

Overall Survival Rate Analysis For Risk Factors In Women With Neuroendocrine Carcinoma of The Cervix Using Surveillance, Epidemiology, And End Results (SEER) Database

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Abstract

Background: Neuroendocrine carcinoma of the cervix is rare and aggressive disease, of which prognosis information and the effectiveness of the therapies is unclear.

Methods: A retrospective study using data from the SEER database for the first diagnosed Neuroendocrine carcinoma of the cervix patients was conducted. We performed univariate and multivariate Cox models to screen for independent prognostic factors for overall survival. Subgroup analysis and sensitive analysis were performed for further study, then again univariate and multivariate analyses of Cox regression analysis were performed based on the sensitivity analysis data set.

Results: A total of 250 Neuroendocrine carcinoma of the cervix cases was included, tumor subtype, age, marriage, race, number of regional lymph nodes, number of positive lymph nodes, radiotherapy, surgery, and FIGO stage were all factors affecting OS, and multivariate analysis identified FIGO staging (HR, 2.4; 95% CI, 1.505-3.828, $P < 0.001$) and surgery (HR, 0.467; 95% CI, 0.358-0.609, $P < 0.001$) treatment as independent indicators. With respect to the factors associated with treatments, we found that patients who underwent surgery (yes vs. no vs. unknown) or radiation (yes vs. no) experienced prolonged survival, both $P < 0.001$

Conclusions: Our investigation shows that for patients with NECC surgery seems to be the effective treatment. Chemotherapy cannot improve the prognosis of NECC patients, and the effectiveness of radiation should be further verified.

Introduction

Cervical cancer is the fourth most common malignancy diagnosed and the fourth leading cause of cancer death in women worldwide, with an estimated 530,000 new cases and 270,000 deaths every year. Primary treatment options for patients with cervical cancer may include surgery, a concurrent chemoradiotherapy, radiotherapy and brachytherapy. [1] Cervical neuroendocrine carcinomas are considered rare, aggressive neuroendocrine neoplasms within the neuroendocrine cell lineage spectrum, which has many characteristics distinguished from all the other subtypes of cervical cancers. Considering their rarity, data of histological and clinical features consistent with current classification are scant or lacking, and our current understanding of the disease is very limited. A review of articles was published in 2017 by Angiolo G, they summarized histology, pathogenesis, prognosis and the mainly approached therapeutic of cervical neuroendocrine tumors, and suggested treatment algorithm tailored to tumor stage. They also strongly recommended that treatment guidelines, based on prospective, well-designed clinical trials need needed urgently. [2] Other related articles of medium or large scale of cases were really limited in the exiting public literature database. So, the analysis of the public database in order to get more knowledge of the clinical characteristics of the disease is necessary.

In this study, we analyze a total of 250 cervical neuroendocrine carcinoma cases with full treatment information included in the Surveillance, Epidemiology, and End Results (SEER) database during the year

2000 to 2018. This approach allows us to have the largest patient number of this kind of disease, with information included patient demographics, tumor data and treatment data, until now. We aimed to retrospectively analyze and identify the clinicopathologic features and independent prognostic factors of patients with cervical neuroendocrine carcinoma. Based on the identified prognostic factors by regression analysis methods, the nomograms were constructed to evaluate the OS of each individual. Based on the identified prognostic factors by regression analysis methods, our finding may identify the comprehensive clinical features of patients with NECC.

Materials And Methods

The SEER Program database is currently the largest publicly available cancer database, covering about 28% of the US population. In this study, patients were recruited from the SEER Program of the United States National Cancer Institute, released in 2021. Data were extracted using the SEER Stat version 8.3.8 of National Cancer Institute (NCI). Available data included patient demographics (e.g., age, gender, race, marital status), tumor data (histology, stage), and treatment data (surgery, radiation, chemotherapy). However, some data elements (e.g., The International Federation of Gynecology and Obstetrics (FIGO) staging, details of surgical therapy, tumor size, lymph node involvement) are consistently available only in more recent time periods.

Histologically diagnosed cases were identified by the specific codes (8041/3, 8013/3, 8246/3, 8240/3) of the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) for small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), neuroendocrine carcinoma NOS and atypical carcinoid, the amount of which is so small that it is calculated together with neuroendocrine carcinoma NOS, respectively. The primary end point of our study is overall survival (OS). OS was measured from the date of diagnosis to the date of death occurring as a result of all causes or the last follow-up.

