Nomogram for predicting the overall survival of cervical cancer patients with nonsurgical treatment

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Abstract

Background: Surgery is an important treatment for cervical cancer, but some patients choose not to operate on the primary site. The purpose of this study was to establish nomogram for predicting overall survival (OS) in nonsurgical cervical cancer on the primary site(NSCC) patients by using cases in the public database.

Methods: All patients diagnosed between 2004 and 2015 were randomly divided into training (n=4283) or validation (n=1832) cohort. Cox regression analysis was used on the training cohort to select independent prognostic factors to construct nomogram for predicting 3- and 5-year OS. In two cohorts, receiver operating characteristic curve (ROC), Harrell's concordance index (C-index), calibration curves and decision curve analysis (DCA) were used to evaluate the accuracy and the reliability of the model. We made a risk stratification system based on the model and performed Kaplan-Meier survival analysis on the risk level.

Results: In the training set, ten clinicopathological factors were significantly correlated with survival outcomes and were included in the nomogram. In the training cohort and validation cohort, the C-index, ROC and calibration plots exhibited an excellent consistency between actual OS and model predictions. DCA indicated great clinical benefit. Compared with FIGO staging, nomogram's evaluation effect is superior.

Conclusions: Age, histological type, grade, tumor size, extension, lymph node involvement, distant metastasis, lymph node removed, chemotherapy and radiotherapy were independent prognostic factors for OS in NSCC patients. The model showed more satisfactory accuracy and clinical practicability than FIGO staging system, and may provide integration and improvement for therapeutic decisions.

Introduction

Cervical cancer is a common type of gynecological malignancies and the fourth leading cause of cancer-related death in the female population[1]. The significant declines in cervical cancer mortality in developed countries have benefited from the popularization of vaccine and screening, but the success has not been replicated in the developing world[2]. Although immunotherapy has made rapid progress in the field of cancer treatment in recent years[3, 4], treatment guidelines for cervical cancer are based on radiation, except in the early stages[5–7]. The final decision is usually based on the clinician's opinion and the patient's wishes, which leads to patients who have never accepted surgical treatment even in the early stages.

In 2018, the International Federation of Gynecology and Obstetrics(FIGO) approved the amendment staging system based on cutting-edge researches and discussed the management of cervical cancer based on the system. Although the preferred treatment is surgery, including multiple styles in the early stages [5], radiotherapy has the same effect in local control and survival for patients with contraindications to surgery or anesthesia[8–10]. As for locally advanced cervical cancer, concurrent

chemoradiotherapy (CCRT) became the recommended treatment following 1999 National Cancer Institute report [5]. And studies have shown that pelvic and para-aortic lymph node resection is beneficial for locally advanced cervical cancer[11, 12]. Cases with distant metastases are relatively rare, and surgical treatment is not recommended[13]. So we could know that nonsurgical treatments have massive value in all stages of cervical cancer.

In our review of the literature, we found that rare studies have been done on this subset of patients. Therefore, we had an idea to create first method for predicting individualized survival of NSCC patients, and a nomogram is an excellent approach to achieve this objective, especially in cancer patients [14]. Nomogram is a practical model for accurately predicting the survival outcome of individual clinical patients[15]. The FIGO staging system is the most commonly used for the clinical evaluation of cervical cancer[16]. However, the updated system of patients with lymph node-positive status into a single-stage could produce a highly heterogeneous population with significant differences in survival. Researches have hinted that bulk of tumors may be a more accurate predictor than lymph node metastases[17]. What's more, cases from the Surveillance, Epidemiology, and End Results (SEER) database contains data ranged from 2004 to 2015, prior to the release of the new FIGO staging system in 2018, resulting in SEER not including updated FIGO data. Therefore, we redid the FIGO staging with reference to the latest changes. By using regression analysis of potential prognostic factors, meaningful variables were involved in the creation of a nomogram.

In our study, we analyzed the clinicopathologic characteristics and treatment information of NSCC from SEER, a public database that combines multiple the United States agencies without personal information of patients[18].

