A Prognostic Model using FIGO 2018 Staging and MRI- derived Tumor Volume to Predict Long-term Outcomes in Patients with Uterine Cervical Squamous Cell Carcinoma Who Received Definitive Radiotherapy

Lele Zang
Fujian Medical University Cancer Hospital, Fujian cancer Hospital
Qin Chen
Fujian Medical University Cancer Hospital, Fujian cancer Hospital
An Lin
Fujian Medical University Cancer Hospital, Fujian cancer Hospital
Jian Chen
Fujian Medical University Cancer Hospital, Fujian cancer Hospital
Xiaozhen Zhang
University of Traditional Chinese Medicine
Yi Fang
University of Traditional Chinese Medicine
Min Wang (wangmin20220505@163.com)
Fujian Medical University Cancer Hospital, Fujian cancer Hospital

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Abstract

Background

Uterine cervical carcinoma is a severe health threat worldwide, especially in China. The International Federation of Gynecology and Obstetrics (FIGO) has revised the staging system with emphasise the strength of magnetic resonance imaging (MRI). We aim to investigate long-term prognostic factors for FIGO 2018 stage II-IIIC2r uterine cervical squamous cell carcinoma following definitive radiotherapy and establish a prognostic model using MRI-derived tumor volume.

Methods

Patients were restaged according to the FIGO 2018 staging system and randomly grouped into training and validation cohorts (7:3ratio). Optimal cutoff values of squamous cell carcinoma antigen (SCC-Ag) and tumor volume derived from MRI for the training cohort were generated. A nomogram was onstructed based on overall survival (OS) predictors, which were selected using univariate and multivariate analyses. The performance of the nomogram was validated and compared with the FIGO 2018 staging system. Risk stratification cutoff points were generated, and survival curves of low-risk and high-risk groups were compared.

Results

We enrolled 396 patients (training set, 277; validation set,119). The SCC-Ag and MRI-derived tumor volume cutoff values were 11.5 ng/mL and 28.85 cm3, respectively. A nomogram was established based on significant prognostic factors, including SCC-Ag, poor differentiation, tumor volume, chemotherapy, and FIGO 2018 stage. Decision curve analysis indicated the net benefits of our model were higher. The high-risk group had significantly shorter OS than the low-risk group in both the training ($p < 0.0001$) and validation sets ($p = 0.00055$).

Conclusions

Our nomogram predicted long-term outcomes in patients with FIGO 2018 stage II-IIIC2r uterine cervical squamous cell carcinoma. This tool could assist both gynecologic oncologists and patients in treatment planning and prognosis.

Introduction

Uterine cervical carcinoma ranks fourth among malignant tumors for women worldwide, after breast cancer, colorectal cancer, and lung cancer. In China, it is also the fourth leading cause of cancer death among women and is the most prevalent cancer in women (1). Most uterine cervical carcinomas are

squamous cell carcinomas, and the main therapies are surgery, radiotherapy, and chemotherapy. However, surgery is recommended only for early-stage patients, and most patients are at advanced stages when diagnosed; thus,radiotherapy or chemoradiotherapy play a crucial part in the treatment of these patients (2).

The International Federation of Gynecology and Obstetrics (FIGO), a global professional organization, developed a staging system for independent prognostic risk factors that have been widely accepted and used in clinical practice. The FIGO staging system is a clinical staging system, based primarily on physical examination findings. In the FIGO 2009 staging system, lymph node metastasis was not included as a prognostic factor, despite it being proven to be a strong prognostic factor for uterine cervical carcinoma by several studies (3, 4). Therefore, the FIGO staging system was revised in 2018 and 2019 to account for lymph node status and emphasize the role of imaging in prognosis (5, 6).

A nomogram can convert complicated results of multivariate analyses into a visual graph that is simple and easy to understand. There have been many studies on establishing a prognostic model using a nomogram for patients with uterine cervical carcinoma who received definitive radiotherapy (7–9). However, these studies did not use the latest FIGO 2018 staging system.

Magnetic resonance imaging (MRI) plays a central role in the staging of uterine cervical cancer because it provides excellent contrast resolution, especially for soft tissue, and offers multiparametric imaging. Therefore, it has the advantages of delineating tumor extent and discriminating lymph node metastasis with accuracy (10–12). Numerous studies have shown that tumor diameter is an independent prognostic risk factor for uterine cervical carcinoma (8, 13, 14).

However, for a malignant tumor, it is inaccurate to estimate the tumor volume based only on a single diameter because of its complicated and irregular shape. Kim et al. demonstrated that MRI-derived pretreatment tumor volume, but not pretreatment tumor diameter, was significantly correlated with the prognosis of patients with uterine cervical carcinoma who received concurrent chemotherapy and radiotherapy(15).

This study aimed to investigate the long-term prognostic factors in patients with uterine cervical squamous cell carcinoma who received definitive radiotherapy and develop a model to predict prognosis in the context of the FIGO 2018 staging system and the widespread application of MRI.

Methods

Participants

We reviewed the medical records of patients with uterine cervical carcinoma who were diagnosed between 2013 and 2014 and received definitive radiotherapy in our institute. Cases of pathologically confirmed squamous cell carcinoma of the uterine cervix that was restaged as stage II-IIIC2r according to the FIGO 2018 staging system and received definitive radiotherapy and underwent an enhanced

abdominopelvic MRI scan prior to treatment were enrolled (The flowchart is shown in Fig. 1). Patients with any of the following circumstances were excluded from the study: radiographic evaluation other than MRI, missing data, secondary cancer, or refusal to participate in this study. Overall survival (OS) was defined as the time between diagnosis and death.

MRI analysis

A superconducting MRI scanner (Signa 1.5T Excite iii HD, GE) was used to obtain the images before any treatment was started. The MRI scan sequences included fast spin echo (FSE), T1-weighted imaging (T1WI), FSE T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and coronal FSE T2WI. DWI was performed using a spin echo, plane echo sequence. After plain scanning, gadopentetic acid was injected at 3 mL/s through the cubital vein at 0.1 mmol/kg, and then axial, sagittal, and coronal scans using a liver acquisition with volume acceleration sequences were carried out on gradient echo T1WI of 3D volumetric interpolation. On axial T2-weighted images showing the largest tumor, tumor length was defined as the largest diameter in the left-right direction and tumor width as the vertical diameter in the anterior-posterior direction. On sagittal T2- weighted images showing the largest tumor, tumor thickness was defined as the longest diameter in the foot-head direction. The tumor volume was calculated using the following equation: π × tumor length (cm) × tumor width (cm) × tumor thickness(cm)/6 = V. Enlarged lymph nodes with short diameters of >1 cm were considered to be metastatic lymph nodes. All MRI data and medical records were retrospectively reviewed and confirmed by two radiologists with more than 10 years of experience in interpreting gynecologic oncology images.

Definitive radiotherapy

All patients received definitive radiotherapy. Radiotherapy in this study consisted of two parts: external beam radiotherapy (EBRT) and brachytherapy. In EBRT, some patients received conventional radiotherapy, while others received intensity-modulated radiotherapy, which was administered through 6 MV photons once a day, 5 days a week. The prescription dose of EBRT was 45-56 Gy at 1.8-2.0 Gy per fraction. Patients with FIGO 2018 stage IIIc2r or IIIc1r with common iliac lymph node metastasis received extended-field irradiation, which included both the whole pelvic and the para-aortic lymph node area. All these patients received high-dose-rate brachytherapy, which was started 2 weeks after the beginning of EBRT and was performed once a week, with the A point dose of 7 Gy per fraction. Brachytherapy was administered 3-7 times. Subsequently, both the EBRT and brachytherapy doses were converted into 2-Gy equivalent doses (EQD2), respectively, using the following linear-quadratic model: prescription dose × (α/β + fractionated dose)/ (α/β + 2) = EQD2, where α/β = 10.

The EQD2 forEBRT and brachytherapy were then summed up to obtain the dose for analysis in this study.

Chemotherapy

Most patients in this study received chemotherapy, except for those who were older, had contraindications, and refused to receive it. These patients also received different chemotherapy regimens, including single-agent or concurrent paclitaxel and platinum regimens, taxane-platinum regimen, gemcitabine plus platinum regimen in case of allergic reaction to paclitaxel, and taxane-platinum plus bleomycin interventional chemotherapy in those with a bulky tumor. Considering these scenarios, we included the presence of chemotherapy as a factor in the analysis.

Statistical analysis

Patient information was anonymized prior to analysis. Using computer-generated random numbers, we grouped the patients into training and validation cohorts at a ratio of 7:3. The function “surv_cutpoint” in the R package “survminer” as implemented to generate the optimal cutoff values of squamous cell carcinoma antigen (SCC-Ag) and tumor volume for the training cohort (16). Continuous parameters presented as means ± standard deviation or medians with interquartile ranges were compared between the training and validation sets using Student’s t-test or the Mann–Whitney U test, as appropriate. The chi-squared test or Fisher’s exact test was used to compare the frequency distribution of categorized parameters.

