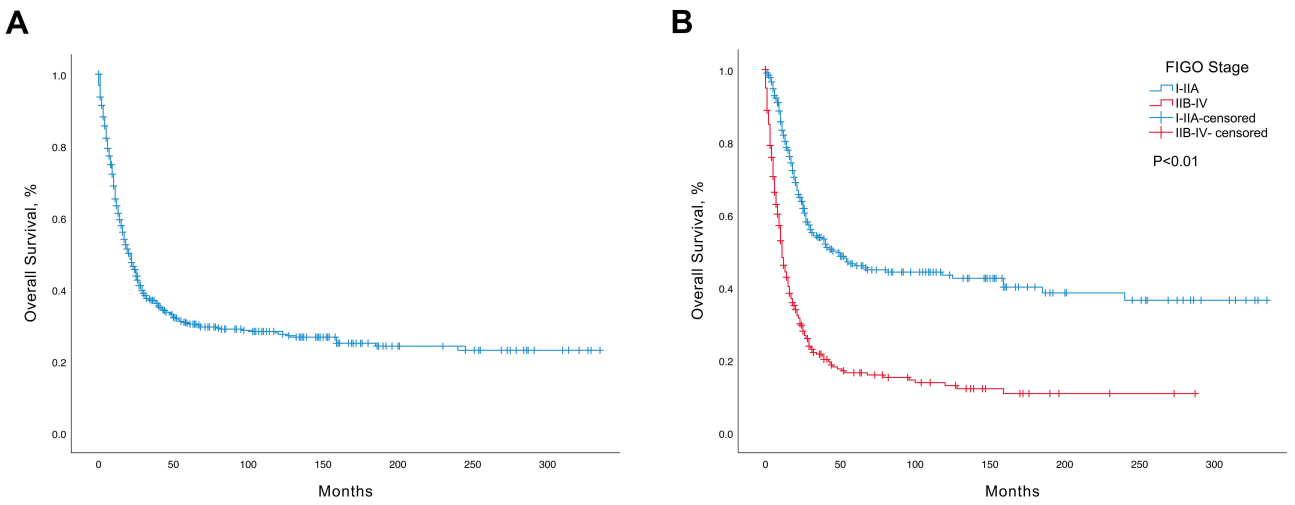


Figure 1 Kaplan–Meier curves for overall survival in (**A**) the overall cohort and (**B**) according to the FIGO stage.

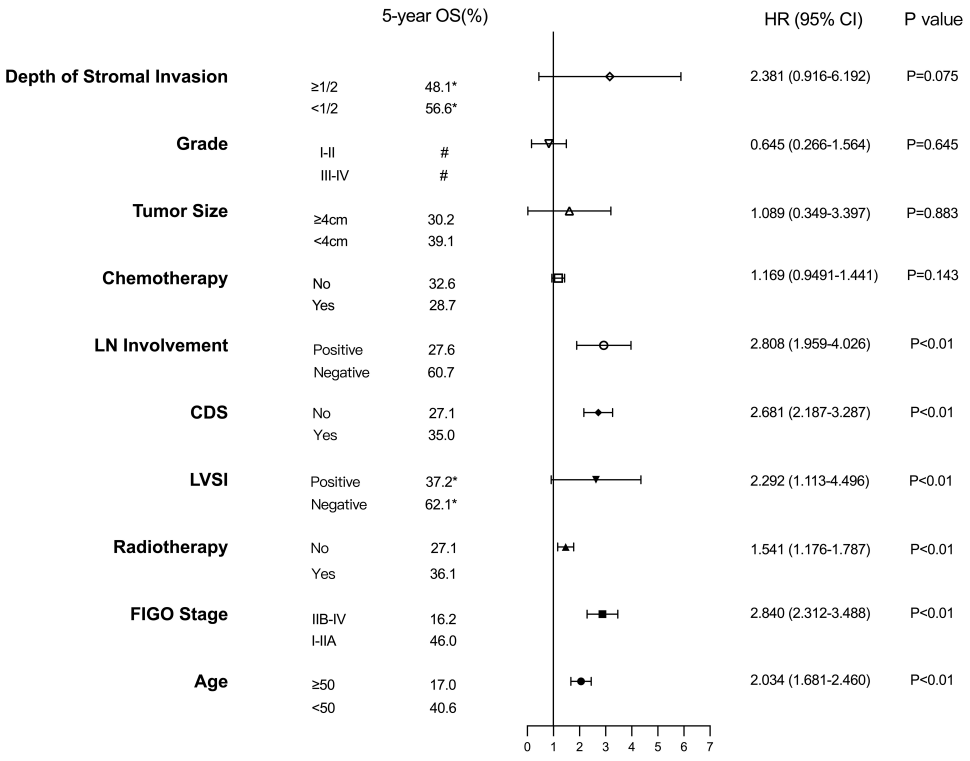


Figure 2 Univariate analysis of the overall survival (OS) in the overall cohort. *The 5-year OS could not be determined as most patients in one of the groups had died within 60 months.#The 5-year OS could not be calculated as the population of one group was too small.

