

A prognostic model guides surgical resection in cervical squamous cell carcinoma

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Background: To explore the independent risk factors of cervical squamous cell carcinoma and establish a Nomogram model to predict the prognosis of patients.

Methods: We randomly divided the total data of patients with cervical squamous cell carcinoma from 2010 to 2015 obtained from the SEER database and cleaned them into training and verification cohorts. The Cox proportional hazard regression model was used to perform univariate and multivariate analyses on the three cohorts of data including the total data. After the intersection, the independent factors and their nomograms with statistical significance were obtained, and the degree of differentiation and calibration between predicted results and real values were obtained by using C-index and calibration map respectively. In addition, the ROC curve was used for correction and evaluation, and the 1-, 3- and 5-year overall and specific survival rates of patients were finally predicted.

Results: We found age, surgical condition of the primary site and tumor size were all independent factors of cervical cancer. The high-risk survival rates of patients at 1, 3 and 5 years were 77.7%, 48.6% and 36.4%, respectively. We determined that minimally invasive hysterectomy and uterine-preserving surgery (UPS) have a better survival rate for early (stage I) tumors or tumor diameter less than 20 mm. For the late (stage III–IV) or tumor diameter greater than 20 mm, auxiliary open hysterectomy after radiotherapy, and requires careful evaluation of the postoperative residual tumor is the best policy.

Conclusions: The constructed nomograms could predict overall survival with good performance, and guide surgical resection in cervical squamous cell carcinoma.

Keywords: Cervical squamous cell carcinoma; SEER database; COX risk regression model; survival analysis; ROC curve; nomogram

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Introduction

Cervical squamous cell carcinoma is one of the most common malignancy of the female reproductive system in the world, the third most common female cancer in the world, and the fourth most common cause of cancerrelated death. It is reported that there were 569,847 new cases (3.2%) and 569,847 deaths (3.3%) in 2018 alone (1). Women without insurance or regular health care providers have a higher risk of developing the disease. Worldwide, the incidence rate is higher in developing countries with inadequate medical services and lower in developed countries such as North America and West Asia. The squamous cell carcinoma, adenocarcinoma, and squamous cell carcinoma are common in cervical cancer, in which squamous cell carcinoma accounts for more than 80% (2). The vast majority of cervical cancer patients are middleaged women aged around 40 (3).

Surgery, radiotherapy and chemotherapy are all important methods for the treatment of cervical cancer. Due to limited data, we only studied the effect of surgery on the prognosis of cervical cancer patients. However, the clinical role of hysterectomy in locally advanced cervical cancer (LACC) remains unclear (4,5). Another study showed that single-mode surgery or radiation therapy was the preferred treatment for cervical cancer, but the combination of the two treatments had a higher incidence (6). Therefore, in this study, we need to explore the prognosis of cervical cancer patients with surgery and explore which surgery is more effective.

Methods

Data sources

Data in this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Database including the patient's age, race, sex, year of diagnosis, the primary lesion, grade, TNM stage, the primary site, tumor size, tumor surgery information coding, tumor-infiltrating degree, treatment plan, the cause of death and marital status, etc., for clinical oncology research, provides a good data to support. Established in 1973 by the National Cancer Institute (NCI), the SEER database includes data from patients who have been treated at the Cancer Accreditation Center Committee, covering approximately 70% of newly diagnosed cancer cases in more than 1,500 hospitals in the United States and 28% of the population in the US. The database has a large sample size and high accuracy, and records the pathogenesis, treatment, pathology, prognosis and other information of millions of patients.

Study population

In this study, the clinical pathology and follow-up data of 94,179 patients with cervical cancer from 1973 to 2015 were obtained by SEER*Stat. The data included patient age, sex, race, age of diagnosis, grade, primary site, derived AJCC stage group, CS tumor size, lymph nodes, age of diagnosis, marital status at diagnosis and so on. We first excluded the first tumor is not a cervical cancer patient data, and then clear the errors, blank, no record, unavailability of the pathological data, and then excluded the subtypes of cervical cancer except squamous cell carcinoma. The 5,620 patients with cervical squamous cell carcinoma screened from 2010 to 2015 were included in this study. We randomly divided 2,248 cases into the training cohort and the remaining 3,372 cases into the verification cohort. The data cleaning process was shown in *Figure 1*.

Statistical analysis

We used Excel 2016 version to collate the data, and then used createDataPartition function in the Caret package in R software 3.5.3 version to conduct simple random sampling of the data, and randomly divided the patients into training cohort and verification cohort.

In the first step, we used the Cox proportional hazard regression model to perform univariate and multivariate analysis of the training cohort. If the variable had P>0.05 and no NA in both analyses, the variable was statistically significant with cervical cancer. Then we screen out the statistically significant variables, calculate the hazard ratio (HR) and its confidence interval (95% CI), and use the coxph function of the Survival package to calculate the C-index. At the same time, we obtain the degree of differentiation between the predicted values of the Cox proportional risk regression model and the real values, and then constructed the nomogram. The independent risk factors that can be derived from the nomograms predict the survival rate of cervical cancer patients at 1 year, 3 years, and 5 years. At this point, we use the rcorr.cens function of the Hmisc package to calculate the C-index, and obtain the degree of discrimination between the results of the nomogram prediction and the real results. At the same time, the Bootstrap method is used to carry out 1,600 times of simulated operation training cohort data (b=1,600).



Figure 1 The flow chart of study population data cleaning. After obtaining the original data, the data of patients whose primary tumor was not cervical cancer were excluded. After clearing the pathological data of errors, blanks, unrecorded and unavailable data in the data, the cervical cancer subtypes other than squamous cell carcinoma are excluded. Screening patients with cervical squamous cell carcinoma were randomly divided into a training cohort and a verification cohort. Then, univariate and multivariate COX risk regression analysis was carried out for the three groups of data to obtain their own significant risk factors. Finally, independent risk regression factors were obtained through the intersection.

Then we draw the calibration, we get the calibration degree between the survival rate of the nomogram prediction and the real result. Next, we calculated the risk score of each patient, and used the risk scoring system to evaluate the accuracy of the model through the ROC curve. AUC indicates the area under the ROC curve (7).

In the second step, we use the same method as the training cohort to analyze the verification cohort. Univariate and multivariate analyses were conducted on the data of the verification cohort with the Cox proportional risk regression model. We screened out the meaningful variables in the verification cohort, and obtained the corresponding HR, 95% CI and Nomogram. Then we use C-index to obtain the degree of discrimination between the Cox proportional hazard regression model of the verification cohort and the real value, and use the Bootstrap method to obtain the calibration degree. Finally, we use the ROC curve to evaluate the predictive model, but the risk

scoring system uses the data from the verification cohort.

Third, the Cox proportional risk regression model was again used to conduct univariate and multivariate analyses of the total data before grouping. The significant variables obtained from the multivariate variables were intersected with the significant variables obtained from the training cohort and the verification cohort, and the real variables with statistical significance for cervical cancer were finally determined. Next, according to the final obtained variables, we obtained the overall nomogram, the corresponding discrimination degree and calibration degree between Cox proportional risk regression model and the real value and the AUC used to evaluate the accuracy of the model by ROC curve.

Finally, according to the intersection variables of statistically significant variables from the training cohort, the verification cohort and the overall group, we obtained the total risk score of the total data. Then, we used the Kaplan-Meier method to predict the overall data, calculate 1714

the high-risk and low-risk survival rate of cervical cancer, and map the high-risk survival curves of cervical cancer for 1, 3, and 5 years, and the 1-, 3-, and 5-year survival curves of the three independent risk factors.

The C-index is similar to the AUC in the ROC curve and is used to measure the predictive value of the Nomogram. The minimum value is 0.5 and the maximum value is 1.0. The higher the C-index is, the higher the predictive value is. The Bootstrap method is a simulated sampling statistical inference method based on the original data and re-sampling. The sampling concept is the same, and the number of times can be denoted as B, which can be used to analyze the distribution characteristics of a certain statistic. The AUC value can be used as the evaluation standard of the ROC curve. The value range is generally between 0.5 and 1, where the AUC is less than or equal to 0.5 without any prediction ability, 0.71< AUC <0.9 has moderate accuracy prediction ability, AUC >0.9 has high accuracy prediction ability.

Results

Clinical and pathological features

The data included in this study included 5 years of followup from 2010 to 2015. During the recording period, 154 patients died from other diseases besides the tumor, 1,023 died from the tumor, and 4,443 survived at the end of the recording period.