Only the first diagnosis of cervical cancer was included, and the cases with previous malignant tumor history were excluded. For each case, the following information from SEER was also obtained: race, age, marital status, primary site, FIGO staging (version 2009), radiation, chemotherapy, surgery, number of regional lymph nodes found during surgery, number of regional positive lymph nodes and histological subtype. In addition, cases were excluded from the study if they had incomplete information on any of these characteristics. Patients who were followed up for less than one month were also excluded. Considering that the number of cases with FIGO staging is available only during 2010-2016, in order to further demonstrate the robustness of the prognostic differences of pathological types, the first diagnosed Neuroendocrine carcinoma of the cervix cases available in SEER database are used as a new dataset for sensitivity analysis, all the cases between 1975-2016 are included (a total of 250 cases).

We made the following adjustments to variables violating this assumption: age was converted into a grade variable through the quartile method (ages 0 to 39, 40 to 44, 45 to 59 and 60 years older). The number of regional lymph nodes found is a continuous variable. Through the survMisc package in R

version 4.0, the optimal cutoff value is determined to be 12, and converted to negative (0), 0 to 12 and 13 and above; Positive lymph nodes are also continuous variables. Through the survMisc package in R, the optimal cutoff value is determined to be 3, then we converse it into 3 categorical variables, 0, 0 to 3 and 4 and more; Marital status is a multi-category data, uniformly converted into: single/unmarried, married, divorced and other status; The primary lesions are divided into C53.0, C53.1, C53.8, C53.9, considering the frequency distribution, the variables are sorted and converted into 2 categorical variables, C53.0 (cervix) and others; The FIGO staging is converted to three categories, I~IIA, IIB~IVA and IVB.

In this article we use overall survival (OS) as the first outcome indicator. Survival curves were plotted by Kaplan–Meier method. The proportional hazard Cox model was used for univariate and multivariate survival analysis. Characteristics with $P < 0.05$ in the univariate logistic regression analysis were then further analyzed using the Cox regression model. Interaction test for single factor and multi-factor results adjusted for other factors were also performed. Then, sensitivity analysis with the aforementioned data set was conducted. The predictive performance of the data set was measured by Expect value(E-value). We explored the potential for unmeasured confounding between subgroups of potential predictors by calculating E-value. The E-value quantifies the required magnitude of an unmeasured confounder that could negate the observed association. The sensitivity analysis of both multivariate and univariate Cox regression analysis was carried out, the result of which were performed by forest plot, and each variable satisfies the Ph test. The survival package in R was used to draw the Kaplan-Meier survival curves based on the median survival time and time-point survival rate of all variables in the sensitivity analysis data set.

Results

Demographic and clinical characteristics

From 2000 to 2018, our study cohort included a total of 250 cases. Among them, 150 patients with SCC, 27 with LCC and 73 with other types of cancer. The demographic and clinical characteristics of cervical neuroendocrine carcinoma patients are shown in Table 1. In this cohort, 143(57%) of patients are dead of the disease, 99(40%) are alive or dead of other causes, and 8(3%) remained unknown. Moreover, there were 71(28%) patients with FIGO stage I~IIA, 80(32%) with stage IIB~IVA, and 99(40%) with FIGO stage IVB. Chi-square test showed no significant differences in some variables and treatment patterns, including diagnosis age, race, marital status, primary sites, number of regional lymph nodes, primary lesions, and FIGO stage.

Table 1 The demographic and clinical characteristics of cervical neuroendocrine carcinoma patients

