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Clinicopathologic features and outcome of cervical cancer: implications for treatment

B.-Q. LIANG[1,2,3], S.-G. ZHOU[4], J.-H. LIU[1], Y.-M. HUANG[1,5], X. ZHU[1,2,3,5]

[1]Guangdong Key Laboratory for Research and Development of Natural Drugs, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang, Guangdong, China
[2]Southern Marine Science and Engineering Guangdong Laboratory (Zhanjiang), Zhanjiang, China
[3]The Marine Biomedical Research Institute of Guangdong Zhanjiang, Zhanjiang, Guangdong, China
[4]Department of Gynecology, Maternity and Child Healthcare Hospital of Anhui Medical University, Hefei, China
[5]The Key Lab of Zhanjiang for R&D Marine Microbial Resources in the Beibu Gulf Rim, Guangdong Medical University, Zhanjiang, China

B.-Q. Liang and S.-G. Zhou contributed equally to this work

Abstract. – OBJECTIVE: We used a regression analysis of the SEER database to establish a new Nomogram for predicting prognosis of cervical cancer patients and guiding the treatment.

MATERIALS AND METHODS: We divided the data into the training cohort and the verification cohort. Univariate and multivariate Cox risk regression analysis was used to identify independent prognostic factors and establish a Nomogram model. The verification cohort was used for external verification, and the accuracy was evaluated with C-index and AUC. Finally, Nomogram was used to establish 1-year, 3-year and 5-year survival curves of cervical cancer patients.

RESULTS: In this study, 5691 patients with cervical squamous cell carcinoma were included. Data obtained from the training cohort were independent risk factors of cervical cancer AJCC stage (p = 0.039), RX Summ - Surgery Primary Site (p = 0.012), radiation (p = 0.031), chemotherapy (p = 0.013), tumor size (p = 0.009), race (p = 0.039). The 1-year, 3-year, and 5-year overall survival rates for cervical cancer patients were 77.2%, 47.8%, and 35.2%, respectively.

CONCLUSIONS: The Nomogram model can better screen out more reasonable comprehensive treatments for patients at different stages. And it is of great help to improve the survival rate and reduce the recurrence rate of cervical cancer patients.

Key Words:
Cervical squamous cell carcinoma, SEER database, Nomogram, Chemotherapy, Radiation therapy, Prognostic factors, Overall survival.

Introduction

Uterine Cervical Cancer (UCC) is one of the most common gynecologic malignant tumors in the United States. In 2019 alone, there were 61,880 new cases of cervical cancer and 12,160 deaths[1]. UCC has been on the rise in the United States since 1975 because of increased rates of human papillomavirus and the use of oral contraceptives[1-3]. Cervical cancer is the fourth leading cause of cancer death in women, with its morbidity and mortality second only to breast cancer[4]. After decades of research, there have been relatively effective treatments for each stage. Stage I-IIA cervical cancer is usually curable with surgery and can also be treated with adjuvant chemoradiotherapy. Chemoradiotherapy is also the main treatment of IB-IVA. The 5-year survival of stage IVB patients is poor, with about 50% of patients dying within 1 year[5,6]. So, patients with stage IVB, persistent or recurrent disease usually undergo systemic chemotherapy after completion of primary treatment[7-9]. Although there are clear clinical guidelines for the treatment of cervical cancer, the morbidity and mortality are still high. This suggests that the prediction of cervical cancer is more important.

Nomogram is a simple, multivariate visualization tool for tumor prediction and quantification of individual patient survival[10-12]. In contrast to the current AJCC staging system, Nomogram focuses on personalized outcomes.

Corresponding Authors: X. Zhu, MD; e-mail: xzhu@gdmu.edu.cn; Y.-M. Huang, MD; e-mail: huangym@gdmu.edu.cn

On the other hand, it has significant value for risk classification, personalized clinical management, and even clinical trial design. Therefore, the purpose of this study was to integrate multiple independent risk factors, establishing a prognostic Nomogram. Then, we aimed at predicting the survival rate for patients with cervical cancer at all stages, and analyze the appropriate stages for different treatment methods. These may be helpful for clinical treatment and prevention.

Patients and Methods

Data Sources

Data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database, a population-based registry established in 1973 by the National Cancer Institute (NCI). The database covers about 70% of newly diagnosed cancer cases in more than 1,500 U.S. hospitals and about 28% of the U.S. population. The database records the morbidity, treatment, pathology and prognosis of millions of patients, with a large sample size and high data accuracy.

Study Population

Data in this study were obtained from the SEER*Stat software of the National Cancer Institute of the United States. The clinicopathological and follow-up data of 95,218 cervical cancer patients from 1975 to 2016 were obtained. Inclusion criteria for this study included cervical squamous cell carcinoma as the first tumor; actively cooperate and finish on schedule; complete clinicopathological data are available. After excluding invalid data inconsistent with the purpose of this study, the pathology of 5,691 patients with cervical squamous cell carcinoma from 2010 to 2015 was included in this study. For the nomogram construction and verification, we randomly assigned 2,279 patients to the training cohort and 3,412 to the verification cohort (Figure 1).

Our data collected the basic characteristics of these patients including: age, tumor grade, AJCC stage, AJCC stage T, AJCC stage N, AJCC stage M, CS tumor size, CS extension, SEER cause-specific death classification, SEER other cause of death classification, survival months, total number of in situ/malignant tumors for patient, race, age at diagnosis, marital status at diagnosis.

At the same time, each case treatment data included RX Summ - Surgery Primary Site, Radiation sequence with surgery, Radiation and Chemotherapy.

Statistical Analysis

We used the createDataPartition function in the Caret package in version 3.5.3 of R software to conduct simple random sampling of the overall data and randomly divided the patients into a training cohort of 2,279 and a verification cohort of 3,412.