A nomogram was constructed based on significant predictors of overall survival (OS) selected by multivariate Cox proportional hazards regression using a stepwise selection method that included variables with a p-value of <0.05 in the univariate analysis and of clinical importance. In the nomogram, points were assigned by drawing a line upward from the corresponding values to the “Points” line. The sum of the points, plotted on the “Total Points” line, corresponds to predictions of 3-year, 5-year, and 7-year OS rates in patients with uterine cervical squamous cell carcinoma. Based on the concordance index (C-index) and the area under the time-dependent receiver operating characteristic curve (AUC), the predictive accuracy of the constructed nomogram was evaluated. Calibrating this constructed nomogram, we used bootstraps of 1000 resamples with calibration curves. The performance of the nomogram was internally validated using the validation set and compared with that of the FIGO 2018 staging system. To measure the improvement in the predictive effect of our model, we used the net reclassification improvement (NRI) and integrated discrimination improvement (IDI). It is only possible to evaluate a diagnostic method by assessing its receiver operating characteristic curve from the specificity and sensitivity plot, and although this is accurate, the patients are not guaranteed to benefit from it. A method of evaluating devised by Vickers et al. was called decision curve analysis (DCA), which is capable of calculating the net benefits of the model. In this study, the sum score of each patient was calculated from the nomogram. Subsequently, cutoff points for risk stratification (low and high) were generated using the “surv_cutpoint” function of “survminer.” The log-rank test was used to compare the Kaplan–Meier survival curves of low-risk and high-risk groups using the training and validation sets. Our statistical analyses were performed using R software (version 4.0.3). We considered a p-value of 0.05 to be statistically significant.

Results

Patient OS and grouping

A total of 484 patients with uterine cervical squamous cell carcinoma were restaged according to the FIGO 2018 staging system. Four patients who had other malignancies, 72 patients who underwent non-MRI scanning prior to any treatment, and 12 patients who were lost to follow-up were excluded. Finally, 396 patients were enrolled in this study. The date of the last follow-up was December 12, 2021. The median follow-up time was 89.77 months. The 3-year, 5-year, and 7-year OS rates were 87.1%, 83.3%, and 81.8%, respectively.

Cutoff values, patient characteristics, and results of univariate and multivariate analyses of factors for OS

In total, 277 and 119 patients were randomized to the training and validation sets, respectively. The cutoff value of SCC-Ag derived from the training set was 11.5 ng/mL (Fig. 2). The cutoff value of tumor volume derived from MRI was 28.85 cm^3 using the same method as that for SCC-Ag (Fig. 3). SCC-Ag and tumor volumes were converted into categorical variables depending on their cutoff values. The patient characteristics in both the training and validation sets are shown in Table 1. There were no significant differences between the training and validation sets in terms of age at diagnosis, SCC-Ag level, MRI-derived tumor volume, radiotherapy modality, presence of chemotherapy, time of radiotherapy, EQD_2 of point A, pathologically poor differentiation, hemoglobin level before treatment, status of parametrial invasion, FIGO 2018 stage, and survival status. In the multivariate analysis, SCC-Ag level, pathologically poor differentiation, MRI-derived tumor volume, presence of chemotherapy, and FIGO 2018 stage were found to be significant prognostic factors for uterine cervical squamous cell carcinoma (Table 2).

Table 1
Patients' characteristics for both training set and validation set.

Variables	Training set n = 277	Validation set n = 119	P value
Age (year, meas ± standard deviation)	55.0 ± 9.5	54.2 ± 9.9	0.4622
SCC-Ag			0.708
≤ 11.5ng/ml	200(72.20%)	83(69.75%)	
11.5ng/ml	77(27.80%)	36(30.25%)	
Tumor volume(cm^3)			0.6936
≤ 28.85	131(47.29%)	53(44.54%)	
>28.85	146(52.71%)	66(55.46%)	
Poor differentiation			0.853
No	229(82.67%)	100(84.03%)	
Yes	48(17.33%)	19(15.97%)	
Hemoglobin concentration(g/L)			0.4388
≥ 120	209(75.45%)	83(69.75%)	
90g/L ~ 119	46(16.61%)	26(21.85%)	
< 90	22(7.94%)	10(8.40%)	
Parametrial invasion			0.6113
No	24(8.66%)	10(8.40%)	
Parametrial invasion	139(50.18%)	66(55.46%)	
Pelvic wall extension	114(41.16%)	43(36.13%)	
FIGO2018 stage			0.4027
	97(35.02%)	49(41.18%)	
a& b	64(23.10%)	19(15.97%)	
c1r	99(35.74%)	43(36.13%)	
c2r	17(6.14%)	8(6.72%)	
Chemotherapy			0.5438
No	53(19.13%)	19(15.97%)	
Yes	224(80.87%)	100(84.03%)	

Variables	Training set n = 277	Validation set n = 119	P value
Radiotherapy modality			0.6598
Conventional radiotherapy	157(56.68%)	71(59.66%)	
IMRT	120(43.32%)	48(40.34%)	
Time of radiotherapy(day)			0.3521
≤ 56	101(36.46%)	50(42.02%)	
>56	176(63.54%)	69(57.98%)	
EQD2 dose of point A(Gy)			0.8446
≤ 85	45(16.25%)	21(17.65%)	
> 85	232(83.75%)	98(82.35%)	
Status			0.6846
Alive/Censored	224(80.87%)	99(83.19%)	
Dead	53(19.13%)	20(16.81%)	
Abbreviation: SCC-Ag, squamous cell carcinoma antigen. FIGO, International Federation of Gynecology and Obstetrics. IMRT, intensity modulated radiation therapy. EQD2, 2Gy equivalent dose.			

Table 2
Univariate analysis and multivariate Cox proportional hazards regression of training set using a stepwise-selection method.

Variables	Univariate analysis		Multivariate analysis	
	Coefficient (95%CI)	*P* value	Coefficient(95%CI)	*P* value
Age	0.99(0.96–1.02)	0.677		
SCC-Ag (ng/ml)				
≤ 11.5	Reference		Reference	
>11.5	2.59(1.51–4.44)	0.001	1.91(1.07–3.42)	0.028
Tumor volume (cm^3)				
≤ 28.8	Reference		Reference	
>28.8	3.89(2.00-7.56)	0.000	2.84(1.40–5.74)	0.004
Poor differentiation				
No	Reference		Reference	
Yes	2.33(1.29–4.18)	0.005	2.81(1.52–5.19)	< 0.001
Hemoglobin concentration (g/L)				
≥ 120	Reference			
90g/L ~ 119	2.10(1.12–3.94)	0.021		
< 90	2.49(1.10–5.64)	0.029		
Parametrial invasion				
No	Reference			
Parametrial invasion	1.20(0.36–4.03)	0.764		
Pelvic wall extension	2.19(0.67–7.18)	0.197		
FIGO2018 stage				
	Reference		Reference	
a& b	1.99(0.79–5.05)	0.146	1.42(0.55–3.70)	0.469
c1r	3.80(1.73–8.34)	0.001	2.45(1.07–5.60)	0.034
c2r	6.20(2.25–17.12)	0.000	4.26(1.49–12.17)	0.007
Chemotherapy				

Variables	Univariate analysis		Multivariate analysis	
	Coefficient (95%CI)	*P* value	Coefficient(95%CI)	*P* value
No	Reference		Reference	
Yes	0.71(0.38–1.32)	0.277	0.50(0.27–0.96)	0.037
Radiotherapy modality				
Conventional radiotherapy	Reference			
IMRT	1.26(0.74–2.16)	0.399		
Time of radiotherapy(day)				
≤ 56	Reference			
>56	1.37(0.76–2.47)	0.289		
EQD2 dose of point A(Gy)				
≤ 85	Reference			
> 85	1.60(0.69–3.75)	0.277		
Abbreviation: SCC-Ag, squamous cell carcinoma antigen. FIGO, International Federation of Gynecology and Obstetrics. IMRT, intensity modulated radiation therapy. EQD2, 2Gy equivalent dose.				

Establishment and evaluation of the prognostic model

The established nomogram for predicting OS is shown in Fig. 4. The corresponding score can be calculated through the top “Points” line of the nomogram for each prognostic factor, and then the 3-year, 5-year, and 7-year OS could be estimated by summing up the individual scores and checking the “Total Points” line at the bottom. The C-indices of our nomogram for the training and validation sets were 0.74 (95% confidence interval [CI]: 0.67–0.80) and 0.70 (95% CI: 0.57–0.82), respectively, while those of the FIGO 2018 staging system were 0.66 (95% CI: 0.59–0.73) and 0.63 (95% CI: 0.52–0.75)(Table 3). For our model, the AUCs of the validation set for 3-year, 5-year, and 7-year OS were 0.67, 0.68, and 0.71, respectively. Meanwhile, the corresponding AUCs of the FIGO 2018 staging system were 0.65, 0.66, and 0.65. Notably, our model had higher C-indices and AUCs than the FIGO 2018 staging system, suggesting that our model has a better discrimination ability than the FIGO staging system (Fig. 5). Calibration curves with bootstraps of 1000 resamples also indicated a good agreement between the predicted OS and observed outcomes (Fig. 6).