Materials And Methods

Cases Sources and Study Cohort

The national cancer institute's SEER database contains the most authoritative domestic data on cancer incidence and survival (<https://seer.cancer.gov/>), which covers about 34.6 percent of the United States population [19]. A large population of women with NSCC was retrieved from additional treatment field of SEER 18 Regs Custom Data, Nov2018 Sub via SEERStat software (v8.3.6). We included 26694 cases with nonsurgical treatment, which means explicitly no surgical procedure of primary site. Exclusion criteria : (1) missing follow-up data; (2) incomplete clinicopathological information about diagnostic age, histological type, histological grade, tumor size, extension, lymph node status, metastasis, lymph node removed, chemotherapy, radiotherapy; (3) The primary site (cervix) was operated on. Under the criterion, 20,276 cases were excluded.

In the end, this study included 6115 NSCC patients who were diagnosed during 2004 and 2015. To construct and validate the model, we randomly assigned all patients to the training and validation cohort in a ratio of 7:3 (4283 cases: 1832 cases).

Variables

It is worth noting the specific implications of some variables. In the histological type category, “Other” was defined as the types except for squamous cell carcinoma(SCC) and adenocarcinoma (ADC). In the grade classes, “I-IV” stands for well differentiated, moderately differentiated, poorly differentiated and undifferentiated, respectively. Considering the new FIGO staging system, we set the threshold for the diameter of tumor as 2 cm and 4 cm. Lymph node metastasis is also subdivided into regional positive and distant positive, and “regional” was defined as pelvic lymph node involvement, and “distant” was defined as aortic (para-, peri-, lateral) and other than above lymph node involvement. The meaning of the variable extension was the FIGO staging without lymph nodes and distant metastasis information, which is similar to the T staging. For example, “I” means lesion confined to the cervix, and “IV” means invasion of adjacent pelvic organs. In the metastasis category, the “yes” does not include distant lymph node metastasis. Given the certain inadequacy of new staging system [20], we re-staged the patients according to the 2018 FIGO staging. The time from diagnosis to the last follow-up or death due to any cause was defined as OS. The follow-up deadline was December 31, 2016.

Construction and Validation of the Model

Based on the results of multivariate analysis, the nomogram was constructed in R software by using FOREIGN, RMS and SURVIVAL packages. Nomogram performs dual validation in the training cohort and the validation cohort. The C-index and the area under the receiver operating characteristic curve(AUC) are often used to assess discrimination in clinical models and its high value indicates high accuracy in predicting prognosis [21], whose value between 0.70 and 0.90 indicate that the model has good resolving ability. The calibration plot is often applied to evaluate performance of clinical prediction models, and an outstanding accurate model would present a plot on which predictions would coincide with the 45° diagonal line[19]. DCA is a model for evaluating clinical utility, and the applied value increases as the curve of the nomogram moves away from the two lines representing extreme cases[22]. Our study compared the nomogram with the FIGO staging in C-index, AUC and DCA.

Statistical Analysis

Use the x-tile software to find the best cut-off value for age. The appropriate use of chi-square was performed to compare the clinicopathological features of the training group and the validation group. Univariate and multivariate Cox regression analysis were chosen to determine the variables included in the nomogram. In addition, the risk classification system was created in reference to the upper quartile and lower quartile of total scores in the training cohort and fallen NSCC patients into high, intermediate or low risk subgroup ranked in order of scores from high to low. In the training and validation set, Kaplan-Meier analysis and log-rank test were used to analyze the survival differences of not only the three risk levels but also subgroups with clinical and pathological characteristics. All statistical trials were based on two-sided assumptions, and $P < 0.05$ was considered statistically significant. Data processing, model construction and validation were performed by R software(v 3.6.2).

Results

Clinicopathological Characteristics of the Training and Validation Cohort

The best cut-off value for age are 50 and 75 by x-tile software (Online Resource 1). The clinical and pathological characteristics of included cases were summarized in Table 1.

Table 1
Patient characteristics in the study.