We analyzed the training cohort in univariate Cox proportional risk regression model and obtained statistically significant variables for analysis in multivariate Cox regression model. Based on the determined independent risk factors, the prediction model was established, and Nomograms were constructed. After that, the distinction and calibration of Nomograms were calculated by using C-index and calibration curve, respectively. The accuracy of Nomograms was evaluated by C-index and AUC. We also use ver-

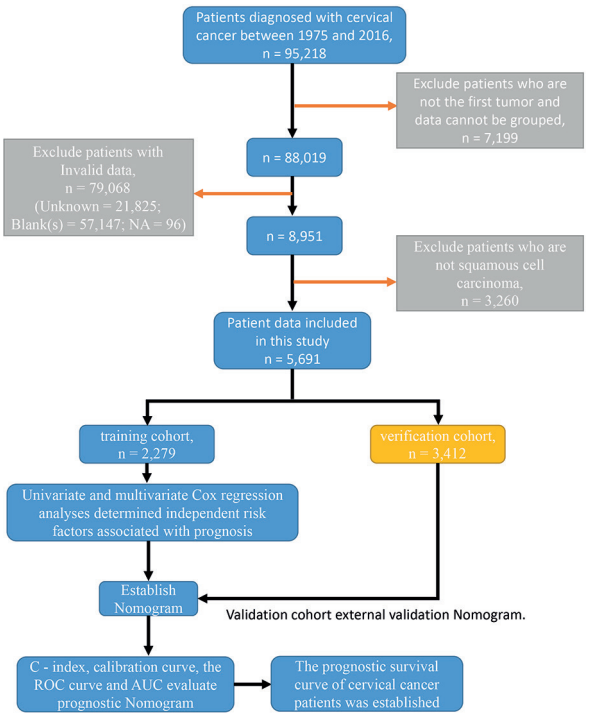

Figure 1. The research progress of this study. This is the operating procedure of this study. Extract the required data from the original data according to the research criteria. Independent risk factors were analyzed from the training cohort and nomograms were established. Finally, the survival curve of cervical cancer patients was established according to the model.

ification cohort for external verification. Finally, we used the Kaplan-Meier method to predict the overall data and calculate the overall survival rate for cervical cancer. The 1-year, 3-year and 5-year survival curves of cervical cancer and 1-year, 3-year and 5-year survival curves of each independent risk factor were plotted (Figure 1).

The calibration curve verifies the deviation between the predicted value and the actual value. The calibration curve in this study is basically consistent with the diagonal of 45°, which can be used as a prediction of survival and prognosis.

AUC can be used as the evaluation criterion of the ROC curve. The value range is generally between 0.5 and 1, where AUC less than or equal to 0.5 has no predictive power. $0.50 < AUC < 0.7$ has low accuracy prediction ability, $0.71 < AUC < 0.9$ has medium accuracy prediction ability, and $AUC > 0.9$ has high accuracy prediction ability[13].

Results

Population Characteristics and Clinicopathological Characteristics

The study included 5,691 cases of cervical squamous cell carcinoma from the SEER database from 2010 to 2015. During the recording period, 1,280 patients (22.4%) died of cervical cancer and 206 (3.6%) died of causes other than cervical cancer. Among the women, who were mostly white (74.2%), 3,314 (58.2%) had chemotherapy, 3,271 (57.5%) had surgery for various primary lesions, 3,761 (66.0%) had radiation, and 1,134 (19.9%) had three treatments. The population characteristics and clinical characteristics of patients included in this study are shown in Table I.

Determination of Independent Risk Factors Affecting Prognosis of Patients

We used Cox regression model to conduct univariate analysis on all variables in the training cohort, and the results were as follows: Age ($p < 0.001$), Grade ($p < 0.001$), AJCC stage ($p < 0.001$), AJCC stage T ($p < 0.001$), AJCC stage N ($p < 0.001$), AJCC stage M ($p < 0.001$), RX Summ--Surgery Primary Site ($p < 0.001$), Radiation sequence with surgery ($p < 0.001$), Radiation ($p < 0.001$), Chemotherapy ($p < 0.001$), Tumor size($p < 0.001$), Extension ($p < 0.001$), SEER cause-specific death classification ($p < 0.001$), SEER other cause of death classification ($p < 0.001$), Race ($p = 0.019$), Age at diagnosis ($p < 0.001$), Marital status at diagnosis ($p = 0.026$) were statistically significant and correlated with overall survival rate, so they were screened to conduct multivariate Cox regression analysis. Multivariate Cox regression analysis showed that the risk AJCC stage ($p = 0.039$), RX Summ--Surgery Primary Site ($p = 0.012$), Radiation ($p = 0.031$), Chemotherapy ($p = 0.013$), tumor size ($p = 0.009$), Race ($p = 0.039$) are independent risk factor for overall survival (Table II).

Nomogram Production and Inspection

We identified independent risk factors in the training cohort (AJCC stage, RX Summ--Surgery Primary Site, Radiation, Chemotherapy, size, Race). In Nomogram, each variable got the corresponding score of each item according to the small points in the first row corresponding to the tumor situation. And then we added the score to the overall points, corresponding to the downward, and the overall survival rate of 1, 3 and 5 years could be obtained (Figure 2).

The c-index was 0.942 (95%CI, 0.936-0.948) in the training cohort and 0.940 (95%CI, 0.934-0.946) in the verification cohort. In the 1-year, 3-year and 5-year calibration diagrams of the training cohort and the verification cohort, the fitting blue line basically matches the diagonal. It indicates a good consistency between the predicted values of the model and the actual observed values. The 1-year, 3-year and 5-year AUC in the training cohort was 0.842, 0.829 and 0.812, respectively, and in the verification cohort was 0.850, 0.812 and 0.802, respectively. The AUC of both the training cohort and the verification cohort was $0.71 < AUC < 0.9$, indicating that Nomograms had good predictive power (Figure 3 and Figure 4).