Variables	Total (n = 250)	SCC (n = 150)	LCC (n = 27)	Others (n = 73)	p
Outcome, n (%)					0.781
Dead	161 (64)	95 (63)	19 (70)	47 (64)	
Live	89 (36)	55 (37)	8 (30)	26 (36)	
Outcome2, n (%)					0.655
Dead	143 (57)	81 (54)	17 (63)	45 (62)	
Live. or Died other causes	99 (40)	63 (42)	9 (33)	27 (37)	
Unknown	8 (3)	6 (4)	1 (4)	1 (1)	
Outcome3, n (%)					0.664
Died of cervical cancer	143 (57)	81 (54)	17 (63)	45 (62)	
Died other causes	10 (4)	8 (5)	1 (4)	1 (1)	
Live	89 (36)	55 (37)	8 (30)	26 (36)	
Unknown	8 (3)	6 (4)	1 (4)	1 (1)	
Age, Median (IQR)	46.0 (36.0, 57.0)	46.0 (35.0, 56.8)	45.0 (38.0, 63.0)	43.0 (36.0, 53.0)	0.368
Race, n (%)					0.103
Black	46 (18)	34 (23)	1 (4)	11 (15)	
Others	32 (13)	16 (11)	5 (19)	11 (15)	
White	172 (69)	100 (67)	21 (78)	51 (70)	
Primary.site, n (%)					0.672
Cervix uteri	213 (85)	125 (83)	24 (89)	64 (88)	
Others	37 (15)	25 (17)	3 (11)	9 (12)	
Surgery, n (%)					0.696
NO	130 (52)	80 (53)	12 (44)	38 (52)	
YES	120 (48)	70 (47)	15 (56)	35 (48)	
Radiation, n (%)					0.491
NO	182 (73)	106 (71)	22 (81)	54 (74)	
YES	68 (27)	44 (29)	5 (19)	19 (26)	

Chemotherapy, n (%)					0.277
NO	37 (15)	27 (18)	3 (11)	7 (10)	
YES	213 (85)	123 (82)	24 (89)	66 (90)	
Marital, n (%)					0.661
Divorced	57 (23)	37 (25)	6 (22)	14 (19)	
Married	100 (40)	55 (37)	14 (52)	31 (42)	
Single/UnMarried	83 (33)	53 (35)	6 (22)	24 (33)	
Unknown	10 (4)	5 (3)	1 (4)	4 (5)	
Regional.nodes, n (%)					0.209
0	156 (62)	99 (66)	12 (44)	45 (62)	
0~12	38 (15)	23 (15)	5 (19)	10 (14)	
13~	56 (22)	28 (19)	10 (37)	18 (25)	
Nodes.positive, n (%)					0.832
0	215 (86)	127 (85)	23 (85)	65 (89)	
0~3	28 (11)	19 (13)	3 (11)	6 (8)	
4~	7 (3)	4 (3)	1 (4)	2 (3)	
FIGO, n (%)					0.136
I~IIA	71 (28)	38 (25)	10 (37)	23 (32)	
IIB~IVA	80 (32)	53 (35)	3 (11)	24 (33)	
IVB	99 (40)	59 (39)	14 (52)	26 (36)	
Age.cat, n (%)					0.066
~39	90 (36)	55 (37)	8 (30)	27 (37)	
40~44	30 (12)	15 (10)	5 (19)	10 (14)	
45~59	73 (29)	45 (30)	3 (11)	25 (34)	
60~	57 (23)	35 (23)	11 (41)	11 (15)	

Survival analysis and prognostic factors for NECCs

Kaplan-Meier analysis determined the impact of variables on survival. As expected, there were significantly lower rates of death in patients with lower FIGO staging (I-IIA vs. IIB~IVA vs. IVB; $P < 0.001$) (Figure 1A). We also found that patients with less regional lymph nodes had poorer survival outcomes in cervical neuroendocrine carcinoma (0 vs. 0-12 vs. 13 and above; $P < 0.001$) (Figure 1B). But the number

of positive lymph nodes showed no significant effect on survival (P=0.403) (Figure 1C). Among all age groups, young age (0-39 vs. 40-44 vs. 45-59 vs. >60 years; P < 0.001) was associated with better prognosis (Figure 1D). More interestingly, married people showed better outcomes than the other groups (single/unmarried vs. married vs. divorced vs. other status; P < 0.001) (Figure 1E). Among all tumor subtypes, SCC had the most favorable survival, whereas LCC was associated with the worst prognosis (Figure 1F). With respect to the factors associated with treatments, we found that patients who underwent surgery (yes vs. no), or chemotherapy (yes vs. no), or radiation (yes vs. no) all experienced a significantly prolonged survival (Figure 2A-C) (All P ≤0.01).