Variables	Total cohort, n (%)	Training cohort	Validation cohort	p-value
Age(y)				0.008
< 50	2657(43.45%)	1858(43.38%)	799(43.61%)	
50 ≤ x<75	2863(46.82%)	1976(46.14%)	887(48.42%)	
≥ 75	595(9.73%)	449(10.48%)	146(7.97%)	
Histological Type				0.059
Squamous cell neoplasms	4948(80.92%)	3461(80.81%)	1487(81.17%)	
Adenomas and adenocarcinomas	819(13.39%)	560(13.07%)	259(14.14%)	
Other	348(5.69%)	262(6.12%)	86(4.69%)	
Grade				0.686
I	363(5.94%)	250(5.84%)	113(6.17%)	
II	2607(42.63%)	1831(42.75%)	776(42.36%)	
III	2963(48.45%)	2068(48.28%)	895(48.85%)	
IV	182(2.98%)	134(3.13%)	48(2.62%)	
Tumor Size(cm)				0.983
< 2	172(2.81%)	121(2.83%)	51(2.78%)	
≥ 2	678(11.09%)	473(11.04%)	205(11.19%)	
≥ 4	5265(86.10%)	3689(86.13%)	1576(86.03%)	
Extensive				0.875
I	1398(22.86%)	986(23.02%)	412(22.49%)	
II	2457(40.18%)	1728(40.35%)	729(39.79%)	
III	1909(31.22%)	1324(30.91%)	585(31.93%)	
IV	351(5.74%)	245(5.72%)	106(5.79%)	
Lmyph node involvement				0.887
Not	3785(61.90%)	2655(61.99%)	1130(61.68%)	
Regional	2265(37.04%)	1581(36.91%)	684(37.34%)	
Distant	65(1.06%)	47(1.10%)	18(0.98%)	

Variables	Total cohort, n (%)	Training cohort	Validation cohort	p-value
Metastasis				0.130
Not	5465(89.37%)	3811(88.98%)	1654(90.28%)	
Yes	650(10.63%)	472(11.02%)	178(9.72%)	
Lymph node removed				0.474
Done	481(7.87%)	330(7.70%)	151(8.24%)	
Not Done	5634(92.13%)	3953(92.30%)	1681(91.76%)	
Chemotherapy				0.002
Done	5082(83.11%)	3518(82.14%)	1564(85.37%)	
Not Done	1033(16.89%)	765(17.9%)	268(14.63%)	
Radiotherapy				0.017
Done	5613(91.79%)	3908(91.24%)	1705(93.07%)	
Not Done	502(8.21%)	375(8.76%)	127(6.93%)	

Independent Prognostic Factors in the Training Cohort

The training set was used to establish the nomogram. After the univariate analysis and multivariate analysis, diagnostic age, histological type, grade, tumor size, extension, lymph node involvement, distant metastasis, lymph node removed, chemotherapy, radiotherapy were significantly associated with OS. The obtained details of the results were presented in Table 2.

Table 2
Risk factors for OS according to the Cox proportional hazards regression model.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age(y)				
< 50	1		1	
50 ≤ x<75	1.321(1.206,1.447)	< 0.001	1.146(1.044,1.258)	0.004
≥ 75	2.341(2.262,2.658)	< 0.001	1.916(1.674,2.194)	< 0.001
Histological Type				
Squamous cell neoplasms	1		1	
Adenomas and adenocarcinomas	1.085(0.959,1.226)	0.194	1.064(0.937,1.207)	0.339
Other	1.574(1.343,1.843)	< 0.001	1.330(1.125,1.572)	< 0.001
Grade				
I	1		1	
II	1.101(0.900,1.345)	0.349	1.165(0.949,1.431)	0.144
III	1.404(1.151,1.711)	< 0.001	1.312(1.071,1.607)	0.009
IV	1.701(1.181, 2.260)	< 0.001	1.514(1.128,2.032)	0.006
Tumor Size(cm)				
< 2	1		1	
≥ 2	1.067(0.793,1.437)	0.667	1.117(0.826,1.512)	0.047
≥ 4	1.364(1.041,1.788)	0.025	1.382(1.046,1.827)	0.023
Extensive				
I	1		1	
II	1.221(1.080,1.381)	0.001	1.333(1.175,1.513)	< 0.001
III	2.502(2.217,2.824)	< 0.001	2.326(2.045,2.645)	< 0.001
IV	4.015(3.378,4.771)	< 0.001	2.742(2.288,3.287)	< 0.001
Lymph node involvement				
Not	1		1	
Regional	1.637 (1.503,1.782)	< 0.001	1.444(1.316,1.585)	< 0.001
Distant	2.126(1.496,3.022)	< 0.001	2.138(1.500,3.047)	< 0.001