In this study, data of 5,620 patients were divided into the training cohort and verification cohort, and their clinical and pathological characteristics were shown in Table 1. Among all patients, cervical cancer was most likely to occur in middle-aged and elderly women aged 30 to 55 (constituent ratio >10%), with a median age of 48.6 (45-49 years old), and the survivors were generally normally distributed. Among the vulnerable races, there were 4,177 cases (74.3%) in Caucasians, which may be due to the fact that most of the races recorded in the SEER database were Caucasians. In the tumor grade, grade II and grade III periods account for most of the tumor, there were 2,689 cases (47.8%) and 2,394 cases (42.6%). Surgery is one of the most effective methods to treat cervical cancer. In the display of the RX Summ-Surg Prim Site, most patients have received different degrees of surgical treatment. The majority of patients (n=1,326, 23.6%) underwent a radical hysterectomy, extended radical hysterectomy, modified radical hysterectomy or extended hysterectomy. There were

279 patients (5.0%) who underwent total hysterectomy without removal of tubes and ovaries, 827 patients (14.7%) who underwent total hysterectomy with removal of tubes and/or ovary, and 16 patients (0.3%) who underwent pelvic clearance. However, there were still 2,375 patients (42.2%) who had no primary site surgery. In RX Summ-Surg Oth Reg/Dis, an investigation or post-mortem autopsy found that virtually none of the patients underwent metastatic surgery, which may be related to the infrequent involvement of cervical cancer in the lymph nodes. From 2010 to 2015, 2,254 cases (40.1%) were diagnosed with tumor size less than or equal to 30 mm. The degree of tumor infiltration was uneven, and the degree of infiltration in the ≥ 200 and < 300 interval accounted for 2,071 cases (36.8%). Lymph nodes of 3,938 patients (70.1%) were not invaded by a tumor, and most tumors did not metastasize at the time of diagnosis (90.1%). Only 1,023 patients died of cervical cancer (18.2%); by the end of the investigation, 4,443 patients (79.0%) survived. Most patients had only one primary tumor (95.4%). Almost all were malignant (99.8%), but most patients had only one malignant tumor (96.2%); the tumor was diagnosed in all adult female age groups, with more women in their 40s diagnosed with cervical cancer. The majority of patients with cervical cancer were married or cohabiting (42.4%).

Determination of independent risk factors affecting the prognosis of patients

The Cox proportional risk regression model was used to conduct a univariate analysis of all variables in the training cohort, and the results showed that age, race, grade, Derived AJCC Stage Group, Derived AJCC T, Derived AJCC N, Derived AJCC M, RX Summ-Surg Prim Site, tumor size, CS extension, CS lymph nodes, CS Mets at dx, SEER cause-specific death classification, SEER other cause of death classification, age at diagnosis, marital status at diagnosis are all correlated with the prognosis of cervical cancer patients (P<0.05), which has statistical significance (Table S1). The meaningful variables obtained by univariate Cox proportional risk regression analysis were carried out for multivariate Cox proportional risk regression analysis. Age, grade, Derived AJCC M, RX Summ-Surg Prim Site, tumor size, CS Mets at dx were independent risk factors affecting the prognosis of cervical cancer patients (Table S1).

Then, the COX proportional risk regression model was used for univariate analysis of all variables in the verification cohort, and the results showed that age, race,

.,	Before cleaning (n=94,179)		After cleaning (t	otal cohort) (n=5,	Grouping			
Variable	All subjects (n=94,179)	All subjects (n=5,620)	Alive (n=4,443)	Dead of this cancer (n=1,023	Dead of other diseases (n=154)	Training cohort (n=2,248)	Verification cohort (n=3,372)	
Age								
1–19	172	0	0	0	0	0	0	
20–29	6,147	336 (6.0)	283 (6.4)	51 (5.0)	2 (1.3)	144 (5.1)	192 (5.7)	
30–34	8,809	563 (10.0)	468 (10.5)	92 (9.0)	3 (1.9)	214 (9.5)	349 (10.3)	
35–39	10,958	652 (11.6)	578 (13.0)	73 (7.1)	1 (0.6)	260 (11.6)	392 (11.6)	
40–44	11,866	750 (13.3)	625 (14.1)	117 (11.4)	8 (5.2)	291 (12.9)	459 (13.6)	
45–49	10,914	716 (12.7)	561 (12.6)	141 (13.8)	14 (9.1)	287 (12.8)	429 (12.7)	
50–54	9,598	687 (12.2)	530 (11.9)	139 (13.6)	18 (11.7)	280 (12.4)	407 (12.0)	
55–59	8,343	553 (9.8)	430 (9.7)	106 (10.4)	17 (11.0)	237 (10.5)	316 (9.4)	
60–64	7,316	481 (8.6)	367 (8.3)	95 (9.3)	19 (12.3)	194 (8.6)	287 (8.5)	
65–74	11,069	559 (9.9)	407 (9.2)	117 (11.4)	35 (22.7)	223 (9.9)	336 (10.0)	
≥75	8,987	323 (5.7)	194 (4.4)	92 (9.0)	37 (24.0)	118 (5.2)	205 (6.0)	
Race								
Black	13,556	818 (14.6)	591 (13.3)	193 (18.9)	34 (22.1)	328 (14.6)	490 (14.5)	
White	70,994	4,177 (74.3)	3,342 (75.2)	725 (70.9)	110 (71.4)	1,670 (74.3)	2,507 (74.3)	
Other	8,811	625 (11.1)	510 (11.5)	105 (10.3)	10 (6.5)	250 (11.1)	375 (11.1)	
Unknown	818	0	0	0	0	0	0	
Grade								
Grade I	7,816	462 (8.2)	418 (9.4)	35 (3.4)	9 (5.8)	199 (8.8)	263 (7.8)	
Grade II	23,526	2,689 (47.8)	2,194 (49.4)	422 (41.2)	73 (47.4)	1059 (47.1)	1630 (48.3)	
Grade III	24,415	2,394 (42.6)	1,774 (39.9)	551 (53.9)	69 (44.8)	956 (42.5)	1438 (42.6)	
Grade IV	2,361	75 (1.3)	57 (1.3)	15 (1.5)	3 (1.9)	34 (1.5)	41 (1.2)	
Unknown	36,061					0	0	
Stage								
IA	3,147	737 (13.1)	719 (16.2)	8 (0.8)	10 (6.5)	288 (12.8)	449 (13.3)	
IANOS	425	0	0	0	0	0	0	
INOS	410	0	0	0	0	0	0	
IB	4,556	1,736 (30.9)	1,600 (36.0)	106 (10.4)	30 (19.5)	663 (29.5)	1073 (31.8)	
IBNOS	308	0	0	0	0	0	0	
IIA	652	262 (4.7)	206 (4.6)	45 (4.4)	11 (7.1)	111 (4.9)	151 (4.5)	
IIANOS	149	0	0	0	0	0	0	
IIB	1,716	598 (10.6)	485 (10.9)	87 (8.5)	26 (16.9)	253 (11.2)	345 (10.2)	
IINOS	16	0	0	0	0	0	0	

Table 1 Population and clinical characteristics of cervical cancer	r patients from October 2010 to 2015

Table 1 (continued)

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	Before cleaning (n=94,179)		After cleaning (te	otal cohort) (n=5,	,620)	Grouping			
Variable	All subjects (n=94,179)	All subjects (n=5,620)	Alive (n=4,443)	Dead of this cancer (n=1,023)	Dead of other) diseases (n=154)	Training cohort (n=2,248)	Verification cohort (n=3,372)		
	4,194	1,610 (28.6)	1,131 (25.4)	424 (41.4)	55 (35.7)	661 (29.4)	949 (28.1)		
IIINOS	93	0	0	0	0	0	0		
IV	3,138	677 (12.0)	302 (6.8)	353 (34.5)	22 (14.3)	272 (12.1)	405 (12.0)		
NA	158	0	0	0	0	0	0		
UNK stage	1,371	0	0	0	0	0	0		
Blank (s)	73,836	0	0	0	0	0	0		
Stag_T									
то	14	0	0	0	0	0	0		
T1a	3,267	762 (13.6)	741 (16.7)	11 (1.1)	10 (6.5)	297 (13.2)	465 (13.8)		
T1aNOS	492	0	0	0	0	0	0		
T1b	5,760	2,254 (40.1)	2,011 (45.3)	204 (19.9)	39 (25.3)	890 (39.6)	1,364 (40.4)		
T1bNOS	401	0	0	0	0	0	0		
T1NOS	609	0	0	0	0	0	0		
T2a	1,104	465 (8.3)	355 (8.0)	88 (8.6)	22 (14.3)	192 (8.5)	273 (8.1)		
T2aNOS	309	0	0	0	0	0	0		
T2b	2,846	1,014 (18.0)	758 (17.1)	219 (21.4)	37 (24.0)	420 (18.7)	594 (17.6)		
T2NOS	29	0	0	0	0	0	0		
ТЗа	689	191 (3.4)	94 (2.1)	90 (8.8)	7 (4.5)	78 (3.5)	113 (3.4)		
T3b	2,187	730 (13.0)	390 (8.8)	309 (30.2)	31 (20.1)	281 (12.5)	449 (13.3)		
T3NOS	225	0	0	0	0	0	0		
T4	752	204 (3.6)	94 (2.1)	102 (10.0)	8 (5.2)	90 (4.0)	114 (3.4)		
T4b	1	0	0	0	0	0	0		
ТХ	1,500	0	0	0	0	0	0		
NA	158	0	0	0	0	0	0		
Blank (s)	73,836	0	0	0	0	0	0		
Stag_N									
NO	13,700	3,938 (70.1)	3,338 (75.1)	489 (47.8)	111 (72.1)	1,564 (69.6)	2,374 (70.4)		
N1	4,894	1,682 (29.9)	1,105 (24.9)	534 (52.2)	43 (27.9)	684 (30.4)	998 (29.6)		
NA	158	0	0	0	0	0	0		
NX	1,591	0	0	0	0	0	0		
Blank (s)	73,836	0	0	0	0	0	0		