Prognosis and Survival Analysis of Cervical Cancer Patients

Prognosis Nomogram has good recognition. Based on the variables obtained in the training cohort, we found that the 1-year, 3-year, and 5-year high-risk survival rates were 77.2%, 47.8%, and 35.2%, respectively (Figure 5). In the AJCC stage, prognostic analysis showed that the higher the stage, the lower survival rates of 1-year, 3-year, and 5-year. In the primary surgery group, the group without primary surgery or with only pelvic exenteration had significantly lower survival rates in each year than the other groups. Patients who received chemotherapy and radiation had a higher short-term survival rate than

Table I. Population characteristics and clinicopathological characteristics of cervical cancer patients in the study.

Variable	After cleaning (total cohort) (n = 5,691)	Training cohort (n = 2,279)	Verification cohort (n = 3,412)
Age			
20-34	912 (16.0%)	354 (15.5%)	558 (16.3%)
35-44	1413 (24.8%)	570 (25.0%)	843 (24.7%)
45-54	1430 (25.1%)	596 (26.1%)	834 (24.4%)
55-64	1047 (18.3%)	419 (18.3%)	628 (18.4%)
65-74	566 (9.9%)	216 (9.4%)	350 (10.2%)
>=75	323 (5.6%)	124 (5.4%)	199 (5.8%)
Grade			
Grade I	476 (8.3%)	179 (7.8%)	297 (8.7%)
Grade II	2708 (47.5%)	1090 (47.8%)	1618 (47.4%)
Grade III	2429 (42.6%)	969 (42.5%)	1460 (42.7%)
Grade IV	78 (1.3%)	41 (1.7%)	37 (1.0%)
AJCC stage			
Stage I	2512 (44.1%)	1027 (45.0%)	1485 (43.5%)
Stage II	849 (14.9%)	332 (14.5%)	517 (15.1%)
Stage III	1636 (28.7%)	660 (28.9%)	976 (28.6%)
Stage IV	694 (12.1%)	260 (11.4%)	434 (12.7%)
AJCC stage T			
T1	3071 (53.9%)	1251 (54.8%)	1820 (53.3%)
T2	1468 (25.7%)	589 (25.8%)	879 (25.7%)
T3	951 (16.7%)	376 (16.4%)	575 (16.8%)
T4	201 (3.5%)	63 (2.7%)	138 (4.0%)
AJCC stage N			
N0	3979 (69.9%)	1596 (70.0%)	2383 (69.8%)
N1	1712 (30.0%)	683 (29.9%)	1029 (30.1%)
AJCC stage M			
M0	5127 (90.0%)	2054 (90.1%)	3073 (90.0%)
M1	564 (9.9%)	225 (9.8%)	339 (9.9%)
RX Summ--Surgery Primary Site			
0	2420 (42.5%)	941 (41.2%)	1479 (43.3%)
10-19	25 (0.4%)	10 (0.4%)	15 (0.4%)
20-29	560 (9.8%)	213 (9.3%)	347 (10.1%)
30-39	281 (4.9%)	109 (4.7%)	172 (5.0%)
40-49	839 (14.7%)	343 (15.0%)	496 (14.5%)
50-59	1328 (23.3%)	575 (25.2%)	753 (22.0%)
60-62	222 (3.9%)	81 (3.5%)	141 (4.1%)
70-73	16 (0.2%)	7 (0.3%)	9 (0.2%)
Radiation sequence with surgery			
No radiation and/or cancer-directed surgery	3985 (70.0%)	1554 (68.1%)	2431 (71.2%)
Radiation and/or cancer-directed surgery	1706 (29.9%)	725 (31.8%)	981 (28.7%)
Radiation			
Radiation	3761 (66.0%)	1515 (66.4%)	2246 (65.8%)
No Radiation	1930 (33.9%)	764 (33.5%)	1166 (34.1%)
Chemotherapy			
Yes	3314 (58.2%)	1333 (58.4%)	1981 (58.0%)
No/Unknown	2377 (41.7%)	946 (41.5%)	1431 (41.9%)
Size			
<= 20 mm	1642 (28.8%)	668 (29.3%)	974 (28.5%)
>20, <=40	1323 (23.2%)	536 (23.5%)	787 (23.0%)
>40, <=60	1427 (25.0%)	578 (25.3%)	849 (24.8%)
>60, <=100	1194 (20.9%)	459 (20.1%)	735 (21.5%)
>100	105 (1.8%)	38 (1.6%)	67 (1.9%)
Extension			
<=200	1570 (27.5%)	644 (28.2%)	926 (27.1%)
>200, <=400	1762 (30.9%)	714 (31.3%)	1048 (30.7%)
>400, <=600	1211 (21.2%)	482 (21.1%)	729 (21.3%)
>600, <=999	1148 (20.1%)	439 (19.2%)	709 (20.7%)

Continued

Table I *(Continued)*. Population characteristics and clinicopathological characteristics of cervical cancer patients in the study.

Variable	After cleaning (total cohort) (n = 5,691)	Training cohort (n = 2,279)	Verification cohort (n = 3,412)
SEER cause-specific death classification			
Alive or dead of other cause	4411 (77.5%)	1774 (77.8%)	2637 (77.2%)
Dead (attributable to this cancer dx)	1280 (22.4%)	505 (22.1%)	775 (22.7%)
SEER other cause of death classification			
Alive or dead due to cancer	5485 (96.3%)	2195 (96.3%)	3290 (96.4%)
Dead (attributable to causes other than this cancer dx)	206 (3.6%)	84 (3.6%)	122 (3.5%)
Sequence number			
One primary only	5369 (94.3%)	2143 (94.0%)	3226 (94.5%)
1st of 2 or more primaries	322 (5.6%)	136 (5.9%)	186 (5.4%)
Total number of in situ/malignant tumors for patient			
1	5412 (95.0%)	2161 (94.8%)	3251 (95.2%)
2	261 (4.5%)	111 (4.8%)	150 (4.3%)
3	16 (0.2%)	5 (0.2%)	11 (0.3%)
4	2 (< 0.1%)	2 (< 0.1%)	0
Race			
Black	831 (14.6%)	305 (13.3%)	526 (15.4%)
White	4227 (74.2%)	1701 (74.6%)	2526 (74.0%)
Asian or Pacific Islander	569 (9.9%)	242 (10.6%)	327 (9.5%)
American Indian/Alaska Native	64 (1.1%)	31 (1.3%)	33 (0.9%)
Age at diagnosis			
20-34	912 (16.0%)	354 (15.5%)	558 (16.3%)
35-44	1413 (24.8%)	570 (25.0%)	843 (24.7%)
45-54	1430 (25.1%)	596 (26.1%)	834 (24.4%)
55-64	1047 (18.3%)	419 (18.3%)	628 (18.4%)
65-74	566 (9.9%)	216 (9.4%)	350 (10.2%)
> =75	323 (5.6%)	124 (5.4%)	199 (5.8%)
Marital status at diagnosis			
Single	1904 (33.4%)	741 (32.5%)	1163 (34.0%)
Married or partner	2422 (42.5%)	983 (43.1%)	1439 (42.1%)
Separated divorced or widowed	1365 (23.9%)	555 (24.3%)	810 (23.7%)