Table 3
Comparison of C-index for our model and FIGO2018 stage system.

Group	Nomogram (95%CI)	FIGO2018 (95%CI)
Training set	0.74(0.67–0.80)	0.66 (0.59–0.73)
Validation set	0.70 (0.57–0.82)	0.63 (0.52–0.75)
FIGO, International Federation of Gynecology and Obstetrics.		

As shown in Table 4, the NRI values of our nomogram for 3-year, 5-year, and 7- year OS were 0.21, 0.38, and 0.38, respectively, in the validation set (all $p < 0.01$); the corresponding IDI values were 0.08, 0.14, and 0.10 (all $p < 0.01$). These values suggest that the predictive performance of our nomogram was substantially improved. DCA indicated that the net benefits of our model were higher than those of the FIGO staging system at 3, 5, and 7 years (Fig. 7).

Table 4
The NRI and IDI of the nomogram in overall survival prediction for squamous cell uterine cervical carcinoma patients received definitive radiotherapy compared with FIGO2018 stage system in validation set.

Index	Estimate	95% CI	P value
NRI (vs. FIGO2018 stage)			
For 3-year OS	0.21	0.07–0.36	< 0.01
For 5-year OS	0.38	0.23–0.53	< 0.001
For 7-year OS	0.38	0.20–0.56	< 0.001
IDI (vs. FIGO2018 stage)			
For 3-year OS	0.08	0.03–0.13	< 0.01
For 5-year OS	0.14	0.08–0.19	< 0.001
For 7-year OS	0.10	0.005–0.15	< 0.001
Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.NRI, net reclassification improvement. IDI, integrated discrimination improvement. OS, overall survival.			

Risk stratification by the nomogram

The cutoff point for risk stratification (low and high) was 171.21, based on the scores of patients in the training group. The OS of patients in the high-risk group was significantly shorter than that in the low-risk group in both the training ($p < 0.0001$) and validation sets ($p = 0.00055$) (Fig. 8).

Discussion

We established a prognostic model to predict the long-term OS of patients with FIGO 2018 stage II-IIIC2r uterine cervical squamous cell carcinoma who received definitive radiotherapy. In this study, we found that factors such as the SCC-Ag level, pathologically poor differentiation, tumor volume derived from MRI prior to treatment, FIGO 2018 stage, and presence of chemotherapy were predictors of prognosis in these patients.

SCC-Ag levels are elevated in 28–88% of patients with uterine cervical squamous cell carcinoma (17). However, the cutoff value of SCC-Ag for predicting the prognosis of uterine cervical carcinoma remains controversial, with some researchers unable to demonstrate any predictive ability of the parameter at all (18). In contrast, several researchers demonstrated that SCC-Ag levels alone or in combination with other factors were significantly correlated with the prognosis and even had the capacity to predict the efficacy of treatment or risk of recurrence (19– 22). SCC-Ag, which was discovered by Kato et al., is a characteristic biomarker for squamous cell carcinoma (23). SCC-Ag expression emerges synchronously with the squamous formation of the uterine cervix and increases during the neoplastic transformation of the cervical squamous epithelium (24). Murakami et al. showed that SCC-Ag could promote radio-resistance of tumor cells by suppressing radiation-induced cell death (25).

Brambs et al. reexamined the histological slides of 467 patients with surgically treated FIGO stage IB1-IIB uterine cervical carcinoma and found that binary grading (grade 1/2 vs. grade 3) may be more suitable for evaluating prognostic survival than conventional tumor grading based on the degree of keratinization (26). This is also the reason we only considered poor differentiation, and not tumor grade, in our analysis, and our results are consistent with those of other studies. Studies by Xie et al. and Luo et al. found that patients with poor differentiation (grade 3) had a significantly worse OS than those with grade 1/2 uterine cervical carcinoma in the early stage (FIGO stages IA2-IIB) (27, 28). Using data from 31,536 women with uterine cervical squamous cell carcinoma extracted from the Surveillance, Epidemiology, and End Results (SEER) Program between 1983 and 2013, Matsuo et al. found that grade 3 tumors (poor differentiation) were independently associated with decreased cause-specific survival, especially among patients with stage II-III disease (29). These findings could be attributed to the keratin pattern being a component of aggregated cervical squamous cell carcinoma and being related to survival (30). On the contrary, Kumar et al. analyzed patients who were diagnosed with uterine cervical squamous cell carcinoma between 1988 and 2004, using limited data from the SEER Program, and figured out that nonkeratinized squamous cell carcinoma, rather than keratinized squamous cell carcinoma, may be more radiosensitive and associated with a better prognosis (31). Notably, the racial composition of the Asian population was 11.4%, and the proportion of poorly differentiated cases in our study was approximately 16% – a reason

why the results of the above-mentioned studies are different from ours and why our findings are only applicable to Chinese patients.

FIGO 2018 is a clinical staging system based on physical exam and imaging. Gynecologists rely heavily on physical examination when evaluating primary tumors. However, palpation as a component of physical examination is a subjective method that can only determine the axial diameter of the tumor but cannot estimate the contribution of normal cervical tissue. Thus, clinical estimation of tumor size through palpation cannot adequately represent the actual tumor volume (32). Narayan et al. demonstrated in their study that tumor volume measured using MRI accurately reflected the extent of local disease and could be used as an objective measurement of the primary site of cervical cancer (33). Other researchers also demonstrated that an increase in tumor volume is associated with lymph node metastasis and poor prognosis (34, 35). Some investigators have even observed that MRI-derived tumor volume provides important prognostic information that is more accurate and useful than that provided by the FIGO staging system (36). However, the staging system used in all these studies was not the FIGO 2018 staging system. In our results, MRI-derived tumor volume was a critical prognostic factor for FIGO 2018 stage II-IIIC2r uterine cervical squamous cell carcinoma.

The FIGO staging system is widely used in the clinical management of uterine cervical carcinoma and is a paramount factor affecting the outcome of treatment. However, there are other prognostic factors that must be considered. Lymph node metastasis could strongly decrease the survival of patients with uterine cervical carcinoma, and in this regard, the FIGO 2018 staging system defined stage IIIC1 as pelvic lymph node metastasis and stage IIIC2 as para-aortic lymph node metastasis, both of which can be suffixed with the letter “r” or “p” to refer to a radiological or pathological finding, respectively (5). Therefore, we contrasted a nomogram using the FIGO 2018 staging system and other clinical factors, with emphasis on MRI-derived tumor volume. NRI and IDI are indices indicating how a model's predictive power improves after a new risk factor or factors are introduced. A value of > 0 indicates improvement. In this study, the NRI and IDI values for 3-year, 5-year, and 7-year OS were all > 0, suggesting that our model achieved a better predictive ability than the FIGO 2018 staging system. Thus, our nomogram could offer patients accurate individual predictions. Moreover, since chemotherapy as a therapeutic factor was included in our model, this means that chemotherapy may improve the OS of patients. This could be a very useful parameter to gynecologic oncologists when creating treatment plans and to patients when deciding to accept those plans. For instance, if a virtual 59-year-old patient with a pathologically confirmed uterine cervical squamous cell carcinoma, whose FIGO stage is b, pretreatment SCC-Ag level is 15.0ng/mL, and MRI-derived tumor volume is 35 cm3, decides to undergo chemotherapy, the total score for all parameters calculated from the nomogram will be 139, and the predictive 3-year, 5-year, and 7-year OS will be 86%, 80%, and 78%, respectively. However, if she refuses to have chemotherapy, the total score will be 187, and the predictive 3-year, 5-year, and 7-year OS will be 73%, 63%, and 60%. Radiotherapy without chemotherapy is associated with an apparent decrease in OS.

There have been several nomograms established by other researchers to predict uterine cervical carcinoma following radiotherapy (9, 37, 38). Other researchers explored the predictive accuracy of the

FIGO 2018 staging system and other significant prognostic factors; however, they have not investigated the value of MRI-derived tumor volume in predicting the prognosis of patients (39, 40). To our knowledge, this nomogram is the first long-term model to predict OS in patients with uterine cervical squamous cell carcinoma who received definitive radiotherapy, using the FIGO 2018 staging system and pretreatment tumor volume derived from MRI.