to the prognosis of early-stage patients, whereas, chemotherapy was the least significant to prognosis. Age, tumor size, CDS, chemotherapy, and radiation were included in constructing the nomogram of FIGO stage IIB-IV patients (Figure 5B). As the model shows, chemotherapy and tumor size play important roles in the prognosis of advanced-stage patients, while surgery is not associated with prognosis; the C-index was 0.67 (95% CI 0.61–0.73) and 0.67 (95% CI 0.62–0.72), respectively, indicating that our nomogram was accurate to an extent in predicting OS. The calibration plots which verified the correlations of OS between the predicted and actual results are presented in Figure 6. This nomogram could be helpful for individualized prognosis assessment in patients with SCCC.

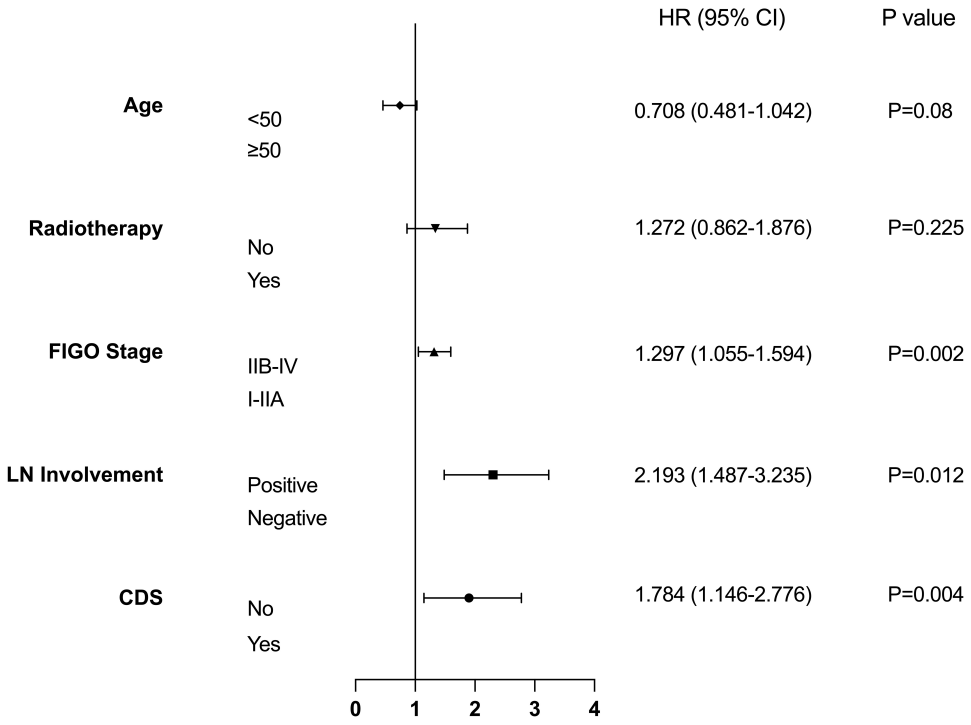


Figure 3 Multivariate analysis of the overall survival in the overall cohort.

Discussion

Most studies on SCCC have sample sizes of <100 patients due to the rarity of the disease. In this study, we evaluated the clinicopathologic characteristics, survival, and optimal local treatment modalities for SCCC using a pooled cohort of 695 patients identified from the SEER database,[12,13] the Chinese Periodical Database, and our institution. SCCC is characterized by an aggressive disease course and poor prognosis, with a 5-year survival rate of only 29% compared to 68% in other cervical cancer subtypes.[1,21,22] In this study, the 1-, 3-, and 5-year OS were 63.3%, 36.9%, and 30.2% respectively. Consistent with the findings of previous studies,[8] we confirmed that the FIGO stage is an important prognostic indicator. Furthermore, survival analysis based on the FIGO stage showed that early-stage patients (FIGO I-IIA) have a better prognosis than did advanced-stage patients (FIGO IIB-IV), with a 5-year survival rate of 46.0% compared to only 15.9% respectively. We also found a significant correlation between LN status and the FIGO stage in SCCC. The positivity rate of LNs was 38.2% in FIGO stage I-IIA patients and 76.0% in FIGO stage IIB-IV patients. LN metastasis was also an independent prognostic factor, consistent with the findings of Huang et al[23] and Tian et al,[24] but in contrast to the report by Cohen et al.[21] In our multivariate analysis according to the FIGO stage, LN status was an independent prognostic factor in patients with early-stage disease, but not in patients with advanced-stage disease. We speculated that this might be because most patients with advanced-stage disease already had LN metastasis. Several studies suggest that SCCC is characterized by a high incidence of early nodal and distant metastases that result in poorer prognosis than other subtypes.[10,25-27] Our findings support this with a 38.2% LN metastasis rate for FIGO stage I-IIA SCCC patients compared with 13% for other subtypes patients. We suspect that this is due to the more aggressive biological behavior of SCCC.[28]