those who received it, but the long-term effect was predicted to be the opposite. After one year of chemotherapy and radiation, survival rates began to decline sharply, 3-year survival rate dropped to 65.0% and 66.8%, respectively. In the tumor size group, the survival analysis results were similar to those of previous studies; the larger the tumor diameter, the lower the survival rate at 1, 3, and 5 years. In this prognostic analysis, 1-year survival rates were similar for all races. But the 5-year survival rates for blacks and American Indian/Alaska Native were significantly lower than those for whites and Asian or Pacific islanders (Figure 6 and Table III).

Discussion

Cervical squamous cell carcinoma is one of the most common subtypes of cervical cancer. In this study, the SEER database of patients with clinical data was analyzed, and it prompts AJCC stage, RX Summ - Surgery Primary Site, Radiation, and Chemotherapy, tumor size, Race are independent risk factors for cervical cancer prognosis. Nomogram was created based on these risk factors to predict 1-year, 3-year and 5-year survival rates for cervical cancer patients.

AJCC stage and tumor size have long been considered independent prognostic factors for cervical cancer survival. Patients also respond differently to surgery, radiation and chemotherapy, depending on AJCC stage and tumor size[14-18]. The choice of different treatment methods for different conditions will have a great impact on the prognosis of cervical cancer patients. Our study is similar to previous studies, that is, the higher the AJCC stage or the larger the tumor size, the worse the prognosis. In the prognostic Nomogram established in this study, both AJCC stage and tumor size have a significant impact on the prediction of survival in patients with cervi-

Table II. Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the Training cohort.

Variable	Univariate analysis					Multivariate analysis		
	HR	95% CI	p	C-Index	se	HR	95% CI	p
Age				0.576	0.012			
20-34	1	Reference				1	Reference	
35-44	1.048	0.776-1.414	0.762			0.851	0.619-1.171	0.323
45-54	1.453	1.094-1.930	0.010			0.834	0.613-1.133	0.245
55-64	1.468 1.736	1.087-1.983	0.012			0.763	0.552-1.054	0.101
65-74	3.615	1.242-2.426	0.001			0.716	0.490-1.045	0.083
>=75		2.573-5.080	< 0.001			0.953	0.635-1.430	0.816
Grade	1			0.567	0.011			
Grade I	2.794 3.877	Reference				1	Reference	
Grade II	3.032	1.686-4.630	< 0.001			0.872	0.510-1.492	0.618
Grade III		2.346-6.410	< 0.001			0.889	0.522-1.515	0.665
Grade IV	1	1.407-6.533	0.005			0.502	0.218-1.155	0.105
AJCC stage	3.084			0.755	0.010			
Stage I	4.460	Reference				1	Reference	
Stage II	16.544	2.299-4.135	< 0.001			1.677	1.027-2.738	0.039
Stage III		3.503-5.677	< 0.001			1.349	0.856-2.124	0.197
Stage IV	1	12.873-21.263	< 0.001			1.709	0.808-3.614	0.161
AJCC stage T	3.371 7.148			0.732	0.010			
T1	14.556	Reference				1	Reference	
T2		2.715-4.185	< 0.001			0.922	0.572-1.488	0.741
T3	1	5.766-8.861	< 0.001			1.119	0.696-	0.642
T4	2.563	10.435-20.305	< 0.001			1.357	1.800	0.334
AJCC stage N				0.615	0.011		0.731-2.520	
N0	1	Reference				1		
N1	6.765	2.180-3.015	< 0.001			1.147	Reference	0.276
AJCC stage M				0.629	0.010		0.896-1.469	
M0	1	Reference				1		
M1	0.172 0.336	5.629-8.130	< 0.001			1.389	Reference	0.289
RX Summ--Surgery Primary Site	0.069 0.205			0.712	0.009		0.757-2.548	
0	0.186 0.248	Reference				1		
10-19	2.283	0.024-1.224	0.079			3.452	Reference	0.243
20-29		0.242-0.466	< 0.001			1.054	0.432-27.612	0.805
30-39	1	0.029-0.167	< 0.001			1.351	0.692-1.607	0.534
40-49	0.653	0.148-0.284	< 0.001			0.753	0.524-3.486	0.201
50-59		0.143-0.241	< 0.001			0.689	0.487-1.164	0.050
60-62	1	0.140-0.440	< 0.001			1.101	0.474-1.000	0.771
70-73	0.369	1.019-5.113	0.045			0.313	0.576-2.103	0.012

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Table II *(Continued)*. Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the Training cohort.