This study has some limitations. First, it is a retrospective study and is therefore prone to selection bias. Second, our prediction model was developed using data from a single institution and therefore needs to be further validated externally. Third, the chemotherapy regimens in this study were heterogeneous: Some patients, who had the opportunity to have surgery or had a strong willingness to undergo further treatment, received neoadjuvant chemotherapy. A proportion of patients received neoadjuvant chemotherapy due to unsatisfactory tumor shrinkage or abnormal SCC-Ag level after radiotherapy, with common iliac artery or para-aortic lymph node metastasis. Thus, we only analyzed the presence of chemotherapy as a factor in our research. Further stratified analysis of the specific chemotherapy regimens is necessary.

Conclusions

We established a nomogram using MRI-derived tumor volume to predict the long-term outcomes of patients with FIGO 2018 stage II-IIIC2r uterine cervical squamous cell carcinoma. The tool may be useful to gynecologic oncologists when creating treatment plans and predicting individual prognosis and to patients when making treatment decisions.

Declarations

Ethics Statement and consent to participate

This study was approved by the Ethics Committee of the Fujian Cancer Hospital (approval no. k2021-087-1). Medical records of patients and images of locally advanced uterine cervical squamous cell carcinomas were retrospectively reviewed, and therefore, informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

Lele Zang: Data collection, Writing – original draft, Writing – review & editing. Qin Chen: Writing – original draft, Writing – review & editing. An Lin: Conceptualization, Writing – review & editing. Jian Chen: Investigation, Writing – review & editing. Xiaozhen Zhang: Investigation, Writing – review & editing. Yi Fang: Investigation, Writing – review & editing. Min Wang: Conceptualization, Project administration, Supervision, Writing– review & editing.

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References

1. M. Arbyn, E. Weiderpass, L. Bruni, S. de Sanjosé, M. Saraiya, J. Ferlay, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8: e191-e203.
2. NCCN. The NCCN cervical cancer clinical practice guidelines in Oncology (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
3. H.S. Bae, Y.J. Kim, M.C. Lim, S. S. Seo, S. Y. Park, S. Kang, et al. Predictors of Radiation Field Failure After definitive Chemoradiation in Patients With Locally Advanced Cervical Cancer. Int J Gynecol Cancer 2016;26; 737 – 42.
4. K. Nanthamongkolkul, and J. Hanprasertpong. Predictive Factors of Pelvic Lymph Node Metastasis in Early-Stage Cervical Cancer. Oncol Res Treat 2018.;41;194–198.
5. N. Bhatla, D. Aoki, D.N. Sharma, and Rengaswamy Sankaranarayanan. Cancer of the cervix uteri. Int J Gynaecol Obstet 2018;143 Suppl 2; 22–36.
6. N. Bhatla, J. S. Berek, M. Cuello Fredes, L. A. Denny, S. Grenman, K. Karunaratne, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet 2019;145;129–135.
7. P.G. Rose, J. Java, C.W. Whitney, F. B. Stehman, R. Lanciano, G. M. Thomas,et al. Nomograms Predicting Progression-Free Survival, Overall Survival, and Pelvic Recurrence in Locally Advanced Cervical Cancer Developed From an Analysis of Identifiable Prognostic Factors in Patients From NRG Oncology/Gynecologic Oncology Group Randomized Trials of Chemoradiotherapy. J Clin Oncol 2015;33;2136–42.
8. J. Yang, G. Tian, Z. Pan, F. Zhao, X. Feng, Q. Liu, et al. Nomograms for predicting the survival rate for cervical cancer patients who undergo radiation therapy: a SEER analysis. Future Oncol 2019;15;3033–3045.

9. A.E. Sturdza, R. P? tter, M. Kossmeier, K. Kirchheiner, U. Mahantshetty, C. Haie-Meder, et al. Nomogram Predicting Overall Survival in Patients with Locally Advanced Cervical Cancer Treated with Radiochemotherapy Including Image-Guided Brachytherapy: A Retro-EMBRACE Study. Int J Radiat Oncol Biol Phys 2021;111; 168–177.
10. K. Stenstedt, A.C. Hellstr? m, S. Fridsten, and L. Blomqvist. Impact of MRI in the management and staging of cancer of the uterine cervix. Acta Oncol 2011.;50; 420–6.
11. Y. Liu, H. Liu, X. Bai, Z. Ye, H. Sun, R. Bai, et al. Differentiation of Metastatic from non-metastatic lymph nodes in patients with uterine cervical cancer using diffusion-weighted imaging. Gynecol Oncol 2011;122; 19–24.
12. C. Balleyguier, E. Sala, T. Da Cunha, A. Bergman, B. Brkljacic, F. Danza,et al. Staging of uterine cervical cancer With MRI: guidelines of the European Society of Urogenital Radiology. Eur Radiol 2011;21; 1102–10.
13. J. Wang, T. Wang, Y.Y. Yang, Y. L. Chai, F. Shi and Z. I. Liu. Patient age, tumor appearance and tumor size are risk factors for early recurrence of cervical cancer. Mol Clin Oncol 2015;3; 363–366.
14. G. Xie, R. Wang, L. Shang, C. Qi, L. Yang, L. Huang, et al. Calculating the overall survival probability in patients with cervical cancer: a nomogram and decision curve analysis-based study. BMC Cancer 2020;20; 833.
15. H.J. Kim, and W.C. Kim. Pretreatment tumor diameter/volume and pelvic Lymph Node status assessed by magnetic resonance imaging for uterine cervical Carcinoma treated with concurrent chemotherapy and radiotherapy. J Obstet Gynaecol Res 2008;34; 529 – 37.
16. L. Sun, X. Ke, D. Wang,H. Yin, B. Jin, H. Xu, et al. Prognostic Value of the Albumin-to-¦Ã-glutamyltransferase Ratio for Gallbladder Cancer Patients and Establishing a Nomogram for Overall Survival. J Cancer 2021;12; 4172. –4182.
17. A. Gadducci, R. Tana, S. Cosio,and A. R. Genazzani. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up Of patients with cervical cancer: a review of the literature. Crit Rev Oncol Hematol 2008;66;10–20.
18. K.N. Gaarenstroom, G.G. Kenter, J.M. Bonfrer, C. M. Korse, M. J. Van de Vijver, J. Fleuren, et al. Can initial serum cyfra 21 – 1, SCC antigen, and TPA levels in squamous cell cervical cancer predict lymph node metastases or prognosis? Gynecol Oncol 2000;77;164 – 70.
19. V. Benito, A. Lubrano, J.F. P¨¦rez-Regadera, A. Torn¨¦, A. Gil-Moreno, G. Tejerizo, et al. Posttreatment squamous cell Carcinoma antigen as a survival prognostic factor in patients with locally advanced Cervical cancer. A Spanish multicenter study. The SEGO Spain-GOG group. Gynecol Oncol 2021.;162;407–412.
20. J.G. Yoo, S.I. Kim, S.G. Yeo, and D. C. Park. Usefulness of Short-Term Imaging and Squamous Cell Carcinoma Antigen to Early Predict Response to Concurrent Chemoradiotherapy in Patients With Cervical Cancer. Cancer Control 2022;29; 10732748221074530.
21. K.H. Choi, S.W. Lee, M. Yu, S. Jeong, J. W. Lee and J. H. Lee. Significance of elevated SCC-Ag level on tumor recurrence and patient survival in patients with squamous-cell carcinoma of uterine cervix

following definitive chemoradiotherapy: a multi-institutional analysis. J Gynecol Oncol 2019;30; e1.