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Metastasis				
Not	1		1	
Yes	4.233 (3.794,4.722)	< 0.001	2.679(2.374,3.023)	< 0.001
Lymph node removed				
Done	1		1	
Not Done	1.678(1.402,2.009)	< 0.001	1.526(1.269,1.835)	< 0.001
Chemotherapy				
Done	1		1	
Not Done	2.156(1.957,2.376)	< 0.001	1.994(1.787,2.226)	< 0.001
Radiotherapy				
Done	1		1	
Not Done	2.997(2.644, 3.398)	< 0.001	1.959(1.708,2.246)	< 0.001

Construction of the Nomogram

Based on all the variables mentioned above that independently predicted OS, a nomogram was established to predict 3 - and 5-year survival rates. By marking each variable on the corresponding point axis of the nomogram, each patient could obtain ten-factor scores, which were added to get a total score. And then a vertical line was drawn down from the corresponding point of the total score to estimate 3 - or 5-year survival rate (Fig. 1).

Validation of the Nomogram

Internal validation and external validation were carried out in the training cohort and the validation cohort, respectively. In training set, the C-index of nomogram and FIGO staging was 0.724 and 0.685, respectively. And in the validation group, the corresponding values were 0.720 and 0.671, respectively. In training set, the 3- and 5-year survival AUCs of the nomogram are 0.732 and 0.735. And corresponding values of FIGO staging are respectively 0.695 and 0.694 (Fig. 2). In the validation group, the AUC for FIGO staging was also lower than that for nomogram. The results demonstrate that the method has an accurate prediction performance of OS and is stronger than the prediction of FIGO staging. The calibration plots for 3- and 5-year OS predictions of the training and validation sets are also satisfactory in Fig. 3. According to the Fig. 4, although comparing the two models produced net benefits, the net benefits of 3- year and 5- year DCA curves for OS of nomogram are higher than that of the FIGO staging system in the two sets.

Risk Classification System

In addition, the upper quartile and lower quartile of total scores of patients in the training cohort were calculated as 129 and 209, respectively. Therefore, a risk stratification system based on nomogram was established and divided into three risk subgroups: low-risk group, score 0–129.0; intermediate-risk group, score 129.1–209.0; high-risk group, score 209.1–600.0. The OS of the three subgroups was expressly isolated by the prediction model (Fig. 5). The log-rank test showed significant differences among risk subgroups ($p < 0.001$). However, under the classification of clinicopathological features, not all comparisons between subgroups are clinically significant. The p values of log-rank test between all subgroups can be queried in Online Resource 2. In Fig. 6, we presented Kaplan-Meier curves of all the clinical and pathological subgroups of the training group, and the corresponding validation group is included in the supplementary materials (Online Resource 3).

Discussion

Cervical cancer is one of the most widespread cancer and the fourth cancer cause leading to death in women on a global scale. We searched the SEER database and found a total of 95,218 cervical cancer cases before 2016, including 26,693 NSCC cases that were about 28 percent of the total. However, due to incomplete data, not all NSCC cases could be included in the study. There is evidence that nonsurgical treatment can be used at all stages of cervical cancer. Although surgical treatment is the primary choice of treatment in the early stage, there are still some patients who do not choose surgical treatment due to intolerance to surgery, contraindications to anesthesia or strong personal aspiration under the premise of not preserving fertility. Furthermore, most treatment guidelines also offer solutions with some differences. FIGO guidelines recommend that IA1-IB2 and IIA1 cases could be treated with radiotherapy, and IB3 and IIA2 cases should be CCRT[5]. Nevertheless, National Comprehensive Cancer Network (NCCN) Guidelines advocate that pelvic external irradiation + cisplatin concurrent chemotherapy + brachytherapy are treated in the range from IB1 to IIB stage, and pelvic external irradiation and brachytherapy are applied for patients with IA stage cervical cancers[6]. We can find similar views in some countries' guidelines[23–25]. Not to mention that in advanced cervical cancer, radiation and chemotherapy are the primary treatment. A meta-analysis suggested that surgical treatment had no effect on OS after radiotherapy or CCRT[26]. So we could know that the amount of patients with NSCC is large, and our research is significative to assess prognosis and take further treatment measures.