Variable	Univariate analysis					Multivariate analysis		
	HR	95% CI	*p*	C-Index	se	HR	95% CI	*p*
Radiation sequence with surgery				0.555	0.009			
No radiation and/or cancer-directed surgery	1	Reference				1	Reference	
Radiation and/or cancer-directed surgery	0.363	0.542-0.786	< 0.001			0.907	0.676-1.216	0.513
Radiation				0.587	0.009			
Radiation	1	Reference				1	Reference	
No Radiation	5.245	0.298-0.458	< 0.001			1.427	1.032-1.972	0.031
Chemotherapy	10.449			0.604	0.010			
Yes	17.747	Reference				1	Reference	
No/Unknown	31.543	0.300-0.440	< 0.001			1.392	1.072-1.808	0.013
Size				0.742	0.009			
<= 20 mm	1	Reference				1	Reference	
>20, <=40	3.206 -5.944	3.442-7.994	< 0.001			1.285	0.764-2.162	0.345
>40, <=60	14.209	6.987-15.627	< 0.001			1.722	1.010-2.936	0.046
>60, <=100		11.910-26.444	< 0.001			2.053	1.197-3.523	0.009
>100	1	18.183-54.717	< 0.001			2.203	1.106-4.389	0.025
Extension	51.427			0.739	0.010			
<=200		Reference				1	Reference	
>200, <=400	1	2.263-4.541	< 0.001			1.094	0.730-1.639	0.663
>400, <=600	5.542	4.214-8.386	< 0.001			0.936	0.532-1.646	0.817
>600, <=999		10.206-19.783	< 0.001			NA	NA	NA
SEER cause-specific death classification	1			0.864	0.007			
Alive or dead of other cause	0.856	Reference				1	Reference	
Dead (attributable to this cancer dx)		40.430-65.410	< 0.001			2.816e+09	0.000-Inf	0.978
SEER other cause of death classification	1			0.547	0.006			
Alive or dead due to cancer	0.994	Reference				1	Reference	
Dead (attributable to causes other than this cancer dx)	0.527	4.396-6.987	< 0.001			2.198e+09	0.000-Inf	0.978
Sequence number	2.251e-06			0.513	0.004			
One primary only		Reference						
1st of 2 or more primaries	1	0.611-1.200	0.368					
Total number of in situ/malignant tumors for patient	0.769 0.790			0.509	0.004			
1	0.797	Reference						
2		0.703-1.406	0.974					
3	1	0.074-3.750	0.523					
4	1.048 1.453	0.000-Inf	0.988					

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Table II *(Continued).* Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the Training cohort.

Variable	Univariate analysis					Multivariate analysis		
	HR	95% CI	*p*	C-Index	se	HR	95% CI	*p*
Race	1.468 1.736			0.524	0.010			
Black	3.615	Reference				1	Reference	
White		0.618-0.958	0.019			0.781	0.618-0.987	0.039
Asian or Pacific Islander	1	0.573-1.091	0.153			0.983	0.692-1.397	0.925
American Indian/Alaska Native	0.805	0.388-1.637	0.536			0/483	0.227-1.026	0.058
Age at diagnosis	1.130			0.576	0.012			
20-34		Reference				1	Reference	
35-44		0.776-1.414	0.762			NA	NA	NA
45-54		1.094-1.930	0.010			NA	NA	NA
55-64		1.087-1.983	0.012			NA	NA	NA
65-74		1.242-2.426	0.001			NA	NA	NA
> = 75		2.573-5.080	< 0.001			NA	NA	NA
Marital status at diagnosis				0.550	0.012			
Single		Reference				1	Reference	
Married or partner		0.665-0.975	0.026			0.830	0.671-1.026	0.086
Separated divorced or widowed		0.920-1.389	0.245			1.170	0.915-1.496	0.212

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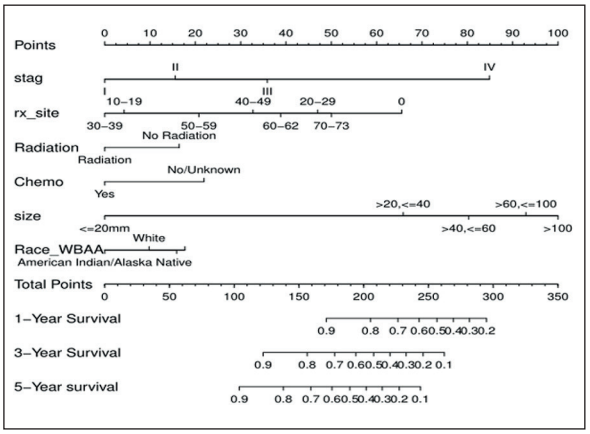

Figure 2. Nomogram, based on independent risk factor associations, predicts survival in patients with cervical cancer. In Nomogram, draw a vertical line between a variable and a small scale, and add up the scores for each variable. The vertical lines of the total score scale and the total survival scale were drawn based on the total score, and then the survival rate of each year was obtained. (Stage: AJCC stage; rx_site: RX Summ - Surgery Primary Site; Chemo: Chemotherapy; Race_WBAA: Race).

cal cancer. In this study we used Cox regression analysis to find that race was also a risk factor. Survival rates for blacks and native American Indian/Alaskan natives were lower in this study. We found that most of the cases included in the study were white, but some clinical studies have shown that blacks are a risk factor for all patients with distant metastases[19,20]. Because there is a large deviation in the proportion of human species included, it can affect the relationship between different races of cervical cancer. Therefore, the influence of race in predicting the prognosis of cervical cancer patients needs to be further studied.