22. Y.F.Wen, T.T. Cheng, X.L. Chen, W. J. Huang, H. H. Peng, T. C. Zhou, et al. Elevated circulating tumor cells and squamous cell carcinoma antigen levels predict poor survival for patients with locally advanced cervical cancer treated with radiotherapy. PLoS One 2018;13; e0204334.
23. H.Kato, and T. Torigoe. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer 1977;40;1621-8.
24. T. Maruo, S. Yoshida, T. Samoto, Y. Tateiwa, X. Peng, S. Takeuchi, et al. Factors regulating SCC antigen expression in squamous cell carcinoma of the uterine cervix. Tumour Biol 1998;19; 494–504.
25. A.Murakami, Y. Suminami, H. Hirakawa, S. Nawata, F. Numa and H. Kato. Squamous cell carcinoma antigen suppresses radiation-induced cell death. Br J Cancer 2001;84; 851–8.
26. C.E. Brambs, A.K. H? hn, B. Hentschel, U. Fischer, K. Bilek and L. C. Horn. The Prognostic Impact of Grading in FIGO IB and IIB Squamous Cell Cervical Carcinomas. Geburtshilfe Frauenheilkd 2019;79; 198–204.
27. X.Z. Xie, K. Song, B. Cui, J. Jiang, Y. Z. Zhang, B. Wang, et al. Clinical and pathological factors related to the prognosis of Chinese patients with stage Ib to IIb cervical cancer. Asian Pac J Cancer Prev 2012;13; 5505–10.
28. H. Luo, H. Yao, X. Xu, Z. Li, H. Zhao and H. Zhu. Prognostic significance of poorly differentiated histology and impact of adjuvant chemotherapy in early squamous cell carcinoma of cervix uteri. Cancer Med 2021;10; 2611–2617.
29. K. Matsuo, R.S. Mandelbaum, H. Machida, S. Purushotham, B. H. Grubbs, L. D. Roman, et al. Association of tumor differentiation grade and survival of women with squamous cell carcinoma of the uterine cervix. J Gynecol Oncol 2018;29; e91.
30. N. Cancer Genome Atlas Research, M. Albert Einstein College of, S. Analytical Biological, H. Barretos Cancer, M. Baylor College of, H. Beckman Research Institute of City of, et al. Integrated genomic and molecular characterization of cervical cancer. Nature 2017;543; 378–384.
31. S. Kumar, J.P. Shah, C.S. Bryant, A. N. Imudia, R. Ali-Fehmi, J. M. Malone, et al. Prognostic significance of keratinization in squamous cell cancer of uterine cervix: a population based study. Arch Gynecol Obstet 2009;280;25-
32. E. Burghardt, J. Baltzer, A.H. Tulusan, and J. Haas. Results of surgical treatment of 1028 cervical cancers studied with volumetry. Cancer 1992.;70; 648 – 55.
33. K. Narayan, A. McKenzie, R. Fisher, B. Susil, T. Jobling and D. Bernshaw. Estimation of tumor volume in cervical cancer by magnetic resonance imaging. Am J Clin Oncol 2003;26; e163-8.
34. M. Trattner, A.H. Graf, S. Lax, R. Forstner, N. Dandachi, J. Haas, et al. Prognostic factors in surgically treated stage ib-iib cervical carcinomas with special emphasis on th e importance of tumor volume. Gynecol Oncol 2001.;82;11 – 6.
35. H. Kim, W. Kim, M. Lee, E. Song and J. J. Loh. Tumor volume and uterine Body Invasion assessed by MRI for prediction of outcome in cervical carcinoma treated with concurrent chemotherapy and radiotherapy. Jpn J Clin Oncol 2007;37; 858 – 66.

36. K. Narayan, R. Fisher, and D. Bernshaw, Significance of tumor volume and corpus uteri invasion in cervical cancer patients treated by radiotherapy. Int J Gynecol Cancer 2006;16; 623 – 30.
37. Y. Seo, S.Y. Yoo, M.S. Kim, K. M. Yang, H. J. Yoo, J. H. Kim, et al. Nomogram prediction of overall survival after curative irradiation for uterine cervical cancer. Int J Radiat Oncol Biol Phys 2011;79; 782–7.
38. S. Polterauer, C. Grimm, G. Hofstetter, N. Concin, C. Natter, A. Sturdza, et al. Nomogram prediction for overall survival of patients diagnosed with cervical cancer. Br J Cancer 2012;107; 918 – 24.
39. X. Yang, J. An, Y. Zhang, Y. Yang, S. Chen, M. Huang, et al. Prognostic Nomograms Predicting Survival in Patients with Locally Advanced Cervical Squamous Cell Carcinoma: The First Nomogram Compared with Revised FIGO 2018 Staging System. Front Oncol 2020;10; 591700.
40. Y. Feng, Y. Wang, Y. Xie, S. Wu, Y. Li and M. Li. Nomograms predicting the overall survival and cancer-specific survival of patients with stage IIIC1 cervical cancer. BMC Cancer 2021;21; 450.

Figures

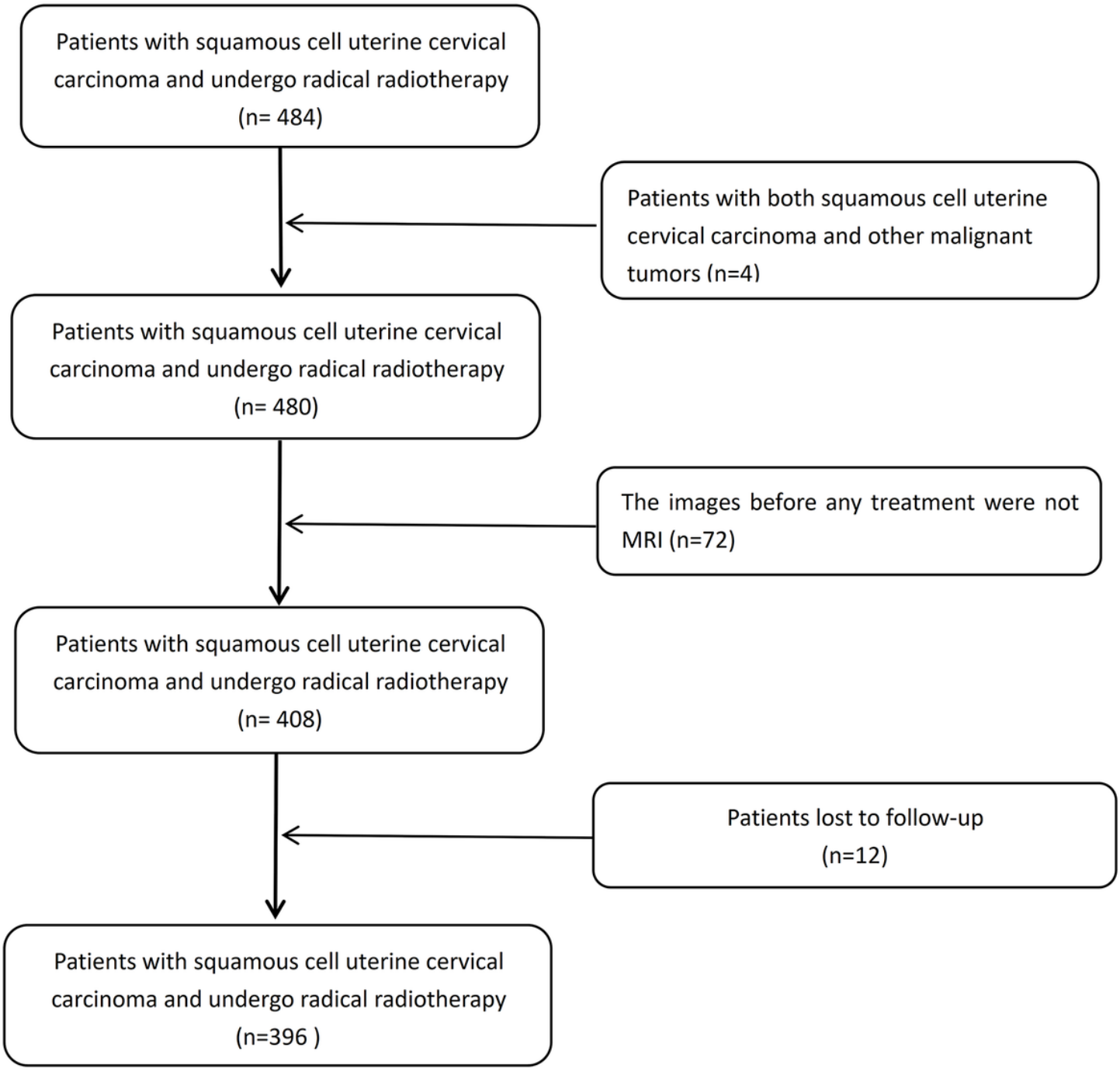

Figure 1

Flowchart for selecting patients.