Table 1 (continued)

Madala	Before cleaning (n=94,179)		After cleaning (i	total cohort) (n=5,6	620)	Grouping		
Variable	All subjects (n=94,179)	All subjects (n=5,620)	Alive (n=4,443)	Dead of this cancer (n=1,023)	Dead of other diseases (n=154)	Training cohort (n=2,248)	Verification cohort (n=3,372)	
Stag_M								
MO	17,452	5,072 (90.2)	4,208 (94.7)	727 (71.1)	137 (89.0)	2,034 (90.5)	3,038 (90.1)	
M1	2,733	548 (9.8)	235 (5.3)	296 (28.9)	17 (11.0)	214 (9.5)	334 (9.1)	
NA	158	0	0	0	0	0	0	
Blank (s)	73,836	0	0	0	0	0	0	
rx_site								
0	25,064	2,375 (42.2)	1,532 (34.5)	743 (72.6)	100 (64.9)	985 (43.8)	1,390 (41.2)	
10	306	24 (0.4)	21 (0.5)	2 (0.2)	1 (0.6)	7 (0.3)	17 (0.5)	
20	6,848	557 (9.9)	481 (10.8)	61 (6.0)	15 (9.7)	217 (9.6)	340 (10.1)	
30	3,305	279 (5.0)	263 (5.9)	14 (1.4)	2 (1.3)	115 (5.1)	164 (4.9)	
40	8,884	827 (14.7)	757 (17.0)	59 (5.8)	11 (7.1)	329 (14.6)	498 (14.8)	
50	11,782	1,326 (23.6)	1,196 (26.9)	107 (10.4)	23 (14.9)	500 (22.2)	826 (24.5)	
60	2,213	216 (3.8)	185 (4.2)	30 (2.9)	1 (0.6)	89 (4.0)	127 (3.8)	
70	204	16 (0.3)	8 (0.2)	7 (0.7)	1 (0.6)	6 (0.3)	10 (0.3)	
90	390	0	0	0	0	0	0	
99	694	0	0	0	0	0	0	
Blank (s)	34,489	0	0	0	0	0	0	
rx_reg								
None	42,000	5,398 (96.0)	4,267 (96.0)	981 (95.9)	150 (97.4)	2,160 (96.1)	3,238 (96.0)	
Other	2,218	222 (4.0)	176 (4.0)	42 (4.1)	4 (2.6)	88 (3.9)	134 (4.0)	
Blank (s)	49,426	0	0	0	0	0	0	
Unknown	535	0	0	0	0	0	0	
Size								
0	23	0	0	0	0	0	0	
≤30	11,173	2,254 (40.1)	2,110 (47.5)	102 (10.0)	42 (27.3)	871 (38.7)	1,383 (41.0)	
>30, ≤50	6,314	1,450 (25.8)	1,147 (25.8)	258 (15.4)	45 (29.2)	594 (26.4)	856 (25.4)	
>50, ≤100	7,396	1,813 (32.2)	1,145 (25.8)	605 (59.1)	63 (40.9)	751 (33.4)	1,062 (31.5)	
>100	622	103 (1.8)	41 (0.9)	58 (5.7)	4 (2.6)	32 (1.4)	71 (2.1)	
888	1	0	0	0	0	0	0	
990	1,025	0	0	0	0	0	0	
999	14,676	0	0	0	0	0	0	
Blank (s)	52,949	0	0	0	0	0	0	
Exten								
<200	7,684	752 (13.4)	732 (16.5)	10 (1.0)	10 (6.5)	293 (13.0)	459 (13.6)	

 Table 1 (continued)

Me de la	Before cleaning (n=94,179)		After cleaning (to	otal cohort) (n=5	,620)	Gro	ouping
Variable	All subjects (n=94,179)	All subjects (n=5,620)	Alive (n=4,443)	Dead of this cancer (n=1,023)	Dead of other diseases (n=154)	Training cohort (n=2,248)	Verification cohort (n=3,372)
≥200, <300	11,438	2,071 (36.8)	1,868 (42.0)	172 (16.8)	31 (20.1)	822 (36.6)	1249 (37.0)
≥300, <500	5,584	643 (11.4)	497 (11.2)	117 (11.4)	29 (18.8)	256 (11.4)	387 (11.5)
≥500, <600	6,011	1,029 (18.3)	768 (17.3)	223 (21.8)	38 (24.7)	428 (19.0)	601 (17.8)
≥600, <700	6,140	921 (16.4)	484 (10.9)	399 (39.0)	38 (24.7)	359 (16.0)	562 (16.7)
≥700, <999	1,438	204 (3.6)	94 (2.1)	102 (10.0)	8 (5.2)	90 (4.0)	114 (3.4)
Blank (s)	52,949	0	0	0	0	0	0
LN							
No involvement of lymph nodes	28,801	3,938 (70.1)	3,338 (75.1)	489 (47.8)	111 (72.1)	1,564 (69.6)	2,374 (70.4)
Lymphoid involvement	12,429	1,682 (29.9)	1105 (24.9)	534 (52.2)	4 (52.2) 43 (27.9)		998 (29.6)
Blank (s)	52,949	0	0	0	0	0	0
Mets_dx							
0	33,973	5,062 (90.1)	4,204 (94.6)	721 (70.5)	137 (89.0)	2,030 (90.3)	3,032 (89.9)
1–99	7,257	558 (9.9)	239 (5.4)	302 (29.5)	17 (11.0)	218 (9.7)	340 (10.1)
Blank (s)	52,949	0	0	0	0	0	0
Canc_dth							
Alive or dead of other cause	20,714	4,597 (81.8)				1,834 (81.6)	2,763 (81.9)
Dead	25,981	1,023 (18.2)				414 (18.4)	609 (18.1)
Dead (missing/ unknown COD)	1,254	0				0	0
N/A not first tumor	6,230	0				0	0
Oth_dth							
Alive or dead due to cancer	73,388	5,466 (97.2)				2,185 (97.2)	3,281 (97.3)
Dead of others	13,307	154 (2.7)				63 (2.8)	91 (2.7)
Dead (missing/ unknown COD)	1,254	0				0	0
N/A not first tumor	6,230	0				0	0
Status							
Alive	49,830	4,443 (79.0)	4,443 (100.0)	0 (0)	0 (0)	1,771 (78.8)	2,672 (79.2)
Dead	44,349	1,177 (20.9)	0 (0)	1,023 (100.0)	154 (100.0)	477 (21.2)	700 (20.8)

Table 1 (continued)