Surgery is one of the most effective treatments for cervical cancer, and this study included only primary surgery. In this study, the 1-year, 3-year, and 5-year survival rates of patients who did not undergo primary surgery were lower than those of all patients who underwent surgery (except pelvic exenteration). Previous studies have shown a good prognosis with hysterectomy for stage IA2-IB1 lesions with a diameter of less than 2 cm[21]. For reproductive age patients with early cancer, the option is to use a cervical resection with the same survival rate as hysterectomy. This allows young women to receive reasonable treatment while preserving fertility[22]. However, it is not recommended to select patients with stage IB1, since the tumor diameter of this stage is greater than 2 cm and the risk is increased, so reasonable treatment and conservation functions cannot be guaranteed at the same time[23-25]. Therefore, women with stage IB with large tumors need to choose carefully. The surgical route also needs to

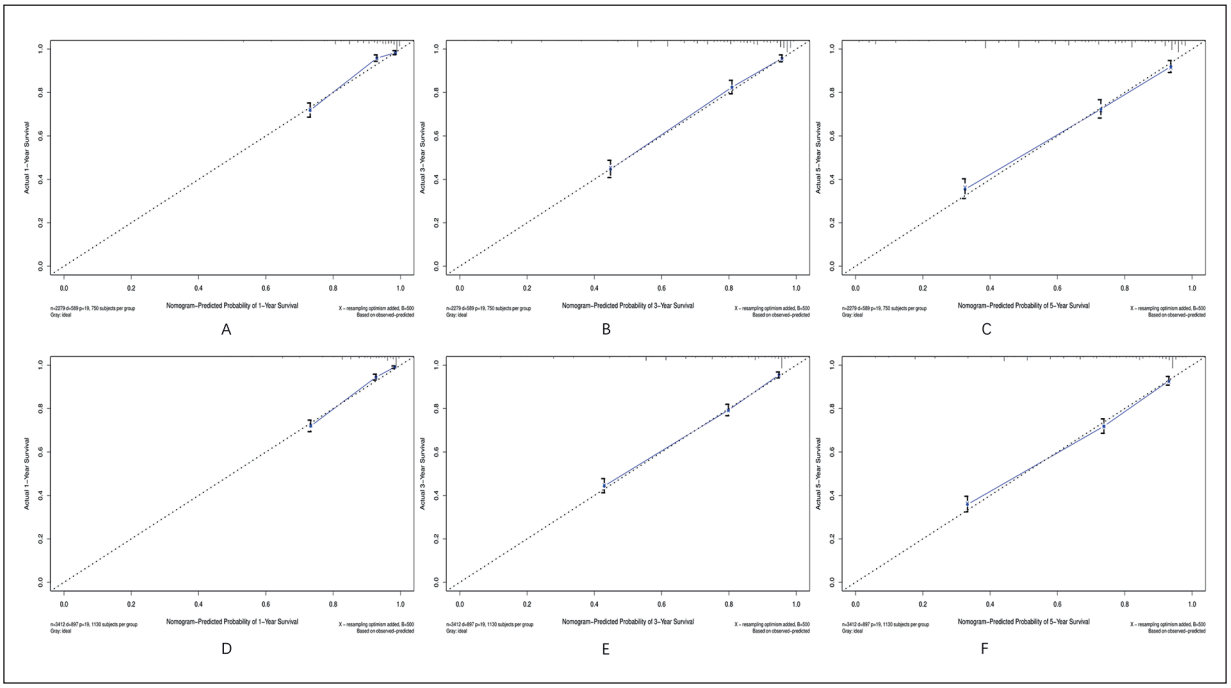

Figure 3. A-F, Calibration graph of 1-year **(A, D),** 3-year (B, E) and 5-year **(C, F)** of the training cohort and the verification cohort. **A-C,** Are the calibration graphs of the training cohort. **D-F,** are the calibration graphs of the verification cohort.

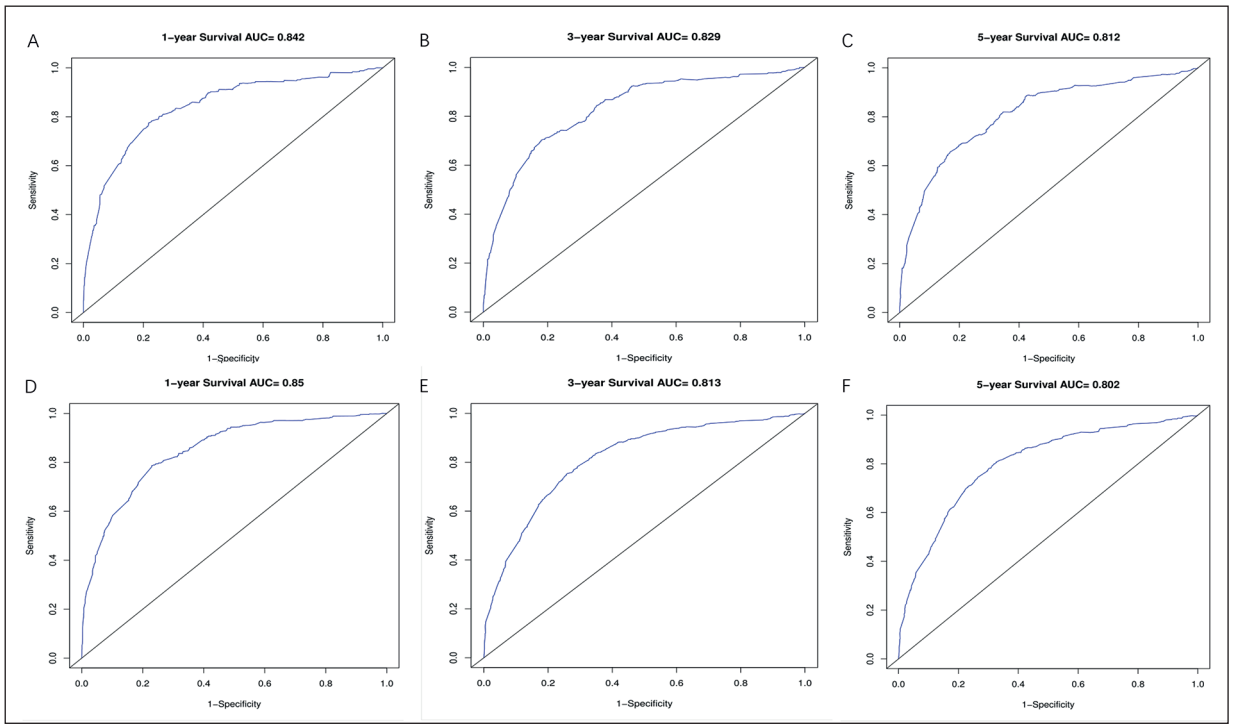

Figure 4. A-F, ROC curves of 1-year **(A, D),** 3-year **(B, E)** and 5-year **(C, F)** of the training cohort and the verification cohort. **(A-C)** ROC curve of 1-year, 3-year and 5-year prognosis in the training cohort. **(D-F)** ROC curve of 1-year, 3-year and 5-year prognosis in the training cohort. ROC: receiver operating characteristic curve; AUC: areas under the ROC curve.