Table 2 shows univariate and multivariate analyses of potential predictors for the OS. Higher FIGO staging, more regional lymph nodes, age above 60, no radiation, no chemotherapy, and no surgery were significantly associated as risk factors for the OS in the univariate analysis. Therefore, these significant risk factors were included in the multivariate analysis. Multivariate analysis identified that higher FIGO staging (IIB~IVA [hazard ratio (HR), 1.934; 95% CI, 1.02–3.668], IVB [HR, 4.465; 95% CI, 2.349–8.487]), no chemotherapy treatment (HR, 0.356; 95% CI, 0.224–0.568), were independent indicators of poor prognosis.

Table 2 Univariate and multivariate analyses of potential predictors

Charateristics	Unadj.HR(95%CI)	P value	Adj.HR(95%CI)	P value
Race				
Black vs. White	1.259(0.903–1.755)	0.175	1.103(0.771–1.579)	0.591
Others vs. White	0.755(0.543–1.049)	0.094	1.049(0.72–1.526)	0.804
FIGO				
IIB~IVA vs. I~IIA	2.464(1.522–3.989)	< 0.001	1.934(1.02–3.668)	0.043
IVB vs. I~IIA	5.674(3.614–8.907)	< 0.001	4.465(2.349–8.487)	< 0.001
Primary.site				
Others vs. Cervix uteri	0.76(0.48–1.202)	0.241	1.027(0.628–1.678)	0.916
Radiation				
YES vs. NO	0.519(0.355–0.758)	< 0.001	0.863(0.495–1.506)	0.605
Chemotherapy				
YES vs. NO	0.39(0.259–0.59)	< 0.001	0.356(0.224–0.568)	< 0.001
Regional.nodes				
0~12 vs. 0	0.571(0.367–0.887)	0.013	0.856(0.394–1.86)	0.694
13~ vs. 0	0.281(0.176–0.448)	< 0.001	0.671(0.312–1.44)	0.306
Nodes.positive				
0~3 vs. 0	0.982(0.608–1.587)	0.941	1.352(0.608–3.009)	0.46
4~ vs. 0	0.654(0.242–1.772)	0.404	0.52(0.153–1.769)	0.295
Marital				
Married vs. Single/UnMarried	1.624(0.977–2.698)	0.061	1.683(0.964–2.938)	0.067
Divorced vs. Single/UnMarried	1.288(0.844–1.966)	0.24	1.38(0.873–2.181)	0.168
Unknown vs. Single/UnMarried	0.667(0.487–0.912)	0.011	0.837(0.597–1.175)	0.304
Surgery				
YES vs. NO	0.377(0.273–0.521)	< 0.001	0.842(0.505–1.405)	0.51
Age.cat				
40~44 vs. ~39	1.566(0.904–2.712)	0.11	1.419(0.8–2.514)	0.231
45~59 vs. ~39	1.752(1.172–2.618)	0.006	1.394(0.909–2.137)	0.128
60~ vs. ~39	2.845(1.883–4.3)	< 0.001	1.547(0.952–2.513)	0.078
Tumor.type				
Others vs. LCC	0.789(0.463–1.345)	0.384	0.701(0.39–1.261)	0.236
SCC vs. LCC	0.7(0.427–1.147)	0.156	0.412(0.236–0.72)	0.002

Subgroup analysis and sensitive analysis for risk factors

Subgroup analysis and sensitive analysis were then performed. Table 3 shows the P value for interaction for those variables, and multivariate analysis identified that patients, who had radiation therapy (HR, 0.886; 95% CI, 0.338-2.32), may contribute to better survival outcomes than those who did not have that (HR, 0.468; 95% CI, 0.317-0.692), the P value for interaction is 0.019. The situation for those who had surgery (HR, 0.831; 95% CI, 0.473-1.464) is the similar, compared with those who didn't (HR, 0.381; 95% CI, 0.24-0.603), the P value for interaction is 0.004. All E-value for sensitivity analysis with the aforementioned data set was performed in Figure 3. The primary finding was robust between the groups who underwent surgery (YES vs. NO, Unknown vs. NO); later FIGO staging (IVB vs. I-IIA, IIB~IVA vs. I~IIA); older aging (60~ vs. ~39); a larger number of regional positive lymph nodes (0~3 vs. 0).