Before cleaning After cleaning (total cohort) (n=5,620) Grouping (n=94,179) Variable Verification All subjects All subjects Dead of this Dead of other Training cohort Alive (n=4,443) cancer (n=1,023) diseases (n=154) (n=94,179) (n=5,620) (n=2,248) cohort (n=3,372) Seq_num 78,299 5,359 (95.4) 4,251 (95.7) 982 (96.0) 126 (81.8) 3,231 (95.8) One primary only 2,128 (94.7) 261 (4.6) 120 (5.3) 1st of 2 or more 15,875 192 (4.3) 41 (4.0) 28 (18.2) 141 (4.2) primaries Unknown seg num 5 0 0 0 0 0 0 Total malig 1 79,161 5,407 (96.2) 4,292 (96.6) 987 (96.5) 128 (83.1) 2,156 (95.9) 3,251 (96.4) 2 12,497 199 (3.5) 140 (3.2) 35 (3.4) 24 (15.6) 87 (3.9) 112 (3.3) 3 2,061 13 (0.2) 10 (0.2) 1 (<0.1) 2 (1.3) 5 (0.2) 8 (0.2) 4 378 0 (0) 0 1 (<0.1) 1 (<0.1) 0 (0) 1 (<0.1) 77 0 0 0 0 0 0 5-10 5 0 0 0 0 0 0 Unknown Total begn 0 93,988 5,608 (99.8) 4,434 (99.8) 1,020 (99.7) 154 (100.0) 2,243 (99.8) 3,365 (99.8) 185 1 12 (0.2) 9 (0.2) 3 (0.3) 0 (0) 5 (0.2) 7 (0.2) 0 0 2 6 0 0 0 0 Age_diag 3-19 172 0 0 0 0 0 0 20-34 14,956 899 (16.0) 751 (16.9) 5 (3.2) 541 (16.0) 143 (14.0) 358 (15.9) 35-39 10,958 652 (11.6) 578 (13.0) 73 (7.1) 1 (0.6) 260 (11.6) 392 (11.6) 40-44 11,866 750 (13.3) 625 (14.1) 117 (11.4) 8 (5.2) 291 (12.9) 459 (13.6) 45-49 10,914 716 (12.7) 561 (12.6) 141 (13.8) 14 (9.1) 287 (12.8) 429 (12.7) 50-54 9,598 687 (12.2) 530 (11.9) 139 (13.6) 280 (12.4) 407 (12.0) 18 (11.7) 55-59 8,343 553 (9.8) 430 (9.7) 106 (10.4) 17 (11.0) 237 (10.5) 316 (9.4) 60-69 13,573 829 (14.8) 623 (14.0) 164 (16.0) 42 (27.3) 332 (14.8) 497 (14.7) 70-99 13,773 514 (9.1) 345 (7.8) 120 (11.7) 49 (31.8) 203 (9.0) 311 (9.2) 100-104 26 0 0 0 0 0 0 Mrit Single 20,585 1,887 (33.6) 1,466 (33.0) 392 (38.3) 29 (18.8) 760 (33.8) 1,127 (33.4) Married or partner 41,892 2,385 (42.4) 1,982 (44.6) 350 (34.2) 53 (34.4) 929 (41.3) 1,456 (43.2) 26,227 Separated divorced 1,348 (24.0) 995 (22.4) 281 (27.5) 72 (46.8) 559 (24.9) 789 (23.4) or widowed Unknown 5,475 0 0 0 0 0 0

grade, Derived AJCC Stage Group, Derived AJCC T, Derived AJCC N, Derived AJCC M, RX Summ-Surg Prim Site, tumor size, CS extension, CS lymph nodes, CS Mets at dx, SEER cause-specific death classification, SEER other cause of death classification, total number of in situ/ malignant tumors for a patient, age at diagnosis, marital status at diagnosis are all related to the prognosis of cervical cancer patients (P<0.05), which have statistical significance (*Table S2*). The meaningful variables obtained by univariate Cox proportional risk regression analysis were carried out for multivariate Cox proportional risk regression analysis. Age, RX Summ-Surg Prim Site, tumor size, Total number of in situ/malignant tumors for patients are independent risk factors affecting the prognosis of cervical cancer (*Table S2*).

Finally, COX proportional risk regression model was used for univariate analysis of the overall data after cleaning, and the results showed that age, race, grade, Derived AJCC Stage Group, Derived AJCC T, Derived AJCC N, Derived AJCC M, RX Summ-Surg Prim Site, tumor size, CS extension, CS lymph nodes, CS Mets at dx, SEER cause-specific death Classification, SEER other cause of death classification, age at diagnosis, and marital status at diagnosis are all correlated with the prognosis of cervical cancer patients (P<0.05), which has statistical significance (Table 2). The meaningful variables obtained by univariate Cox proportional risk regression analysis were carried out for multivariate Cox proportional risk regression analysis. It was concluded that age, grade, RX Summ-Surg Prim Site and tumor size were independent risk factors affecting the prognosis of cervical cancer patients (Table 2).

In summary, through the intersection of the three groups of data results, we found that the variables with statistical significance of cervical cancer are age, RX Summ-Surg Prim Site, tumor size.

Nomogram model and validation

According to the meaningful risk factors obtained by the training group and the validation group, we prepared the corresponding Nomogram respectively, and obtained the final independent risk factors (age, RX Summ-Surg Prim Site, tumor size) and their nomogram through the intersection of the three data cohorts (*Figure 2*). For each variable, the corresponding score of each item was obtained according to the small points in the first line corresponding to the tumor situation, and then the total value was added corresponding to the overall scale at the bottom, and corresponding downward, the overall survival rate of

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patients at 1, 3 and 5 years could be obtained.

The C-index of the training cohort was 0.792, the C-index of the verification cohort was 0.778, and the C-index of the overall group was 0.771, with little difference in values and high accuracy in prediction. The nomogram was internally verified by the Bootstrap method, and the fitting coefficient b=1,600. The calibration of 1-, 3-, and 5-year survival rates in the training cohort (*Figure S1A,B,C*), verification cohort (*Figure S1D,E,F*), and total cohort (*Figure 3A,B,C*) were shown in the figure respectively. It can be seen that the slope of the consistency curve of the calibration graphs of the training cohort and the verification cohort is close to 1, indicating that there is good consistency between the predicted value and the actual observed value.

Finally, the prediction ability of the nomogram was evaluated by ROC curve. The AUC of 1, 3 and 5 years in the training cohort (0.841, 0.8 and 0.795; *Figure S2A,B,C*), the AUC of 1, 3 and 5 years in the verification cohort (0.801, 0.798 and 0.768; *Figure S2D,E,F*) and the AUC of 1, 3 and 5 years in the overall group (0.804, 0.791 and 0.771; *Figure 3D,E,F*) were all located at (0.71, 0.9), and all had a high predictive value of accuracy.

Prognosis and survival analysis of cervical cancer patients

The overall model has good recognition ability. According to the respective nomograms, we obtained the survival curves of the training cohort, the verification cohort and the overall cohort, respectively. According to the nomogram established in this study, the survival curve of our high-risk patients will decline faster (Figure 4A). In the overall group, the 1-, 3- and 5-year high-risk survival rates were 79.2%, 56.0% and 47.5%, respectively, and the low-risk survival rates were 98.0%, 90.9% and 85.5%, respectively (Figure S3A, B; Table 3). The median survival time in the age group greater than 75 years was 37 months. The 5-year survival rates were higher than 80% in patients who had both local tumor resection and hysterectomy, thus not draw the median survival time. On the contrary, for those who had not had primary site surgery or had only pelvic exenteration, the 5-year survival rate was particularly low, and intermediate survival time was 46.2 and 22.5 months, respectively. In the grouping of tumor size, the survival rate was lower as the tumor size increased, and only the median survival time (>50, ≤ 100) and (>100) were shown 41.7 and 13.2 months respectively (Table 3; Figure 4B,C,D). The 1-, 3-, and 5-year survival rates of age, RX Summ-Surg Prim Site, tumor size are shown in Table 3.

Table 2 Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the total cohort

Veriela	Univariate analysis					Multivariate analysis		
variable	HR	95% CI	Р	C-Index	SE	HR	95% CI	Р
Age				0.599	0.009			
20–29	1	Reference				1	Reference	
30–34	0.999	0.714–1.398	0.995			0.606	0.428-0.858	0.005
35–39	0.685	0.482-0.975	0.036			0.654	0.455-0.940	0.022
40–44	0.998	0.724–1.376	0.99			0.664	0.478-0.922	0.015
45–49	1.332	0.975–1.820	0.071			0.63	0.456-0.872	0.005
50–54	1.455	1.066–1.987	0.018			0.602	0.434–0.835	0.002
55–59	1.428	1.035–1.970	0.03			0.595	0.422-0.837	0.003
60–64	1.502	1.084–2.081	0.014			0.606	0.373–0.986	0.044
65–74	1.742	1.275–2.382	< 0.001			0.708	0.477-1.051	0.086
≥75	3.156	2.292-4.345	<0.001			0.902	0.639–1.274	0.558
Race				0.527	0.007			
Black	1	Reference				1	Reference	
White	0.712	0.614-0.824	< 0.001			0.994	0.851-1.160	0.935
Other	0.676	0.540-0.846	0.001			1.118	0.885–1.412	0.349
Grade				0.569	0.008			
Grade I	1	Reference				1	Reference	
Grade II	2.008	1.475–2.733	< 0.001			0.771	0.561-1.060	0.109
Grade III	2.961	2.181-4.020	<0.001			0.795	0.578–1.093	0.158
Grade IV	2.69	1.555-4.656	< 0.001			0.55	0.310-0.979	0.042
Stage				0.766	0.006			
IA	1	Reference				1	Reference	
IB	2.986	1.826-4.881	<0.001			1.134	0.245–5.239	0.872
IIA	10.058	5.914–17.108	< 0.001			1.345	0.284-6.365	0.708
IIB	7.634	4.642-12.554	<0.001			1.206	0.264–5.516	0.81
III	13.91	8.688-22.269	< 0.001			1.099	0.242-4.981	0.903
IV	39.82	24.805–63.924	<0.001			1.406	0.294–6.727	0.67
Stag_T				0.748	0.007			
T1a	1	Reference				1	Reference	
T1b	3.722	2.383–5.813	< 0.001			0.77	0.102–5.789	0.8
T2a	9.859	6.182–15.723	<0.001			0.57	0.076-4.238	0.582
T2b	9.939	6.369–15.508	<0.001			0.353	0.039–3.185	0.353
ТЗа	26.141	16.306–41.907	<0.001			1.53	0.362-6.460	0.563
T3b	24.277	15.621–37.729	<0.001			1.709	0.407-7.169	0.464
Τ4	32.652	20.466-52.093	<0.001			1.665	0.385–7.192	0.495