be taken seriously. Currently, there are minimally invasive surgery and open surgery. Minimally invasive surgery for patients with early cervical cancer can not only achieve the survival rate of open surgery[26], but also the safety of short-term surgery, with fewer complications, less pain, faster recovery and significantly shorter hospital stay[27,28]. However, the data used in this study did not contain the information of the surgical route, so this study did not involve the surgical route. However, the optimal route for the hysterectomy of diseased women still needs further in-depth discussion. But we know that there is a very high survival rate in young women who has surgery at an early stage. So, this segment of the population can tend to score for this factor and increase accuracy.

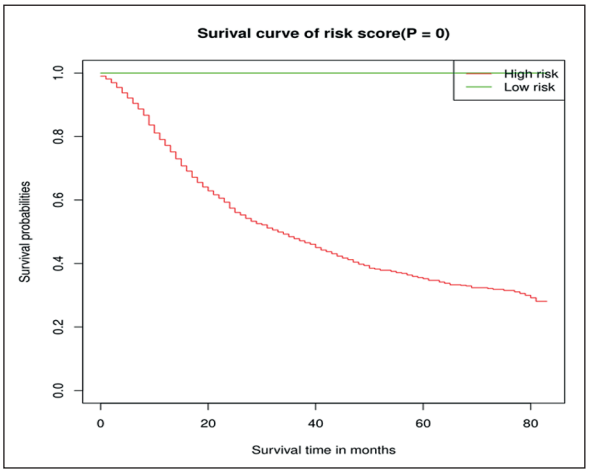

Figure 5. The survival curve of cervical cancer patients is obtained according to the risk score system. The result can be obtained from the survival curve of the risk score that the 1, 3 and 5-year overall survival rates are 77.2%, 47.8% and 35.2%, respectively.

Radiotherapy is one of the most common treatments for cervical cancer. It is usually used alone in tumors or in combination with surgery and/or chemotherapy[29,30]. In this study, Nomogram found an effect of radiation on the prognosis of patients with cervical cancer. However, in the survival curve, the short-term survival rate of patients receiving radiotherapy is significantly higher than that of non-recipients. Especially for early patients, radiotherapy has the same survival rate as surgery, and its incidence of severe disease is lower[30]. But long-term survival rates tend to be the opposite. This is probably because radiation is also a trigger for tumorigenesis, and

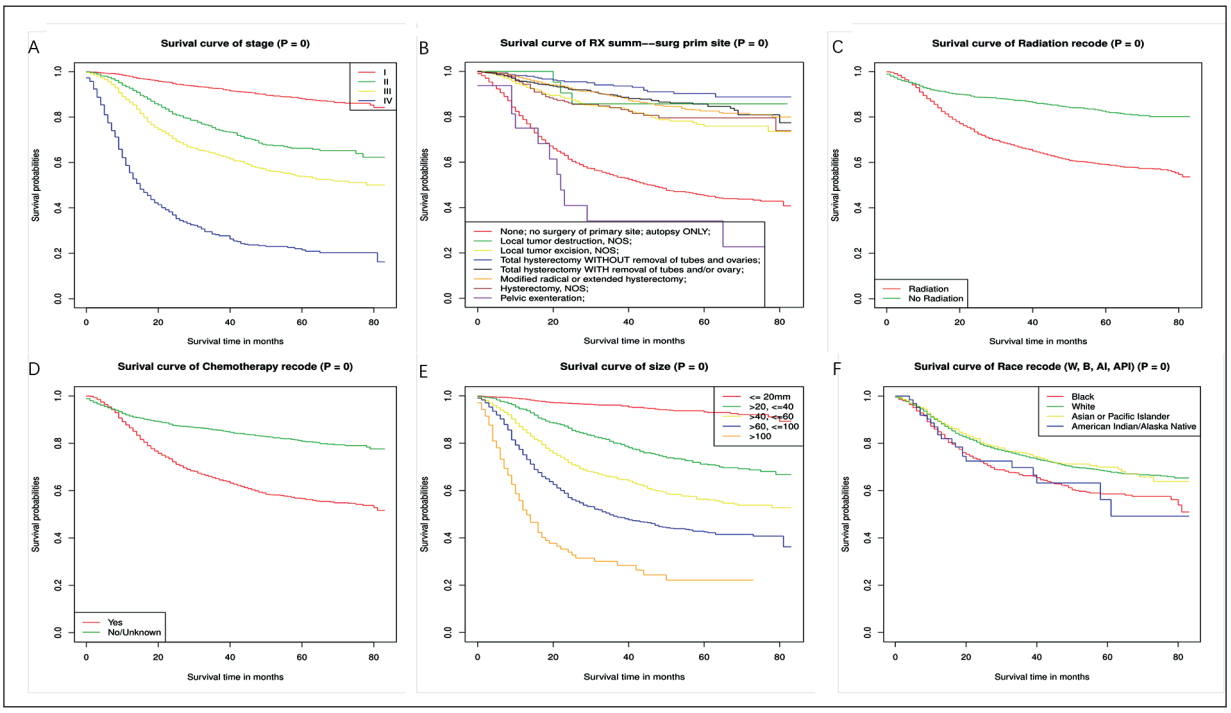

Figure 6. Survival curves in cervical cancer patients stratified by 6 independent risk factors. **(A)** Overall survival curve of AJCC stage. **(B)** Overall survival curve of RX Summ--Surgery Primary Site. **(C)** Overall survival curve of Radiation. **(D)** Overall survival curve of Chemotherapy. **(E)** Overall survival curve of size. **(F)** Overall survival curve of Race.