In the present study, we assessed the prognostic factors that affected survival outcomes of NSCC patients in the SEER database (Tables 1 and 2). We created the nomogram to get the overall score to predict OS for NSCC patients (Fig. 1). We can conclude that ADC causes a worse prognosis than SCC, and it has been reported that the treatment response of ADC is less than optimal compared to SCC, especially radiation[27, 28]. And other types, including neuroendocrine carcinoma, have the worst prognosis[29]. There was no statistically significant difference in well and moderately differentiated survival outcomes, nor between poorly differentiated and undifferentiated(Fig. 6c). The multivariate analysis in our training cohort, the impact of tumor diameter < 2 cm and 2-4cm subgroups on survival

have no significant difference, which may suggest that it is unnecessary to increase this group among NSCC. However, we still chose 2 cm as a critical point to create the nomogram following the new FIGO staging system[30]. Among all variables, extension, lymph node involvement, and metastasis displayed the high discriminating power, followed by chemotherapy and radiotherapy. The lymph node information in the cohort we studied was derived from biopsy or aspiration, but we could exert more clinically feasible methods to predict lymph node metastasis. Research shows that magnetic resonance imaging variables[31] and 18F-fluorodeoxyglucose positron emission tomography [32] can improve the accuracy of predicting lymph node metastasis. Remarkably, degree of invasion and treatment measures had the compelling prognostic value for OS, which coincided with previous reports [33].

C-indexes of nomogram training cohort and validation cohort can confirm the predictive accuracy and appreciable reliability of the model, which were higher than that of FIGO staging. The area under ROC curve (Fig. 2) showed the superiority of nomogram to other clinicopathological features, including FIGO staging. The calibration curves (Fig. 3) models demonstrate the predictive performance of the nomogram. The DCA proves that nomogram has higher net benefit than FIGO staging (Fig. 4). We speculated that the fact that lymph node metastasis increases staging caused an uneven DCA curve for FIGO staging. Although such staging seems to improve net benefit, its rationality is questionable. In summary, our nomogram is a more accurate prognostic model than FIGO staging. Moreover, we can stratify patients according to their scores, and further treatment should be actively pursued if the case is in a high-risk group.

Our nomogram considered the effect of treatment on prognosis. The results suggested that lymphadenectomy had a positive effect on prognosis. Resection of the sentinel node during biopsy was also included. Previous studies have shown that resection of pelvic or para-aortic lymph nodes can be beneficial for locally advanced cervical cancer[11, 12]. It seems that lymphadenectomy plus radiotherapy may be a feasible option. In past studies, the position of radiation in treatment of cervical cancer has been clearly established, and even before 1999, CCRT was not a standardized treatment for advanced cases. Consider that most people received radiation and chemotherapy (regardless of order and regimen) and not just one of them, we divided them into four subgroups according to treatment: no treatment, radiotherapy, chemotherapy, radiotherapy and chemotherapy (R&C). This Kaplan-Meier survival analysis (Fig. 6i) showed that the prognosis of the R&C group was significantly better than that of the other subgroups ($p < 0.01$). The prognosis of radiotherapy alone was the second best, while chemotherapy alone and untreated group has no significant difference in the outcomes ($p > 0.05$). This result suggests that radiotherapy plus chemotherapy is the most beneficial for survival in most NSCC, followed by radiotherapy alone. And chemotherapy alone does not seem to be a worthwhile option. Changing the chemotherapy regimens and improving radiotherapy scheme provide another solution for the high-risk group [34]. Choosing Cisplatin plus 5-Fluorouracil regimen is controversial when External Beam Radiotherapy is combined with platinum-containing chemotherapy, as many studies have shown that its survival outcomes are not significantly different from that of the cisplatin regimen, but acute hematological toxicity and drug resistance are increased[35]. Considering the side effects and quality of life, too aggressive treatment regimens were also discouraged.

In recent years, we can encourage them to actively access potential treatment opportunities, such as participating in clinical trials of cutting-edge drugs [36]. In the GOG240 trial, compared with the chemotherapy group alone, chemotherapy combined with bevacizumab group continued to show significant improvement in OS in persistent, recurrent, or metastatic patients[37]. Two studies illustrated pembrolizumab had established clinical benefits in cervical cancer[38, 39]. More checkpoint inhibitor therapies deserve to be expected. Take a step back we could consider the surgical therapy. Suitable surgery can also be completed after removing contraindications in early-stage, and a pelvic exenteration is an option for advanced patients[40]. As we know from the NCCN guidelines, complementary hysterectomy after concurrent chemoradiotherapy remains controversial for stage IB3 or IIA2 tumors[6]. This approach does not improve OS and increases complications,so at that time the decision to finish surgery should be made more carefully.