Table 2 (continued)

Verieble		Univariate ar	nalysis				Multivariate analysis		
variable —	HR	95% CI	Р	C-Index	SE	HR	95% CI	Р	
Stag_N				0.621	0.008				
NO	1	Reference				1	Reference		
N1	2.712	2.419-3.041	<0.001			1.145	0.975–1.346	0.099	
Stag_M				0.623	0.007				
MO	1	Reference				1	Reference		
M1	5.986	5.251-6.824	<0.001			0.951	0.389–2.322	0.912	
rx_site				0.704	0.007				
0	1	Reference				1	Reference		
10–19	0.248	0.080-0.770	0.016			0.586	0.183–1.874	0.368	
20–29	0.327	0.258-0.413	<0.001			0.986	0.767-1.268	0.915	
30–39	0.104	0.063-0.170	<0.001			0.868	0.517-1.457	0.591	
40–49	0.195	0.153-0.249	<0.001			0.782	0.602-1.016	0.066	
50–59	0.201	0.167-0.242	<0.001			0.735	0.597-0.904	0.004	
60–64	0.311	0.217-0.445	<0.001			0.839	0.576-1.222	0.36	
65–75	1.251	0.623-2.510	0.529			0.451	0.209-0.971	0.042	
rx_reg				0.504	0.003				
None	1	Reference							
Other*	0.938	0.699–1.260	0.672						
Size				0.729	0.007				
≤30	1	Reference				1			
>30, ≤50	3.593	2.946-4.382	< 0.001			1.073	0.866-1.330	0.517	
>50, ≤100	7.846	6.551–9.397	< 0.001			1.509	1.226-1.859	<0.001	
>100	17.017	12.629–22.931	<0.001			1.874	1.344–2.613	<0.001	
Extension				0.753	0.007				
<200	1	Reference				1			
≥200, <300	3.471	2.192–5.494	<0.001			1.891	0.160-22.322	0.613	
≥300, <500	9.403	5.893-15.005	< 0.001			2.647	0.230-30.522	0.435	
≥500, <600	10.352	6.569–16.312	< 0.001			3.67	0.267–50.373	0.33	
≥600, <700	25.492	16.280–39.915	<0.001			NA	NA	NA	
≥700, <999	33.745	20.947–54.362	<0.001			NA	NA	NA	
LN				0.621	0.008				
No involvement of lymph nodes	1	Reference				1			
Lymphoid involvement	2.712	2.419-3.041	<0.001			NA	NA	NA	

Table 2 (continued)

Verieble		Univariate ar	alysis			M	Multivariate analysis		
Variable	HR	95% CI	Р	C-Index	SE	HR	95% CI	Р	
Mets_dx				0.625	0.007				
0	1	Reference				1			
1–99	5.992	5.261-6.826	<0.001			1.476	0.646–3.371	0.356	
Canc_dth				0.871	0.005				
Alive or dead of other cause	1	Reference				1			
Dead	61.379	51.440-73.250	<0.001			3.98E+09	0.000–Inf	0.974	
Oth_dth				0.548	0.004				
Alive or dead due to cancer	1	Reference				1			
Dead of others	6.405	5.404-7.591	<0.001			3.30E+09	0.000–Inf	0.975	
seq_num				0.495	0.003				
One primary only	1	Reference							
1st of 2 or more primaries	1.048	0.822-1.336	0.707						
Total_malig				0.497	0.003				
1	1	Reference							
2	1.128	0.868-1.465	0.369						
3	0.892	0.287-2.771	0.844						
4	<0.001	0.000–Inf	0.981						
Total_begn				0.501	0.001				
0	1	Reference							
1	1.018	0.328–3.161	0.975						
Age_diag				0.598	0.009				
20–34	1	Reference				1			
35–39	0.686	0.519–0.906	0.008			NA	NA	NA	
40–44	0.999	0.787-1.267	0.991			NA	NA	NA	
45–49	1.333	1.064–1.670	0.012			NA	NA	NA	
50–54	1.456	1.163–1.823	0.001			NA	NA	NA	
55–59	1.429	1.125–1.815	0.003			NA	NA	NA	
60–69	1.564	1.267–1.932	<0.001			1.035	0.736–1.456	0.844	
70–99	2.617	2.110-3.246	<0.001			NA	NA	NA	
Mrit				0.567	0.008				
Single	1	Reference				1			
Married or partner	0.709	0.618–0.813	<0.001			0.913	0.789–1.055	0.218	
Separated divorced or widowed	1.204	1.045–1.387	0.01			1.161	0.990–1.360	0.066	

*, it is include non-primary surgical procedure performed, non-primary surgical procedure to other regional sites, non-primary surgical procedure to distant lymph node(s), non-primary surgical procedure to distant site and any combination of surgical procedure to other regional, distant lymph node, and/or distant site (combination of codes 2, 3, or 4). inf, infinite; NA, not application.

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Figure 2 Nomogram to predict the overall survival of cervical cancer patients at 1, 3 and 5 years. In Nomogram, draw the vertical line between the variables and a small scale, which can be drawn to obtain the scores of each variable. Survival rates were predicted based on the total score, and the vertical lines of the total score scale and the total survival scale were plotted. (A) The nomogram of the training cohort; (B) the nomogram of the verification cohort; (C) the nomogram of the total cohort.



Figure 3 Calibration and ROC curves. (A,B,C) Calibration graphs for 1-year (A), 3-year (B), and 5-year (C) survival prediction. (A), (B) and (C) are the calibration graphs of the total cohort. In the calibration graph, the Nomogram basically falls on the diagonal of 45°, indicating higher prediction accuracy. (D,E,F) ROC curves of 1-year (D), 3-year (E) and 5-year (F) survival rates for Nomogram's predictive ability. (D), (E) and (F) are the evaluation results of the total cohort. AUC is used to illustrate the results of ROC curve, A =0.804, B =0.791, C =0.771. The value is greater than 0.71 and less than 0.9, which has a high predictive value of accuracy. ROC, receiver operating characteristic.

Discussion

Cervical squamous cell carcinoma is one of the most common subtypes of cervical cancer. We conducted a practical analysis of patients in the SEER database and established a prognostic Nomogram and risk score system. Nomogram has been used to predict the survival of various cancers. The C-index, calibration, and ROC curves show that Nomogram performs well both internally and externally. Because Nomogram quantifies risk by combining and illustrating the relative importance of various prognostic factors, it has been used in clinical tumor evaluation (8). In the study, six variables were identified as independent prognostic variables for overall survival, including age, RX Summ-Surg Prim Site, and size.