long-term effects increase the risk of secondary tumorigenesis. However, other studies have shown that radiotherapy is more beneficial for stage III/IV patients, by improving the immune response of patients through radiotherapy and thereby improving the effect of radiotherapy[14]. But it also depends on the patient's immune system, and the late-stage tumors are also large in diameter, which increases the dose of radiation from radiation therapy, which is more harmful to other normal cells. Patients with advanced stage have basically metastasized. In addition, some studies suggest that radiotherapy combined with surgery for advanced cervical cancer may be harmful to patients with cervical cancer[31]. So comprehensive means such as palliative treatment or systemic chemotherapy are preferred[7]. In this study, radiotherapy had a lower impact on survival among the six risk factors because our data included all stages. The survival time of early patients after radiotherapy increases, and they are more likely to show the risk of secondary tumor. However, the survival time of late patients themselves does not show the risk of secondary tumor, so this reduces the accuracy of prediction. This is probably a survivor bias. Therefore, radiotherapy should be combined with other methods to reduce the interference to the prognosis of patients.

Chemotherapy is also one of the three most commonly used treatments for cervical cancer. Nomogram in this study showed that the effect of chemotherapy on the prognosis of patients with cervical cancer was relatively low. Our study indicated that the prediction was slightly off. This might be because chemotherapy was mainly applied to the treatment of patients with advanced cervical cancer, while the data used in our study included all stages of cervical cancer. Research has shown the role of chemotherapy in metastatic cervical cancer in the prognostic value of OS[19]. Metastatic cervical cancer is the end of cervical cancer. At this stage, not suitable for surgical treatment, chemoradiotherapy is the best choice. Moreover, chemotherapy is still valuable for drug resistant recurrent metastatic cervical cancer[32]. To date, clinical studies have shown that multidrug chemotherapy is justified, and has rapid response and tolerable adverse event in patients with advanced cervical cancer[33]. Therefore, chemotherapy is a major influence on the prognosis of advanced patients.

Table III. Survival analysis of AJCC stage, RX Summ--Surgery Primary Site, Radiation, Chemotherapy, Size and Race, 1-year, 3-year, and 5-year survival rates.

Variable	Median survival time	1-year survival rate	3-year survival rate	5-year survival rate
Risk-level	32.8	0.772	0.478	0.352
AJCC stage				
I	NA	0.979	0.926	0.880
II	NA	0.927	0.746	0.658
III	NA	0.865	0.636	0.537
IV	14.3	0.555	0.282	0.215
RX Summ--Surgery Primary Site 0				
10-19	45.0	0.788	0.540	0.453
20-29	NA	0.952	NA	NA
30-39	NA	0.938	0.832	0.759
40-49	NA	0.978	0.935	0.887
50-59	NA	0.956	0.895	0.845
60-62	NA	0.969	0.890	0.819
70-73	NA	0.943	0.832	0.738
Radiation	21.7	0.682	NA	0.227
Radiation				
No Radiation	NA	0.869	0.668	0.591
Chemotherapy	NA	0.919	0.872	0.822
Yes				
No/unknown	NA	0.865	0.650	0.566
Size	NA	0.915	0.856	0.809
< = 20 mm				
> 20, < = 40	NA	0.987	0.958	0.932
> 40, < = 60	NA	0.944	0.800	0.709
> 60, < = 100	NA	0.857	0.657	0.561
> 100	34.6	0.751	0.492	0.425
Race	12.9	0.518	0.284	NA
Black				
White	NA	0.849	0.663	0.581
Asian or Pacific Islander	NA	0.893	0.748	0.681
American Indian/Alaska Native	NA	0.894	0.759	0.691
	60.6	0.836	0.666	0.492

AJCC staging is a common staging system for cancer[34,35]. We compared Nomogram's c-index with AJCC staging and found that both the training group and the validation group had higher c-index than AJCC staging. In addition, as can be seen from the calibration curve and the ROC curve, Nomogram has good predictability and reliability both internally and externally. This shows that our Nomogram can achieve lower bias and better accuracy in practical work. Therefore, the Nomogram we established can obtain more accurate predictive values based on the use of AJCC staging, which can help the clinical design of more consistent treatment methods.

This study has also some shortcomings. Firstly, due to the retrospective study, although some advanced statistical methods are used, some biases are inevitable; secondly, although we know that the patient has received chemotherapy, we do not know the chemotherapy drugs (including dose, cycle, regimen, etc.). Thirdly, although the risk score and Nomogram of this study were established using the same set of data, the test was also verified by subgroups of the data set. The database is based on American patients and cannot be used in other countries probably. So external validation still needs to be done in different countries.

Conclusions

Our study suggests that race, AJCC staging, tumor size, primary site surgery, chemotherapy and radiotherapy are independent prognostic factors for cervical cancer OS. In addition, we established Nomogram to predict 1-year, 3-year and 5-year OS survival rates for cervical cancer patients with good accuracy. It has certain advantages in predicting preliminaries the prognosis of patients. But for each stage of patients, because of the different

treatment methods, the treatment methods need to have a certain degree of deviation. So, we also need to look at each stage-specific prediction model to improve its prediction of survival.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

The work was approved by Guangdong Medical University Ethics Committee, and in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent forms are not required for patient data extracted from SEER database.

Data Availability Statement

All data generated or analyzed during this study are included in this published article files. Statistical codes are available from the corresponding authors with reasonable request.

Authors' Contribution

BL performed the statistical analyses. XZ checked the statistical accuracy as an expert in statistics. BL performed the literature search and wrote the first draft of the manuscript. SZ, JL and YH revised and edited the final version of the manuscript. All authors read and approved the final manuscript.

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