The impact of LVSI and stromal invasion on the prognosis of SCCC has been conflicting. Tian et al[24] and Intaraphet et al[29,30] suggested that the depth of stromal invasion was a prognostic factor of SCCC. However, Huang et al[31] reported that the depth of stromal invasion and LVSI were not significantly correlated with the prognosis of SCCC. In our study, the multivariate analysis confirmed that LVSI, but not the depth of stromal invasion, was associated with SCCC prognosis. More research is needed to evaluate the prognostic value of LVSI and depth of stromal invasion in patients with SCCC.

Our study findings emphasized the effect of primary surgery on the prognosis of early-stage patients. In the

Table 2 Cox regression model according to the FIGO stage

Univariate Cox regression model						
Variance	**FIGO I-IIA**			**FIGO IIB-IV**		
	5-year OS (%)	**P value**	**HR (95% CI)**	**Year OS (%)**	**P value**	**HR (95% CI)**
Age		0.000	2.254		0.000	1.656
≧50	27.7		(1.633-3.110)	10.8		(1.282-2.139)
<50	55.1			22.0		
Tumor Size		0.649	0.914		0.021	1.960
≧4	50.7		(0.622-1.344)	18.2		(1.105-3.478)
<4	42.3			36.9		
Radiation		0.019	0.683		0.012	1.550
No	51.1		(0.497-0.938)	12.9		(1.101-2.182)
Yes	40.1			30.3		
Chemotherapy		0.052	0.668		0.000	2.683
No	56.7		(0.436-1.023)	12.5		(1.957-3.678)
Yes	41.1			18.1		
LN Involvement		0.001	2.368	β	0.156	2.330
Positive	30.2		(1.531-3.661)			(0.986-5.506)
Negative	60.3					
CDS		0.000	2.267		0.000	1.982
No	28.6		(1.594-2.999)	11.8		(1.431-2.746)
Yes	54.8			29.3		

Multivariate Cox regression model			
Variance	**Subset**	**P value**	**HR (95% CI)**
FIGO I-IIA			
CDS	No VS Yes	0.004	3.678(1.535-8.810)
Age	≧50 VS <50	0.240	1.361(0.814-2.274)
Radiation	No VS Yes	0.115	0.566(0.379-1.149)
LN Involvement	Positive VS Negative	0.003	2.021(1.263-3.232)
FIGO IIB-IV			
Age	≧50 VS <50	0.041	1.435(1.014-2.030)
Tumor Size	≧4 VS <4	0.024	2.081(1.101-3.935)
Radiation	No VS Yes	0.038	1.632(1.027-2.959)
Chemotherapy	No VS Yes	0.000	2.268(1.487-3.454)
CDS	No VS Yes	0.368	1.234(0.781-1.948)

Notes: β, the 5-y OS can't be calculated because the population in one group was too small.
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; CDS, cancer-directed surgery.

early-stage patients, the 5-year survival rate of those who underwent CDS was significantly higher than that of patients who did not undergo CDS. Multivariate analysis also showed that CDS was an independent prognostic factor for early-stage patients. This is consistent with the findings of Zhou et al.[26] However, multivariate analysis showed that CDS was not correlated with prognosis in patients with advanced-stage disease. These results support the Gynecologic Cancer InterGroup recommendation of surgical treatment of SCCC patients with stages I-IIA disease and chemoradiotherapy for patients with stages IIB-IV disease.[25]

The role of chemotherapy is particularly emphasized in the treatment of SCCC. Some researchers believe that