Cervical cancer is one kind of cancer peculiar to women, and it is also a disease closely related to middle age. Meanwhile, there are a large number of elderly patients over the age of 55. Studies by *Landoni* and Quinn *et al.* have shown that the increase in age is an independent hazard ratio for the increased mortality of cervical cancer patients (6,9). In this study, the risk ratio of cervical cancer began to increase significantly in patients aged >45, and the 1-, 3-, and 5-year survival rates began to decline. It is well known that menopause in women between the ages of 45 and 55 results in dramatic changes in physical and psychological functioning, including a lack of sex hormones such as estrogen, as well as physical conditions (10). It is currently known that long-term exposure to sex hormones is one of the risk factors for cervical cancer (11,12). Studies have found that estrogen receptor (ER) and HPV genomes are highly displayed sequences. ER alpha receptor activated by estrogen can be combined with the control elements in the HPV gene to increase the level of HPVE6/E7 mRNA. It promotes the production of viral oncoprotein, while the progression of cervical cancer is related to the increased expression of a viral oncogene (13-15). For example, increasing estrogen levels through the long-term use of oral

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Table 3 Survival analysis of age, RX Summ-Surg Prim Site, tumor size, and 1-, 3-, and 5-year survival rates

Variable	Median survival time	1-year survival rate	3-year survival rate	5-year survival rate
Risk_level				
Training cohort				
High	48	0.79	0.566	0.455
Low	NA	0.98	0.905	0.839
Verification cohort				
High	49.8	0.795	0.559	0.488
Low	NA	0.978	0.914	0.854
Total cohort				
High	47.9	0.792	0.56	0.475
Low	NA	0.98	0.909	0.855
Age				
20–29	NA	0.914	0.789	NA
30–34	NA	0.918	0.784	NA
35–39	NA	0.946	0.849	NA
40–44	NA	0.918	0.783	NA
45–49	NA	0.903	0.74	0.65
50–54	NA	0.875	0.712	0.612
55–59	NA	0.867	0.733	0.904
60–64	NA	0.869	0.698	NA
65–74	NA	0.864	0.66	0.57
≥75	37	0.704	0.508	0.363
rx_site				
0	46.2	0.788	0.539	0.467
10–19	NA	0.938	NA	NA
20–29	NA	0.93	0.83	0.733
30–39	NA	0.977	0.941	NA
40–49	NA	0.959	0.891	0.828
50–59	NA	0.969	0.892	NA
60–64	NA	0.946	0.822	NA
65–75	22.5	0.67	NA	NA
Size				
≤30	NA	0.982	0.922	0.881
>30, ≤50	NA	0.91	0.748	0.644
>50, ≤100	41.7	0.771	0.52	0.448
>100	13.2	0.523	0.289	NA

NA, not application.



Figure 4 The survival curves of risk scores and independent prognostic factors in total cohorts with cervical cancer. P=0 means P<0.001. (A) The survival curve of the risk scores for the total cohort. According to curves, the 1-, 3- and 5-year high-risk survival rates are 79.2%, 56.0% and 47.5%, respectively, and the low-risk survival rates are 98.0%, 90.9% and 85.5%, respectively. (B) The age-related survival curve of cervical cancer patients and their 1-, 3- and 5-year survival rates. (C) The survival curve associated with the RX Summ-Surg Prim Site of cervical cancer patients and their 1-, 3- and 5-year survival rates. (D) The survival curve related to tumor size in patients with cervical cancer and their 1-, 3- and 5-year survival rates.

contraceptives significantly increases the risk of developing cervical cancer (16,17). Estrogen has been identified as one of the major drivers of cervical cancer (18), but the controlled ovarian hyperstimulation (COH) through in vitro fertilization (IVF) does not increase the risk of cervical cancer (19). Among survivors of cervical cancer, estrogen replacement therapy is also used to improve prognosis and increase survival (20). This may be mainly due to decreased expression of sex steroid hormone receptors in irradiated cervical cancer survivors (21). In this way, estrogen replacement therapy can reduce other chronic diseases after estrogen inactivation without inducing the recurrence of cervical cancer. It can be concluded from previous studies that the use of estrogen concentration, frequency, mode, period and other factors will influence the occurrence, treatment and prognosis of cervical cancer. There is an interaction between HPV and estrogen (13). We speculate that there may be two induction mechanisms of HPV. One is the viral oncoprotein, mostly premenopausal. Another is that when estrogen is not released enough after menopause, the virus directly stimulates the upregulation of ER receptors in order to obtain estrogen, so that epithelial cells excessive proliferation, thereby inducing cervical cancer. Because the second type of direct stimulation is more rapid, it may be employed as an explanation for the fact that the postmenopausal survival rate is relatively low. But further experiments are needed on exactly what kind of mechanism it is.

Surgery is one of the most effective treatments for cervical cancer. Radical hysterectomy or chemoradiotherapy is the standard treatment for patients with early cervical cancer (22,23). In this study, the recurrent mortality rate of patients with different degrees of surgery was only 8.04%, and the survival rate was higher than that without surgery. The prognosis of total hysterectomy with tubal and ovary preserved was good, and the 1- and 3-year survival rates were 97.7% and 94.1%, respectively, higher than other surgical procedures. Many studies have also shown that ovarian preservation is an important factor in determining cervical cancer surgery in young women (24,25). At the same time, the study by Zhou et al. also reported that the metastasis rate of non-squamous cell carcinoma was higher than that of squamous cell carcinoma in the case of ovarian reservation, and the metastasis rate was also increased in young patients due to the abundant vascular network. Both conditions reduce the survival rate for tubal sparing and total ovarian hysterectomy. That's why some clinical cases show the lowest survival rates for cervical cancer with surgical sterilization (24). The most common type of recurrence after hysterectomy is the pelvic region, especially in advanced cancer (stage III-IV) (4,26,27). Therefore, the postoperative residual tumor should be carefully assessed. In addition, studies have shown that for patients undergoing preoperative radiotherapy, the overall pathological remission rate of squamous cell carcinoma patients is higher than that of adenocarcinoma patients, which may be related to residual tumor and increased risk of local diseases. However, the data that we have don't have all the data on radiation therapy, so we can't compare the effects of surgery after radiation therapy. At present, hysterectomy is divided into minimally invasive and open. Studies have shown that in the early uterine tumor (stage I), minimally invasive surgery (MIS) and open surgery survival rates are similar (22), and short-term safety of MIS is higher than open surgery, with fewer complications, less pain,

faster recovery, and significantly shorter hospital stays (28). However, other studies have also proved that considering the difference in histological type and tumor size, the risk of MIS is significantly higher than that of open surgery, and the tumor size is greater than 2 cm (29,30), here we hypothesize that this may be due to differences in surgical operator ability that correlate risk with histologic type and tumor size. As opposed to early cervical cancer, multimode treatment, including hysterectomy, can also improve the survival rate of LACC patients, but its clinical role is still unclear (4,6). Urinary toxicity is the most common postoperative complication. One study found that patients who underwent hysterectomy had a twofold increased risk of urinary fistula compared to those who received specific radiation (31). Pelvic exenteration refers to the radical or sweeping resection of the entire pelvic tumor, but this surgery is very harmful to patients. In this study, only 16 patients were performed, but nearly half of the death rate was also found. In the latest Clinical Practice Guidelines for cervical cancer, patients who are locally treated with stage I-II are typically treated with a cervical or hysterectomy followed by radiotherapy. However, similar studies have shown that for cervical adenocarcinoma, chemoradiotherapy plus hysterectomy has a better survival outcome (32). Other studies have also shown that only surgery can accurately evaluate the pathological response to chemoradiotherapy, and in fact, tumors often remain after radiotherapy, which further reflects the advantages of surgical assistance in local treatment (33).

Although hysterectomy has a good prognosis and it is very difficult to maintain the fertility of young women in the future, this type of female prefers uterine-preserving surgery (UPS), but according to NCCN Clinical Practice Guidelines in Cervical Cancer, UPS is only selected for patients before stage IB1. In related studies, in patients undergoing UPS, only 58.8% of the people of the true success of retain fertility (90.8% of the patients with tumor is equal to or less than 20 mm), but this study, comparing the patients have no UPS so not to do detailed analysis (34), but at the same time to preserve fertility and good prognosis of young female patients still need to be careful choice.

Tumor size has long been considered as an independent prognostic factor affecting the survival of cervical cancer. As with the previous studies (35-37), the larger the tumor size, the lower the survival rate. Compared with other statistically significant HR, the risk ratio of tumor size was relatively high (3.071), which was also the most influential factor in Nomogram. Some studies have shown that grade in early

cervical cancer has the most significant effect on prognosis, while tumor size is the most significant in advanced cervical cancer, so the treatment is a little different (35). In our study, only total hysterectomy data were shown, but all patients with diameters of 100 mm or less had undergone a total hysterectomy to varying degrees, and the survival rate reached 80.0%. This more directly reflected in the surgery, the tumor diameter small (less than or equal to 20 mm) can use the uterus to keep operation can achieve good prognosis as well as retain complete fertility, but a hysterectomy in tumor diameter greater than 20 mm more significant effect on the survival rate, survival rate was high, should be a priority. This is more directly reflected in surgical treatment. Small-diameter tumors (less than or equal to 20 mm) can use uterine retention surgery to obtain a good prognosis while retaining intact fertility, and hysterectomy has a greater impact on survival in tumors larger than 20 mm in diameter. But overall, for tumors larger than 20 mm in diameter, the risk of surgical patients also increased with the increase in diameter (29,34,38).

We study one advantage is that it is a population-based study surveyed, the largest U.S. cancer registry. But there are limitations. First, radiotherapy and chemotherapy are the most important strategies for the treatment of cervical cancer, but there is no information on radiotherapy and chemotherapy in the SEER database, so a better treatment plan cannot be analyzed. Second, SEER lacks clinical information, especially the preoperative features and postoperative complications of hysterectomy. Also, our study found that there is a higher survival rate in total hysterectomy with the retention of ovaries and fallopian tubes than with the removal of both; Third, the study was limited to the U.S. population, and the results may not be adaptive to the global population.