The model has practicability and operability for clinical work, which can analyze the prognosis of patients, and provides a visual tool for negotiating treatment plans with patients. What we cannot deny is that this study has certain limitations. Firstly, selection bias may exist as a large number of cases were excluded because of incomplete information. The second limitation stemmed from the deficiency of information about infection status of HPV, values of tumor markers, details of radiotherapy and chemotherapy, and emerging therapeutic applications. Third, this nomogram requires further validation in a prospective cohort because the database is a retrospective collection. Additionally, the SEER database included the United States population, an validation in different countries remained necessary.

In this study, independent prognostic factors for OS in NSCC patients were identified, including age, histological type, grade, tumor size, extension, lymph node involvement, distant metastasis, lymph node removed, chemotherapy and radiotherapy, which participated in the construction of the nomogram prognostic assessment model for NSCC patients. After a series of tests, the nomogram was more accurate and reliable than FIGO staging in predicting 3 - and 5-year OS for NSCC women. The model has great clinical application value. Aggressive treatment is recommended for high-risk patients.

Declarations

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Availability of data and material The datasets generated and/or analysed during the current study are available in the SEER database (<https://seer.cancer.gov/>).

Competing interests The authors declare no potential conflicts of interest.

Ethics approval and consent to participate The study used public databases. This entry is not required.

Consent for publication Not applicable.

Authors' contributions Xiaoyu Ji has made substantial contributions to conception and design , acquisition of data, analysis and interpretation of data, and draft manuscript. Kejuan Song, T ng Lv , Yuchao Diao ,Nannan Xia have made substantial contributions to analysis and interpretation of data. Kejuan Song and Qin Yao have been involved in revising it critically for important intellectual content.All authors reviewed the manuscript and agreed to publish it.

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Figures

Figure 1

Cervical cancer with nonsurgical treatment survival nomogram Grade: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated. Extension: the expansion scope is divided by FIGO stages(2018) except IIIC and IVb stage. Regional, pelvic lymph node involvement; Distant, aortic (para-, peri-, lateral) and other than above lymph node involvement.

Figure 2

Receiver operating characteristic curve (a) For the 3-year OS in the training cohort, the AUC was 0.732; (b) for the 5-year OS in the training cohort, the AUC in the training cohort was 0.735; (c) for the 3-year OS in the validation cohort, the AUC was 0.738;(d) for the 5-year OS in the validation cohort, the AUC in the training cohort was 0.730. The AUCs of nomogram were higher than that of FIGO stage and other clinicopathological factors.

Figure 3

The calibration curve for predicting patient survival at 3 year (a) and 5 years (b) in the training cohort and at 3 year (c) and 5 years (d) in the validation cohort. Nomogram-predicted probability of overall survival is plotted on the x-axis, actual overall survival is plotted on the y-axis.

Figure 4

Decision curve analysis set for 3- (a) and 5- (b) year survival from the training cohort and 3- (c) and 5- (d) year survival from the validation cohort. Horizontal means that all samples are negative, not all of them are treated, and the net benefit is zero. The slash indicates that all samples are positive. The red curve line represents nomogram, and the blue curve represents FIGO stages.

Figure 5

Kaplan-Meier curves of overall survival for risk stratification Kaplan-Meier curves of OS for risk stratification within the training (a) and the validation cohort (b). The green line represents the low-risk group, the blue line represents the intermediate-risk group, and the red line represents the high-risk group. All log-rank P values for trends were <0.05 .

Figure 6

Kaplan-Meier curves of overall survival for age(a), histological type(b), grade(c), tumor size(d), extension(e), lymph node involvement(f), metastasis(g), lymph node removed(h), therapy (i) See the upper right corner legend for the specific meaning of each line .R&C, radiotherapy and chemotherapy group; C, chemotherapy group; R, radiotherapy group; N, no treatment group; SCC, squamous cell carcinoma; ADC, adenocarcinomas. Grade: I, well differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated.

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