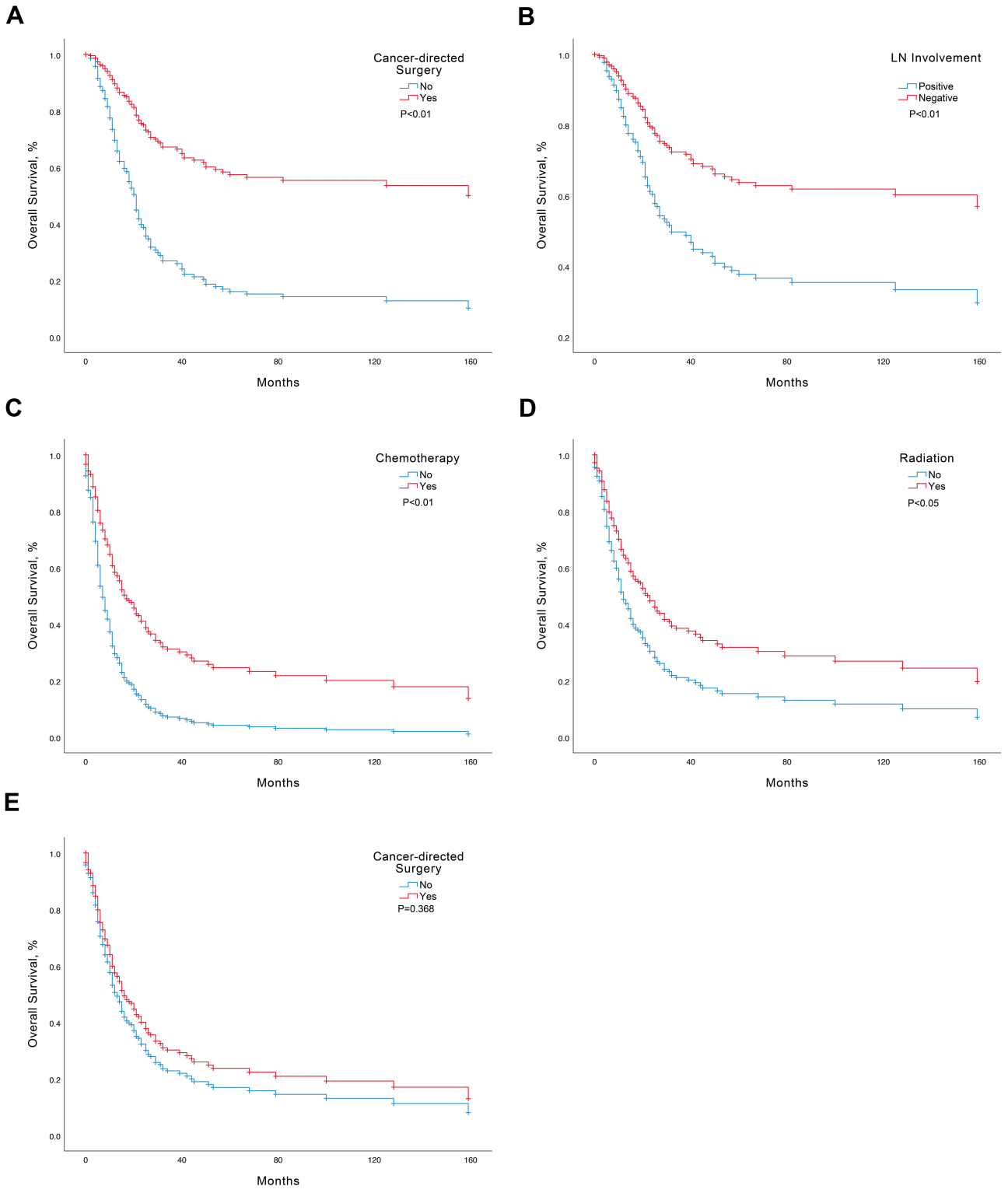


Figure 4 Cox overall survival curve of patients with small-cell carcinoma of the cervix (SCCC) (**A**) FIGO stage I–IIA, according to CDS treatment status; (**B**) FIGO stage I-IIA, according to lymph node status; (**C**) FIGO stage IIB-IV SCCC, according to chemotherapy treatment status; (**D**) FIGO stage IIB-IV according to radiation treatment status, and (**C**) FIGO stage IIB-IV, according to CDS treatment status.

SCCC has similar invasiveness to small cell lung cancer;[32,33] thus, the treatment of SCCC is similar to that of small cell lung cancer, which is mainly treated by chemotherapy,[34–38] postoperative adjuvant chemotherapy is recommended even in early-stage disease. In our study, chemotherapy had a prognostic benefit only in

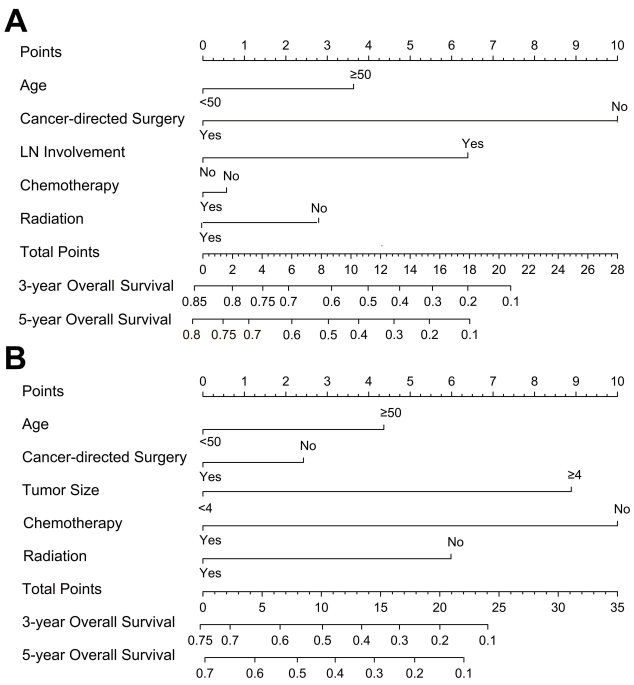


Figure 5 Nomogram evaluation of patients with small-cell carcinoma of the cervix (**A**) FIGO stage I-IIA and (**B**) FIGO stage IIB-IV.