In summary, our study determined that age, RX Summ-Surg Prim Site and tumor size at the distance were independent risk factors for cervical cancer. In addition, for early (stage I) or tumor diameter of less than 20 mm, minimally invasive hysterectomy had better surgical success rate and higher survival rate of the patients with uterine surgery can be preserved to keep women's fertility; Advanced cases of stage IIB and above are usually not treated with surgery. For most patients with stage III–IV or tumor diameter greater than 20 mm, chemoradiotherapy is still used.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2020.02.71). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

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Table S1 Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the training cohort

Verieble		Univar	riate analysis			Μ	ultivariate analysis	
variable —	HR	95% CI	Р	C-Index	SE	HR	95% CI	Р
Age				0.613	0.013			
20–29	1	Reference				1	Reference	
30–34	1	0.589–1.701	0.997			0.417	0.233-0.746	0.003
35–39	0.72	0.414-1.253	0.245			0.669	0.371-1.206	0.182
40–44	0.926	0.554–1.549	0.771			0.744	0.431-1.284	0.288
45–49	1.407	0.866-2.286	0.168			0.93	0.551-1.571	0.787
50-54	1 55	0.955-2.517	0.076			0.621	0.364–1.060	0.08
55-59	1.634	1 002-2 667	0.049			0.643	0.374-1.106	0.00
55-55 60 64	1 609	0.080.0.707	0.049			0.645	0.374-1.100	0.11
00-04	1.020	0.980-2.707	0.06			0.004	0.300-1.474	0.315
65-74	2.012	1.241-3.263	0.004			0.894	0.470-1.701	0.733
≥75	3.496	2.117–5.772	<0.001			1.133	0.647–1.983	0.662
Race				0.539	0.011			
Black	1	Reference				1	Reference	
White	0.622	0.497-0.779	<0.001			1.016	0.789–1.307	0.904
Other	0.553	0.385–0.794	0.001			1.28	0.854–1.921	0.232
Grade				0.578	0.012			
Grade I	1	Reference				1	Reference	
Grade II	1.821	1.161–2.858	0.009			0.648	0.403-1.040	0.072
Grade III	2.883	1.848-4.498	<0.001			0.665	0.414-1.066	0.09
Grade IV	2.167	0.921–5.097	0.076			0.313	0.122-0.803	0.016
Stage				0.756	0.011			
IA	1	Reference				1	Reference	
IB	2.305	1.086-4.889	0.03			2.016	0.205–19.823	0.548
IIA	8.831	3.967-19.660	< 0.001			1.86	0.179–19.281	0.603
IIB	7 /01	3 565-15 740	<0.001			1 59	0 164-15 449	0.689
	10 //9	6 140 25 230	<0.001			1.536	0.164 14.343	0.706
111 1)/	12.440	15 940 65 917	<0.001			1.330	0.169 17 770	0.700
	32.29	15.642-05.617	<0.001	0.750	0.014	1.720	0.100-17.770	0.040
Stag_1		5 (0.753	0.011		5 (
11a	1	Reference				1	Reference	
T1b	2.895	1.455–5.763	0.002			1.152	0.090–14.770	0.913
T2a	9.258	4.537–18.893	<0.001			0.786	0.066–9.431	0.849
T2b	9.617	4.880 –18.953	<0.001			0.285	0.035–2.314	0.24
ТЗа	25.02	12.136–51.582	<0.001			0.98	0.120-8.015	0.985
T3b	24.571	12.518–48.230	<0.001			1.52	0.188–12.281	0.695
T4	25.276	12.332–51.810	<0.001			1.094	0.131–9.117	0.934
Stag_N				0.61	0.012			
N0	1	Reference				1	Reference	
N1	2.499	2.088-2.992	<0.001			1.13	0.874-1.461	0.352
Stag_M				0.615	0.011			
M0	1	Reference				1	Reference	
M1	5.506	4.474–6.777	<0.001			0.049	0.010-0.232	<0.001
rx site				0.693	0.01			
0	1	Reference				1	Reference	
10-19	0.299	0.042-2.129	0 228			0.518	0.067-4.031	0.53
20.20	0.200	0.208 0.508	<0.001			0.010	0.657 1.467	0.00
20-29	0.422	0.290-0.398	<0.001			1.007	0.635 0.774	0.920
30-39	0.141	0.073-0.273	<0.001			0.701	0.035-2.774	0.452
40-49	0.223	0.153-0.324	<0.001			0.781	0.506-1.206	0.265
50–59	0.187	0.136–0.257	<0.001			0.858	0.595–1.236	0.411
60–64	0.366	0.214–0.625	<0.001			0.92	0.515–1.644	0.778
65–75	0.675	0.168–2.710	0.579			0.127	0.026-0.630	0.011
rx_reg				0.501	0.005			
None	1	Reference						
Other*	1.239	0.808–1.902	0.325					
Size				0.726	0.01			
≤30	1	Reference				1	Reference	
>30, ≤50	3.36	2.451-4.606	<0.001			1.151	0.815-1.626	0.424
>50, ≤100	7.87	5.918–10.468	<0.001			1.522	1.096–2.112	0.012
>100	17.793	10.334–30.637	<0.001			3.071	1.661–5.674	<0.001
Extension				0.759	0.011			
<200	1	Reference				1	Reference	
>200. <300	2.486	1.240-4.986	0.01			0.864	0.206-3.629	0.841
>300 <500	8.377	4 154–16 894	<0.001			12	0.347-4.229	0 776
>500 <600	0.563	4 856-18 836	<0.001			NA	NA	NA
≥500, <000	04.029	4.030-10.030	<0.001					
≥000, <700	24.230	12.405-47.302	<0.001				NA	
≥700, <999	24.838	12.118-50.911	<0.001			NA	NA	NA
LN				0.61	0.012			
No involvement	1	Reference				1	Reference	
Lymphoid	2 490	2.088-2 002	<0 001			NΔ	NΔ	N۵
involvement	2.700	L.000-L.39L	~0.00 I					11/7
Mets_dx				0.618	0.011			
0	1	Reference				1	Reference	
1–99	5.544	4.509-6.815	<0.001			35.55	7.917–159.604	<0.001
Canc_dth		-		0.871	0.008			
Alive or dead of	1	Reference				1	Reference	
other cause	-							
Dead	56.66	43.150–74.390	<0.001			3.76E+09	0–inf	0.982
Oth_dth				0.547	0.007			
Alive or dead	1	Reference				1	Reference	
due to cancer								
Dead of others	6.236	4.779–8.138	<0.001			2.88E+09	0–inf	0.982
Seq_num				0.511	0.005			
One primary	1	Reference						
only								
1st of 2 or more	0.814	0.548–1.210	0.309					
				0 51	0.004			
iotal_malig				U.51	U.UU4			
1	1	Reference	-					
2	0.776	0.490–1.227	0.278					
3	0.914	0.128-6.506	0.929					
Total_begn				0.502	0.001			
0	1	Reference						
1	<0.001		0.986					
Age_diag				0.613	0.013			
20–34	1	Reference				1	Reference	
35–39	0.719	0.461–1.123	0.148			NA	NA	NA
40–44	0.926	0.624–1.374	0.702			NA	NA	NA
45–49	1.406	0.984–2.009	0.061			NA	NA	NA
50–54	1.55	1.086-2.211	0.016			NA	NA	NA
55–59	1.634	1.137–2.347	0.008			NA	NA	NA
60-69	1.694	1.211_2 360	0.002			0.97	0.566-1 661	0.91
70_99	3 011	2 143-1 2000	<0.002			NA	NIA	NA
, J JJ	0.011	£.1+0 ⁻ 4.∠3U	<u>_0.001</u>	0 504	0.010	11/7	11/21	11/4
Cinala	4	Deferrer		0.364	0.013	4	Deferrer	
Single	1		0.000			1		0.055
iviarried or partner	U./17	0.575-0.894	U.U03			U.978	U./68–1.245	U.857
Separated	1.387	1.115–1 725	0.003			1.271	0.981-1.648	0.07
divorced or		0 1.120	5.000				0.001 1.040	5.01
widowed								

*, it is include non-primary surgical procedure performed, non-primary surgical procedure to other regional sites, non-primary surgical procedure to distant lymph node(s), non-primary surgical procedure to distant site and any combination of surgical procedure to other regional, distant lymph node, and/or distant site (combination of codes 2, 3, or 4). inf, infinite; NA, not application.