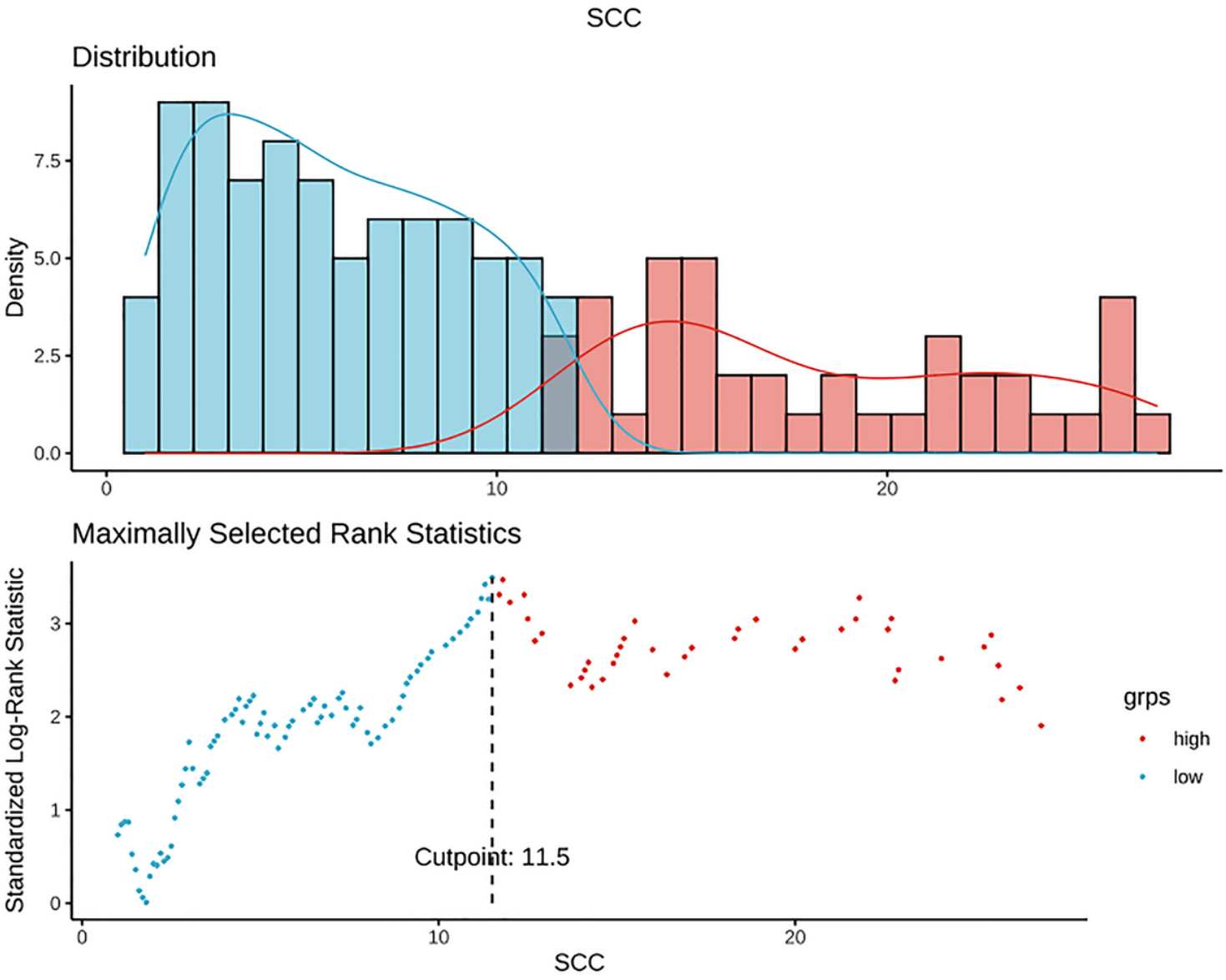

Figure 2

Cut-off point for squamous cell carcinoma antigen (SCC-Ag).

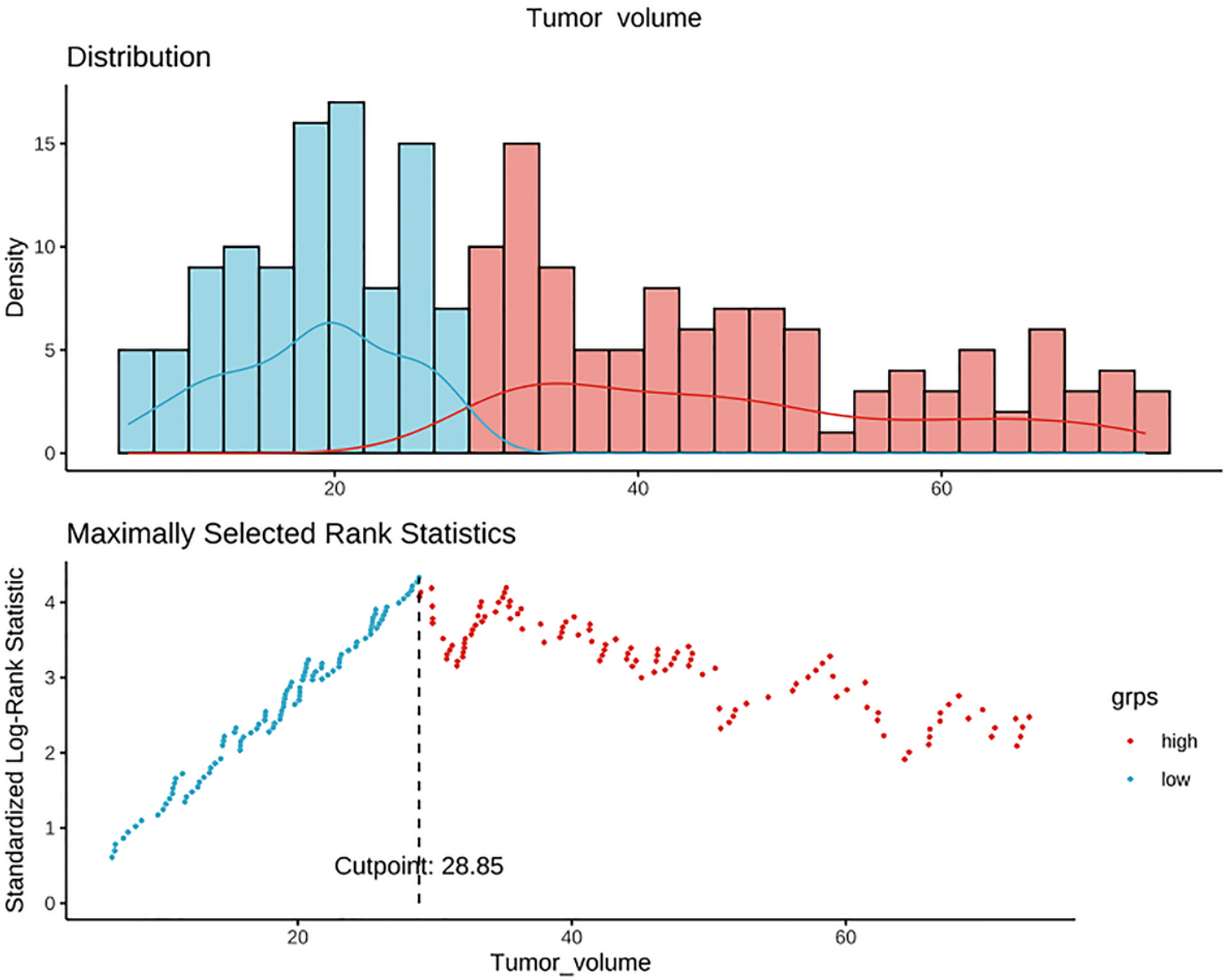

Figure 3

Cut-off value of tumor volume derived from magnetic resonance imaging(MRI).

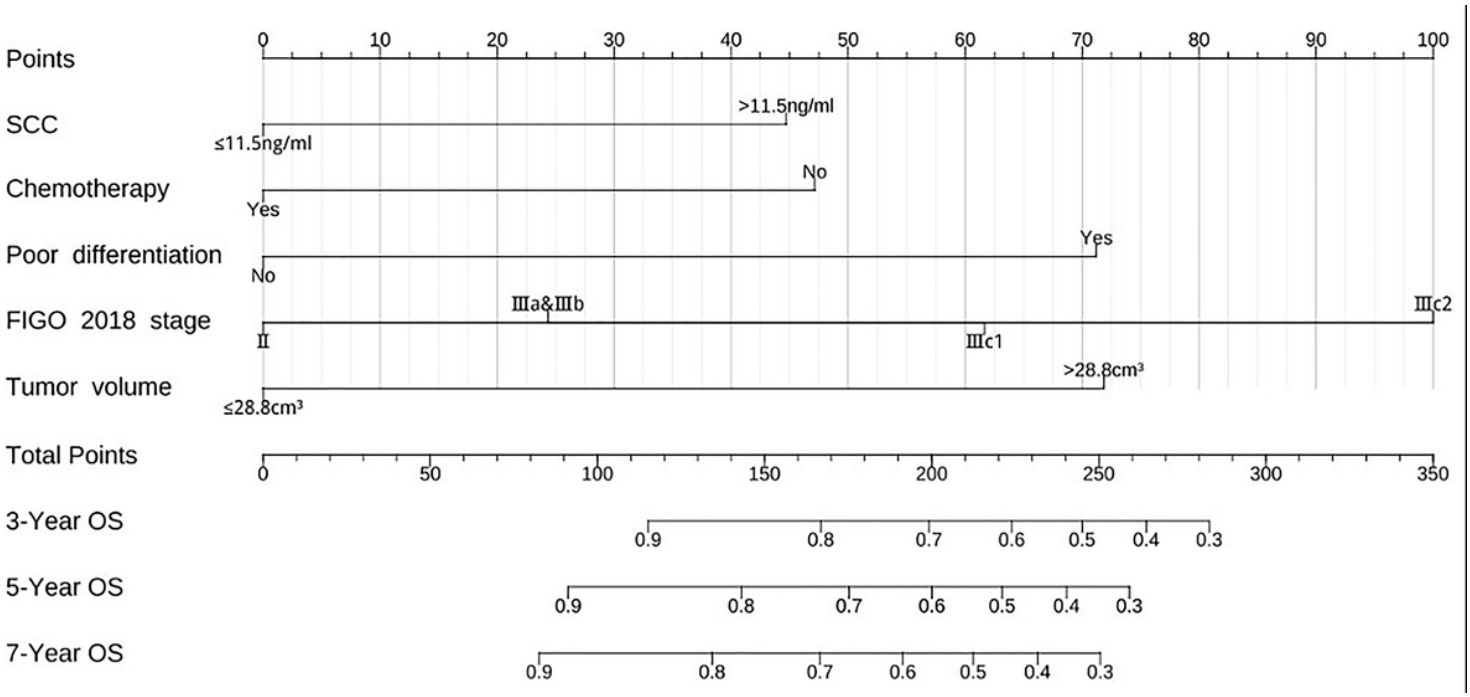

Figure 4

Nomogram to predict 3-year, 5-year and 7-year overall survival (OS) of uterine cervical squamous cell carcinoma received definitive radiotherapy.