advanced-stage patients, but not in early-stage patients. This finding is consistent with the report by Cohen et al.[21] Furthermore, Tian et al[24] reported that postoperative adjuvant chemotherapy does not seem to improve the 5-year survival rate of early-stage SCCC patients. In contrast, Zhang et al[39] reported that even early-stage disease patients who received adjuvant chemotherapy achieved better outcomes. No standardized guideline for the selection of chemotherapy regimens in SCCC has been developed. Because the SEER database[12,13] does not include data on the specific chemotherapy regimen and treatment course, these were not evaluated in the current study. Huang et al[31] found that platinum-based chemotherapy (etoposide or paclitaxel combined with cisplatin) could improve the survival rate; whereas, Yuan et al[40] reported that patients who received Taxotere and cyclophosphamide chemotherapy (paclitaxel combined with carboplatin) could achieve a better prognosis. Meanwhile, Frumovitz et al[9] suggested that topotecan, paclitaxel, and bevacizumab could improve the progression-free survival of

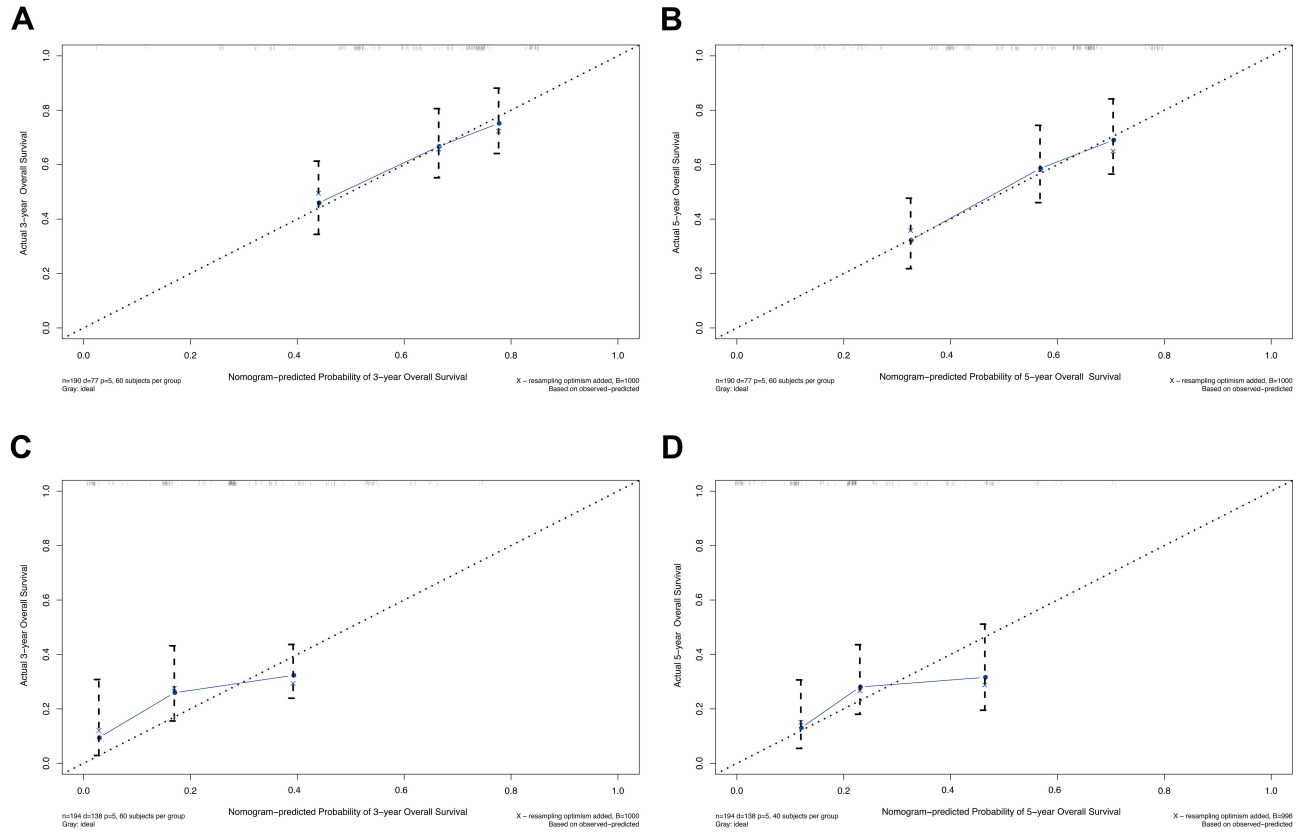


Figure 6 Calibration plots for 3- and 5-year OS of patients with small-cell carcinoma of the cervix (**A, B**) FIGO stage I-IIA and (**C, D**) FIGO stage IIB-IV.