Variable			Training cohort			Ň	Verification cohort	
variable —	HR	95% CI	Р	C-Index	SE	HR	95% CI	Р
Age				0.59	0.012			
20-29	1	Reference	0.000			1	Reference	0.000
30-34	0.99	0.641-1.530	0.966			0.817	0.516-1.294	0.389
40-44	1.034	0.684-1.564	0.873			0.647	0.419-1.007	0.05
45-49	1.274	0.848-1.914	0.244			0.521	0.335-0.808	0.004
50–54	1.388	0.925–2.085	0.114			0.682	0.439–1.057	0.087
55–59	1.276	0.831-1.959	0.266			0.617	0.388-0.982	0.042
60–64	1.419	0.928-2.170	0.106			0.66	0.342-1.272	0.214
65–74	1.571	1.043-2.367	0.031			0.752	0.438-1.289	0.3
≥75	2.946	1.945–4.464	<0.001			0.803	0.507-1.274	0.352
Race				0.519	0.009			
Black	1	Reference	0.011			1	Reference	0.000
Other	0.778	0.641-0.944	0.011			1.0946	0.768-1.165	0.602
Grade	0.772	0.579-1.020	0.077	0.564	0.01	1.094	0.004-1.400	0.309
Grade I	1	Reference		0.001	0.01	1	Reference	
Grade II	2.175	1.424–3.323	<0.001			0.916	0.582-1.443	0.706
Grade III	3.055	2.004-4.656	<0.001			0.939	0.598–1.476	0.786
Grade IV	3.191	1.555-6.546	0.001			1.795	0.830–3.881	0.137
Stage				0.773	0.008			
IA	1	Reference				1	Reference	
IB	3.517	1.830-6.756	<0.001			1.244	0.138–11.167	0.846
IIA	11.004	5.410-22.384	<0.001			1.488	0.159-13.959	0.728
IIB	7.63	3.903-14.915	<0.001			1.565	0.173-14.135	0.69
IV	46.171	24.497-87.024	<0.001			1.401	0.196–17.893	0.587
Stag_T				0.745	0.009			
T1a	1	Reference				1	Reference	
T1b	4.348	2.418–7.816	<0.001			0.9	0.115–7.039	0.92
T2a	10.273	5.541-19.046	<0.001			0.84	0.108-6.517	0.868
T2b	10.103	5.603-18.214	<0.001			0.845	0.070-10.214	0.894
T3a	26.967	14.466–50.269	<0.001			1.314	0.162–10.672	0.798
T3b	24.197	13.511–43.337	<0.001			1.31	0.161–10.622	0.801
14 Stan N	აყ.286	21.221-12.709	<0.001	0 620	0.01	1.407	11.944–1944	U.154
NO	1	Reference		0.029	0.01	1	Reference	
N1	2.866	2.470-3.325	<0.001			1.16	0.934-1.441	0.178
stag_M	-	*		0.628	0.009	-	-	
M0	1	Reference				1	Reference	
M1	6.349	5.362-7.518	<0.001			1.332	0.434-4.092	0.617
rx_site				0.712	0.008			
0	1	Reference				1	Reference	
10–19	0.226	0.056-0.907	0.036			0.764	0.176-3.320	0.719
20-29	0.273	0.198-0.375	<0.001			1.037	0.735-1.462	0.838
30-39 40-49	0.078	0.037-0.164	<0.001			0.809	0.563-1.140	0.002
50-59	0.208	0.166-0.262	<0.001			0.69	0.531-0.898	0.006
60–64	0.276	0.170-0.447	<0.001			0.861	0.512-1.448	0.573
65–75	1.753	0.784–3.922	0.172			1.226	0.505–2.977	0.652
rx_reg				0.507	0.003			
None	1	Reference						
Other*	0.77	0.512-1.156	0.207					
Size		- /		0.731	0.009		5.4	
≤30 × 00 × 50	1	Reference	0.001			1	Reference	0.50
>30, ≤50	3.754 7.811	2.908-4.840 6 187-9 862	<0.001			1.081	1 162_2 027	0.59
>100	16.9	11.786-24.233	<0.001			1.678	1.102-2.556	0.016
Extension				0.749	0.009			
<200	1	Reference				1	Reference	
≥200, <300	4.292	2.322-7.934	<0.001			1.364	0.074–25.198	0.835
≥300, <500	10.231	5.464–19.157	<0.001			1.936	0.108–34.725	0.654
≥500, <600	10.907	5.907-20.140	<0.001			1.375	0.053–35.469	0.848
≥600, <700	26.619	14.554–48.683	<0.001			NA	NA	NA
≥700, <999	42.235	22.297-80.002	<0.001			NA	NA	NA
LN	1	Poforonco		0.629	0.01	1	Poforonco	
involvement	I	Reference				I	Reference	
of lymph nodes								
Lymphoid	2.866	2.470-3.325	<0.001			NA	NA	NA
involvement								
Mets_dx		- /		0.63	0.009		5.4	
0	1	Reference	-0.001			1	Reference	0.997
Canc dth	0.329	5.351-7.400	<0.001	0.871	0.006	1.077	0.300-2.900	0.007
Alive or	1	Reference		0.071	0.000	1	Reference	
dead of		-						
Dead	64 745	51 300-81 720	<0.001			3 39F+09	0 000–Inf	0 979
Oth_dth				0.549	0.006			-
Alive or	1	Reference				1	Reference	
dead due to cancer								
Dead of	6.509	5.220-8.117	<0.001			3.38E+09	0.000–Inf	0.979
others								
Seq_num				0.498	0.004			
One primary only	1	Reference						
1st of 2	1.255	0.922-1.709	0.149					
or more primaries								
Total_malig				0.503	0.004			
1	1	Reference				1	Reference	
2	1.428	1.038–1.965	0.029			0.583	0.408–0.832	0.003
3	0.881	0.220–3.531	0.858			0.189	0.042–0.856	0.031
4	<0.001	0.000–Inf	0.988			0.777	0.000–Inf	1
Total_begn		_		0.502	0.002			
0	1	Reference	0.005					
1 Age dies	2.684	0.863-8.344	U.U88	0 500	0.010			
Age_alag	1	Reference		0.588	0.012	1	Reference	
20 - 34 35 <u>-</u> 39	і 0.664	0.464_0 950	0.025			I NA	NA	NA
40-44	1.041	0.772-1 404	0.793			NA	NA	NA
45–49	1.282	0.959–1.714	0.094			NA	NA	NA
50–54	1.397	1.046-1.867	0.024			NA	NA	NA
55–59	1.284	0.932-1.769	0.126			NA	NA	NA
60–69	1.486	1.132–1.950	0.004			1.001	0.629–1.593	0.997
70–99	2.387	1.808–3.153	<0.001			NA	NA	NA
Mrit		_		0.556	0.011		-	
Single	1	Reference	0.001			1	Reference	0.470
iviarried or partner	0.702	ບ.ວອບ–0.835	<0.001			U.878	u. <i>121</i> -1.060	U.1/6
Separated	1.084	0.899–1.306	0.399			1.057	0.858–1.304	0.601
divorced or widowed								

Table S2 Univariate and multivariate Cox proportional risk regression models and statistically significant independent risk factors for cervical cancer in the verification cohort

*, it is include non-primary surgical procedure performed, non-primary surgical procedure to other regional sites, non-primary surgical procedure to distant lymph node(s), non-primary surgical procedure to distant site and any combination of surgical procedure to other regional, distant lymph node, and/or distant site (combination of codes 2, 3, or 4). inf, infinite; NA, not application.



Figure S1 The calibration graphs. The Nomogram basically falls on the diagonal of 45°, indicating higher prediction accuracy. (A,B,C) The calibration graphs for 1-year (A), 3-year (B), and 5-year (C) survival prediction in the training cohort. (D,E,F) The calibration graphs for 1-year (D), 3-year (E), and 5-year (F) survival prediction in the verification cohort.



Figure S2 ROC curves in the training cohort and the verification cohort. (A,B,C) ROC curves of 1-year (A), 3-year (B) and 5-year (C) survival rates for Nomogram's predictive ability in the training cohort. AUC is used to illustrate the results of ROC curve, A =0.841, B =0.8, C =0.795. (D,E,F) ROC curves of 1-year (D), 3-year (E) and 5-year (F) survival rates for Nomogram's predictive ability in the verification cohort. AUC is used to illustrate the results of ROC curve, D =0.84, E =0.825, F =0.791. The value is greater than 0.71 and less than 0.9, which has a high predictive value of accuracy. ROC, receiver operating characteristic; AUC, area under the curve.



Figure S3 The survival curve of cervical cancer patients was obtained according to the risk score system. (A) The survival curve of the risk score for the training cohort; (B) the survival curve of the risk score for the verification cohort.