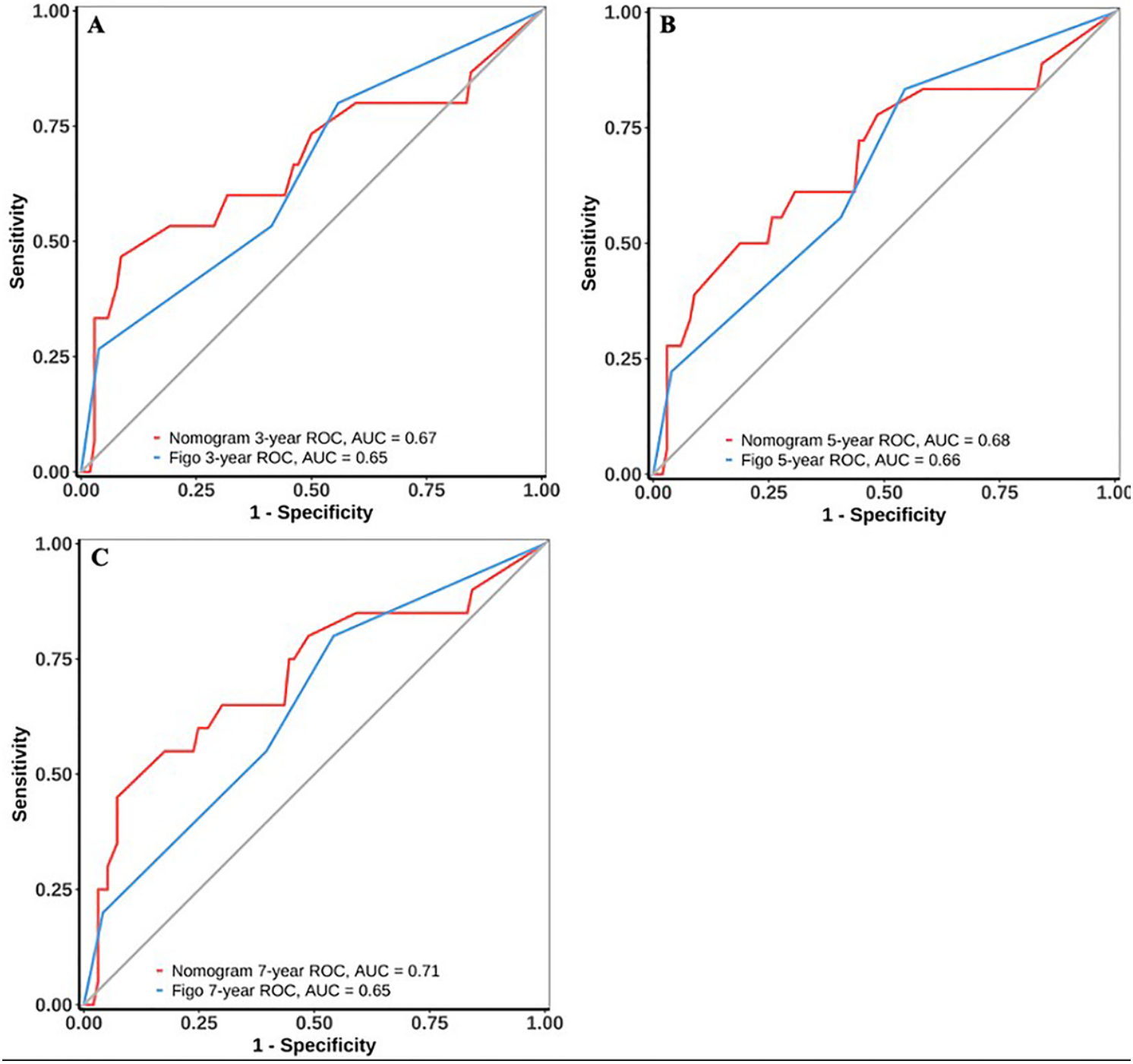

Figure 5

The area under the time-dependent receiver operating characteristic curves for 3-year, 5-year and 7-year OS from the validation set. A, AUC for 3-year OS. B, AUC for 5-year OS. C, AUC for 7-year OS. OS: Overall survival. AUC: Area under the curve. FIGO: International Federation of Gynecology and Obstetrics.

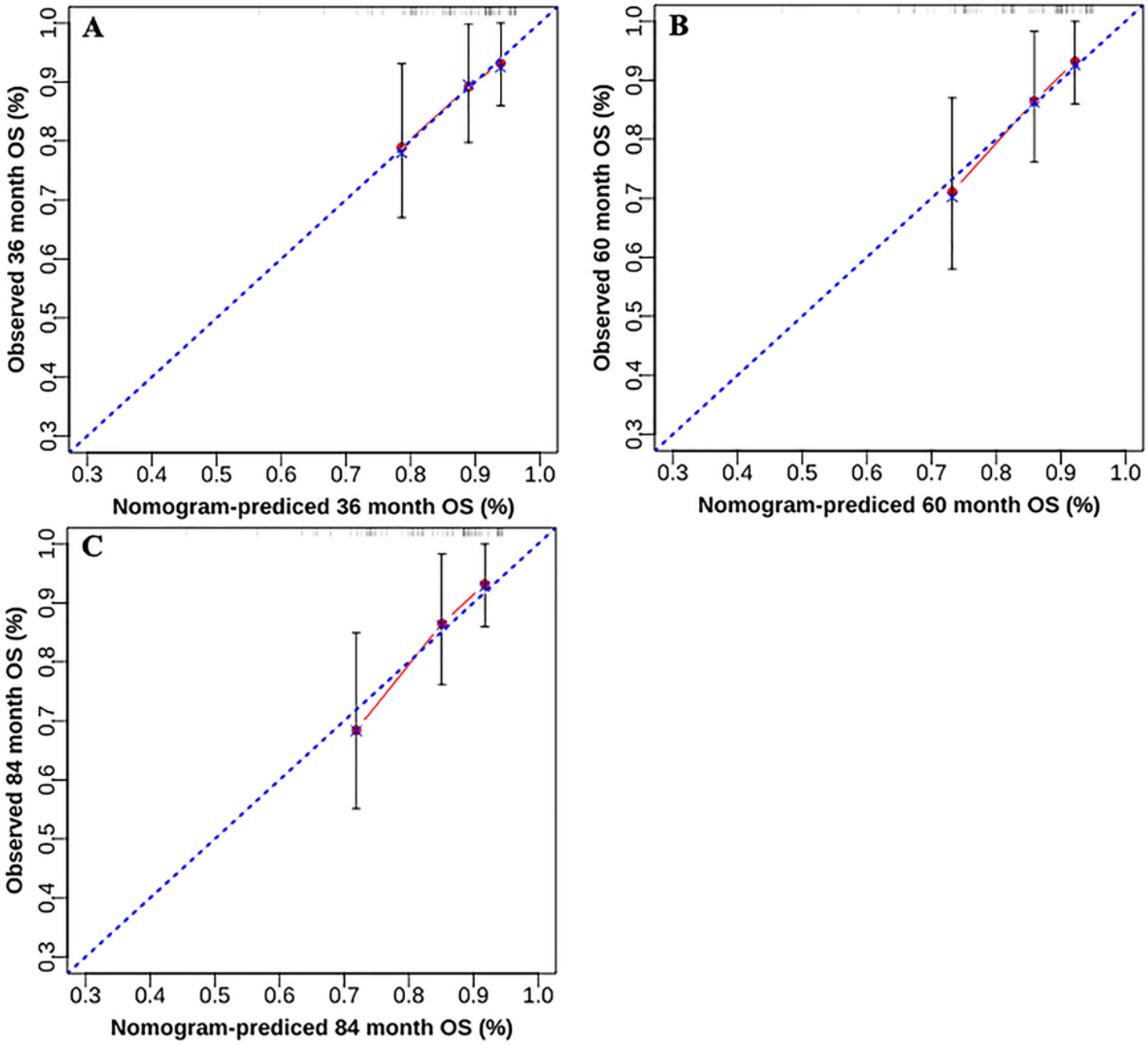

Figure 6

Calibration plots for 3-year, 5-year and 7-year OS from the validation set. A, calibration plots for 3-year OS. B, calibration plots for 5-year OS. C, calibration plots for 7-year OS. OS: Overall survival. FIGO: International Federation of Gynecology and Obstetrics.