patients with recurrence. Given the controversy over the effects of chemotherapy in early-stage patients and the uncertainty of the choice of specific chemotherapy regimens, more prospective research is needed to provide a reference for the treatment of SCCC in the future. As for radiotherapy, Lin et al[41] reported that radiotherapy might play an essential role in the treatment of advanced diseases, and our findings support this.

The nomogram we developed could evaluate individualized prognosis. As calculated in the nomogram for FIGO I-IIA patients, those without surgery had the highest number of points, followed by those with positive LNs, and then, patients aged ≥50 years. Scores on radiation and chemotherapy were low, indicating no evident influence on the prognosis of patients. For FIGO IIB-IV patients, the nomogram shows that patients who did not undergo chemotherapy could have a worse prognosis, followed by patients with tumor size ≥4 cm, and then, those who did not receive radiotherapy. In contrast, CDS had the lowest points. The C-index calculation and calibration were performed to verify the consistency of nomogram-predicted OS with actual OS. We can derive a simple algorithm from this model to individually evaluate the prognosis of patients. Further research in larger prospective cohorts is needed to verify the applicability of the model to increase its generalizability.

Our research has some limitations. First, the majority of the patients were identified from small case series, making it difficult to validate the quality of information; this is an inherent limitation in any retrospective study. Second, due to pathological factors (eg marginal state, parametrial invasion status, LVSI, and stromal invasion) and lack of central pathology review and recurrence status in the SEER database,[12,13] we were unable to ascertain patients' conditions accurately. The SEER database also lacks information on chemotherapy regimens and doses,[12,13] which might affect the evaluation of the clinical value of local treatments. Furthermore, our study is limited by the potential heterogeneity of our patient population between local hospital data and literature data because the diagnostic criteria and the quality of information from the Periodical Database sources are still unknown. However, the main advantage of this study is that population-based studies can be used to describe the epidemiologic and clinicopathologic characteristics, treatment trends, and survival outcomes of this rare disease. Further, our nomogram generated using multivariate analysis effectively evaluated the individualized prognosis of patients.

Conclusion

In conclusion, our study demonstrated that SCCC is characterized by a high degree of invasiveness, even in the early stage of the disease. However, patients with FIGO stage I-IIA disease have better 5-year survival than those with FIGO stage IIB-IV disease (46.0% vs 15.9%). Optimal treatment modalities are radical surgery for early-stage SCCC and chemoradiotherapy for advanced-stage SCCC. Our data provided indices for assessing individual prognosis and choosing personalized treatment modalities.

Abbreviations

CDS, cancer-directed surgery; CI, confidence interval; HR, hazard ratio; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion; OS, overall survival; SCCC, small-cell carcinoma of the cervix; SEER, Surveillance, Epidemiology, and End Results.

Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics and Consent Statement

The data accessed from the SEER database and Chinese Periodical Database are freely available. As the SEER database and Chinese Periodical Database are public-use data, informed consent was not required. Therefore, in this retrospective study, the requirement for informed consent was waived by the Institutional Review Board of the Shanghai East Hospital, given the anonymous and retrospective nature of the data and study, respectively. We ascertain that the privacy of patients enrolled in this study was protected and that the study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for Publication

Patient consent for publication is not applicable in this case as it is a retrospective study using anonymized data.

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Author Contributions

Jingxin Cheng contributed to the conceptualization and methodology of the research, Ru Huang designed and implemented the research and was a major contributor in writing the manuscript, and Qiyu Gan analyzed and interpreted the patient data. All authors read and approved the final manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tempfer CB, Tischoff I, Dogan A, et al. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. *BMC Cancer*. 2018;18(1):530. doi:10.1186/s12885-018-4447-x
2. Patibandla JR, Fehniger JE, Levine DA, Jelinic P. Small cell cancers of the female genital tract: molecular and clinical aspects. *Gynecol Oncol*. 2018;149(2):420–427. doi:10.1016/j.ygyno.2018.02.004
3. Al-Mendalawi MD. Re: small-cell neuroendocrine carcinoma of the cervix masquerading as a cervical fibroid: report of a rare entity. *Sultan Qaboos Univ Med J*. 2018;18(2):e252. doi:10.18295/squmj.2018.18.02.027
4. Zhang D, Ma X. Prognostic factors and outcomes of early-stage small cell neuroendocrine carcinoma of the cervix: 37 cases from a single center. *Peer J*. 2019;7:e6868. doi:10.7717/peerj.6868
5. Nguyen VX, Nguyen BD, Lam-Himlin DM. Positron emission tomography/computed tomography imaging of adrenocorticotropic hormone-producing small-cell neuroendocrine carcinoma of the cervix. *Int J Gynaecol Obstet*. 2017;137(2):197–198. doi:10.1002/ijgo.12104
6. Fukuda H, Tanaka A, Hirashima Y, Ito I. Lambert-eaton myasthenic syndrome associated with synchronous double cancer: a combination of small cell carcinoma of the cervix and breast carcinoma. *Internal Med*. 2018;57(16):2409–2411. doi:10.2169/internalmedicine.0428-17
7. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. *Ann Diagn Pathol*. 2017;29:11–16. doi:10.1016/j.anndiagpath.2017.04.005
8. Zhou J, Wu SG, Sun JY, et al. Clinicopathological features of small cell carcinoma of the uterine cervix in the surveillance, epidemiology, and end results database. *Oncotarget*. 2017;8(25):40425–40433. doi:10.18632/oncotarget.16390
9. Frumovitz M, Munsell MF, Burzawa JK, et al. Combination therapy with topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. *Gynecol Oncol*. 2017;144(1):46–50. doi:10.1016/j.ygyno.2016.10.040
10. Frumovitz M. Small- and large-cell neuroendocrine cervical cancer. *Oncology (Williston Park, NY)*. 2016;30(1):70,77–78, 93.
11. Xu F, Ma J, Yi H, et al. Clinicopathological aspects of small cell neuroendocrine carcinoma of the uterine cervix: a multicenter retrospective study and meta-analysis. *Cell Physiol Biochem*. 2018;50(3):1113–1122. doi:10.1159/000494538
12. Chen L, Weng YM, Hu MX, Peng M, Song QB. Effects of HER2 status on the prognosis of male breast cancer: a population-based study. *Onco Targets Ther*. 2019;12:7251–7260. doi:10.2147/OTT.S209949
13. Chen C, Huang S, Huang A, et al. Risk factors for lymph node metastasis and the impact of adjuvant chemotherapy on ductal carcinoma in situ with microinvasion: a population-based study. *Onco Targets Ther*. 2018;11:9071–9080. doi:10.2147/OTT.S186228
14. Matsuo K, Machida H, Mandelbaum RS, Konishi I, Mikami M. Validation of the 2018 FIGO cervical cancer staging system. *Gynecol Oncol*. 2019;152(1):87–93. doi:10.1016/j.ygyno.2018.10.026
15. Gao Z, Lu T, Song H, et al. Prognostic factors and treatment options for patients with high-grade chondrosarcoma. *Med Sci Monitor*. 2019;25:8952–8967. doi:10.12659/MSM.917959
16. Gargano SM, Sebastiano C, Solomides CC, Griffith CC, HooKim K. Cytohistologic correlation of basaloid salivary gland neoplasms: can cytomorphologic classification be used to diagnose and grade these tumors? *Cancer Cytopathol*. 2019.
17. Li Z, Cen H. Construction of a nomogram for the prediction of prognosis in patients with resectable gastric cancer undergoing fewer than sixteen lymph node biopsies. *Onco Targets Ther*. 2019;12:7415–7428. doi:10.2147/OTT.S216086
18. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. 2015;16(4):e173–180. doi:10.1016/S1470-2045(14)71116-7
19. Groot Koerkamp B, Wiggers JK, Gonen M, et al. Survival after resection of perihilar cholangiocarcinoma-development and external validation of a prognostic nomogram. *Ann Oncol*. 2016;27(4):753. doi:10.1093/annonc/mdw063
20. Wang L, Wan G, Shen Y, et al. A nomogram to predict mortality in patients with severe fever with thrombocytopenia syndrome at the early stage-a multicenter study in China. *PLoS Negl Trop Dis*. 2019;13(11):e0007829. doi:10.1371/journal.pntd.0007829
21. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol*. 2010;203(4):347.e341–346. doi:10.1016/j.ajog.2010.04.019
22. Delgado D, Figueiredo A, Mendonca V, Jorge M, Abdulrehman M, de Pina MF. Results from chemoradiotherapy for squamous cell cervical cancer with or without intracavitary brachytherapy. *J Contemp Brachytherapy*. 2019;11(5):417–422. doi:10.5114/jcb.2019.88116
23. Huang L, Lin JX, Yu YH, Zhang MY, Wang HY, Zheng M. Downregulation of six microRNAs is associated with advanced stage, lymph node metastasis and poor prognosis in small cell carcinoma of the cervix. *PLoS One*. 2012;7(3):e33762. doi:10.1371/journal.pone.0033762
24. Tian WJ, Zhang MQ, Shui RH. Prognostic factors and treatment comparison in early-stage small cell carcinoma of the uterine cervix. *Oncol Lett*. 2012;3(1):125–130. doi:10.3892/ol.2011.439
25. Satoh T, Takei Y, Treilleux I, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for small cell carcinoma of the cervix. *Int J Gynecol Cancer*. 2014;24(9 Suppl 3):S102–108. doi:10.1097/IGC.0000000000000262
26. Zhou J, Yang HY, Wu SG, et al. The local treatment modalities in FIGO stage I-II small-cell carcinoma of the cervix are determined by disease stage and lymph node status. *Cancer Med*. 2016;5(6):1108–1115. doi:10.1002/cam4.687
27. Lee EJ, Hwang J, Kim DW. Small-cell neuroendocrine carcinoma of the uterine cervix with pancreatic metastasis: a case report and a review of the literature. *J Obstetrics Gynaecol*. 2019;39(4):573–575. doi:10.1080/01443615.2018.1534813
28. Joo JH, Kim YS, Nam JH. Prognostic significance of lymph node ratio in node-positive cervical cancer patients. *Medicine*. 2018;97(30):e11711. doi:10.1097/MD.0000000000011711
29. Intaraphet S, Kasatpibal N, Sogaard M, et al. Histological type-specific prognostic factors of cervical small cell neuroendocrine carcinoma, adenocarcinoma, and squamous cell carcinoma. *Onco Targets Ther*. 2014;7:1205–1214. doi:10.2147/OTT.S64714
30. Intaraphet S, Kasatpibal N, Siriaunkgul S, Chandacham A, Sukpan K, Patumanond J. Prognostic factors for small cell neuroendocrine carcinoma of the uterine cervix: an institutional experience. *Int J Gynecol Cancer*. 2014;24(2):272–279. doi:10.1097/IGC.0000000000000059