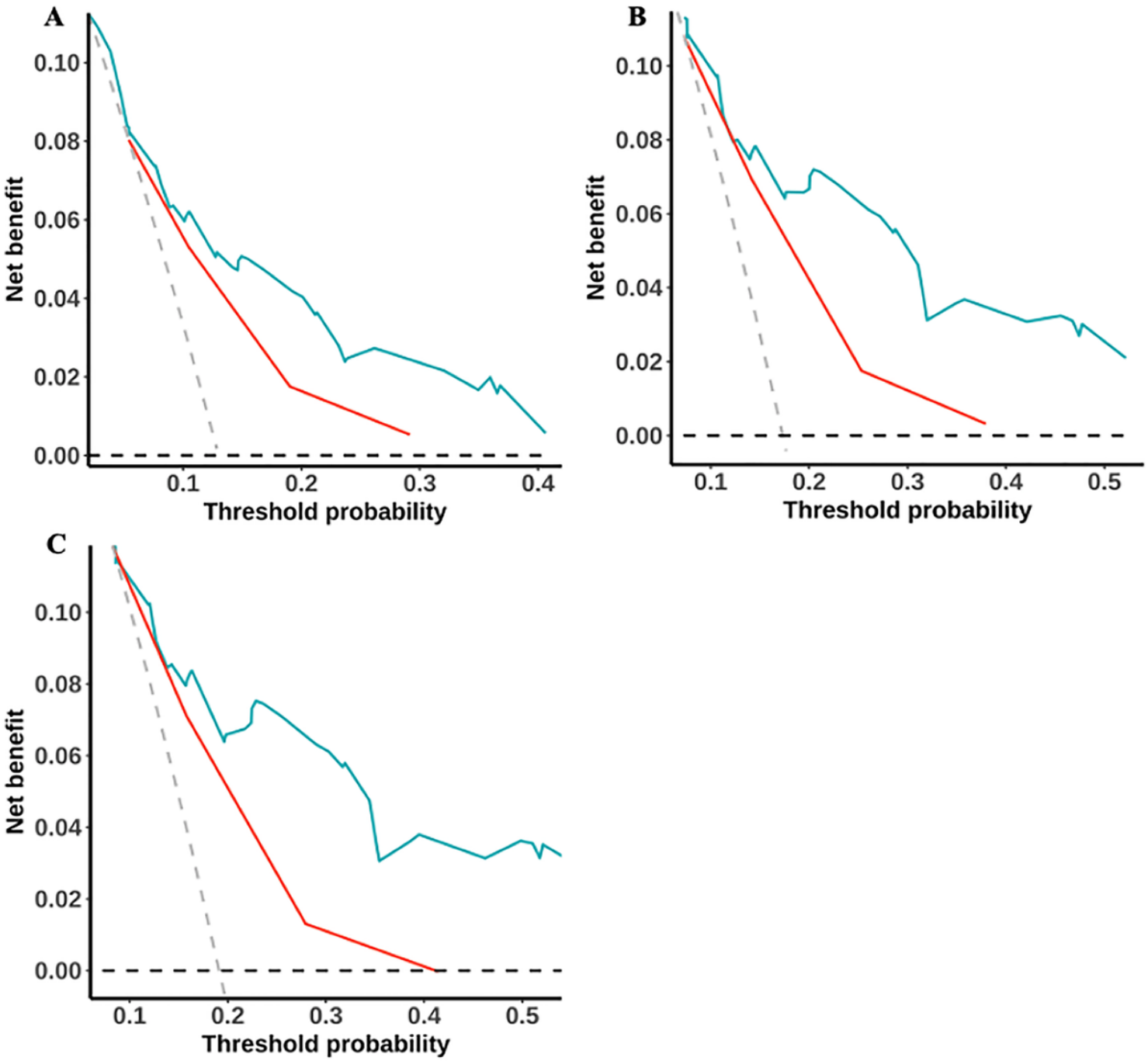

Figure 7

Decision curve analysis (DCA) for our nomogram and FIGO 2018 staging system. A, DCA for 3-year OS. B, DCA for 5-year OS. C, DCA for 7-year OS.DCA, decision curve analysis. OS: Overall survival. FIGO: International Federation of Gynecology and Obstetrics.

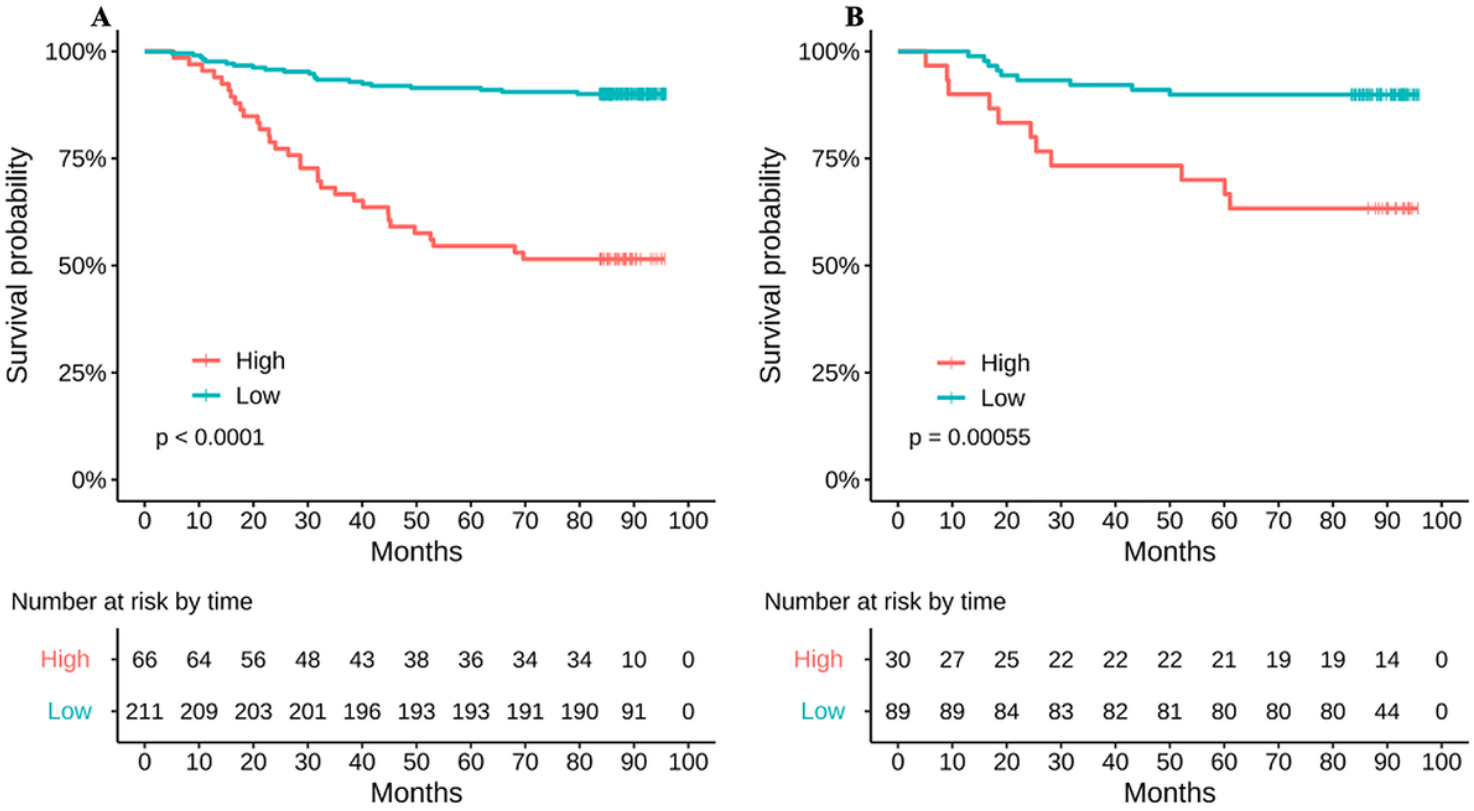

Figure 8

Survival curves of low-risk and high-risk groups using the training and validation sets. A, Curve of survival of the training cohort. B, Curve of survival of the validation cohort.