31. Huang L, Liao LM, Liu AW, et al. Analysis of the impact of platinum-based combination chemotherapy in small cell cervical carcinoma: a multicenter retrospective study in Chinese patients. *BMC Cancer*. 2014;14:140. doi:10.1186/1471-2407-14-140
32. Berniker AV, Abdulrahman AA, Teytelboym OM, Galindo LM, Mackey JE. Extrapulmonary small cell carcinoma: imaging features with radiologic-pathologic correlation. *Radiographics*. 2015;35 (1):152–163. doi:10.1148/rg.351140050
33. Egawa-Takata T, Yoshino K, Hiramatsu K, et al. Small cell carcinomas of the uterine cervix and lung: proteomics reveals similar protein expression profiles. *Int J Gynecol Cancer*. 2018;28(9):1751–1757. doi:10.1097/IGC.0000000000001354
34. Dongol S, Tai Y, Shao Y, Jiang J, Kong B. A retrospective clinicopathological analysis of small-cell carcinoma of the uterine cervix. *Mol Clin Oncol*. 2014;2(1):71–75. doi:10.3892/mco.2013.193
35. Gadducci A, Carinelli S, Aletti G. Neuroendocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. *Gynecol Oncol*. 2017;144(3):637–646. doi:10.1016/j.ygyno.2016.12.003
36. Pei X, Xiang L, Ye S, et al. Cycles of cisplatin and etoposide affect treatment outcomes in patients with FIGO stage I-II small cell neuroendocrine carcinoma of the cervix. *Gynecol Oncol*. 2017;147 (3):589–596. doi:10.1016/j.ygyno.2017.09.022
37. Yin ZM, Yu AJ, Wu MJ, et al. Effects and toxicity of neoadjuvant chemotherapy preoperative followed by adjuvant chemoradiation in small cell neuroendocrine cervical carcinoma. *Eur J Gynaecol Oncol*. 2015;36(3):326–329.
38. Roy S, Ko JJ, Bahl G. Small cell carcinoma of cervix: a population-based study evaluating standardized provincial treatment protocols. *Gynecol Oncol Rep*. 2019;27:54–59. doi:10.1016/j.gore.2019.01.003
39. Zhang Q, Xiong Y, Ye J, Zhang L, Li L. Influence of clinicopathological characteristics and comprehensive treatment models on the prognosis of small cell carcinoma of the cervix: a systematic review and meta-analysis. *PLoS One*. 2018;13(4):e0192784. doi:10.1371/journal.pone.0192784
40. Yuan L, Jiang H, Lu Y, Guo SW, Liu X. Prognostic factors of surgically treated early-stage small cell neuroendocrine carcinoma of the cervix. *Int J Gynecol Cancer*. 2015;25(7):1315–1321. doi:10.1097/IGC.0000000000000496
41. Lin AJ, Hassanzadeh C, Markovina S, Schwarz J, Grigsby P. Brachytherapy and survival in small cell cancer of the cervix and uterus. *Brachytherapy*. 2019;18(2):163–170. doi:10.1016/j.brachy.2018.11.006

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