Table 3 P value for interaction of potential predictors

Charateristics	Unadj.HR(95%CI)	P value	Adj.HR(95%CI)	P value
Race				
Black vs. White	0.917(0.781-1.075)	0.285	0.952(0.809-1.12)	0.553
Others vs. White	0.724(0.603-0.869)	< 0.001	0.876(0.724-1.06)	0.173
FIGO				
IIB~IVA vs. I-IIA	2.381(1.484-3.819)	< 0.001	1.291(0.784-2.127)	0.316
IVB vs. I-IIA	5.392(3.48-8.354)	< 0.001	2.4(1.505-3.828)	< 0.001
Unknown vs. I-IIA	2.509(1.689-3.726)	< 0.001	1.585(1.039-2.418)	0.033
Primary.site				
Others vs. Cervix uteri	0.802(0.64-1.005)	0.055	0.903(0.715-1.141)	0.393
Radiation				
YES vs. NO	0.665(0.555-0.798)	< 0.001	1.071(0.851-1.348)	0.557
Chemotherapy				
YES vs. NO	0.982(0.829-1.163)	0.833	0.815(0.662-1.003)	0.053
Regional.nodes				
0-12 vs. 0	0.59(0.455-0.766)	< 0.001	0.745(0.518-1.071)	0.112
13~ vs. 0	0.389(0.309-0.49)	< 0.001	0.607(0.434-0.85)	0.004
Unknown vs. 0	0.566(0.451-0.711)	< 0.001	0.721(0.552-0.94)	0.016
Nodes.positive				
0~3 vs. 0	0.824(0.625-1.087)	0.172	1.73(1.201-2.493)	0.003
4~ vs. 0	1.094(0.77-1.555)	0.615	2.047(1.338-3.13)	< 0.001
Marital				
Married vs. Single/UnMarried	1.22(0.939-1.584)	0.137	1.016(0.775-1.333)	0.907
Divorced vs. Single/UnMarried	0.891(0.72-1.103)	0.291	0.871(0.698-1.086)	0.22
Unknown vs. Single/UnMarried	0.742(0.638-0.863)	< 0.001	0.879(0.751-1.029)	0.11
Surgery				
Unknown vs. NO	0.511(0.419-0.622)	< 0.001	0.569(0.443-0.731)	< 0.001
YES vs. NO	0.365(0.303-0.441)	< 0.001	0.467(0.358-0.609)	< 0.001
Age.cat				
40-44 vs. ~39	1.23(0.946-1.599)	0.121	1.101(0.842-1.44)	0.481
45-59 vs. ~39	1.628(1.327-1.996)	< 0.001	1.429(1.155-1.769)	0.001
60~ vs. ~39	2.392(1.958-2.922)	< 0.001	1.821(1.45-2.286)	< 0.001
Tumor.type				
Others vs. LCC	0.907(0.632-1.302)	0.596	0.772(0.526-1.132)	0.185
SCC vs. LCC	0.762(0.539-1.075)	0.122	0.564(0.39-0.817)	0.002

Survival analysis for risk factors

Then we calculated the median survival time and overall survival rate of all variables in the sensitivity analysis data, and plotted the KM curve. The survival curve was grouped for five: 0-, 120-, 240-, 360-, 480-. We found that patients with the tumor subtype of LCC had poorer survival than patients whose tumor subtype was SCC (median OS, 15 vs. 21 months; P = 0.022) (Figure 4A). Among all age groups, young age was associated with better prognosis (P < 0.001) (Figure 4B). And interestingly, the median OS of patients who were married was 23 months (95% CI, 20-26), while the median OS of patients who were

single /unmarried was 18 months (95% CI, 16-25) and 14 (95% CI, 11-16) for those who were divorced (P < 0.001) (Figure 4C). Among all races, subtype of other races had the most favorable survival, whereas black was associated with the worst prognosis (P = 0.001) (Figure 4D). Patients, whose FIGO staging is IVB or regional lymph nodes were more than 13, had worst survival than other groups (Figure 4E, 4F). With respect to the factors associated with treatments, we found that patients who underwent surgery (yes vs. no vs. unknown) or radiation (yes vs. no) experienced prolonged survival, both P < 0.001 (Figure 4G, 4H). However, there was no statistical significance between patients who underwent chemotherapy (yes vs. no) (P = 0.843).

We then again performed univariate and multivariate analyses of Cox regression analysis based on the sensitivity analysis data set, the results were shown in Table 3. Higher FIGO staging, more regional lymph nodes, older age, no radiation, and no surgery were significantly associated as risk factors for the OS. And multivariate analysis identified that higher FIGO staging (IVB vs. IA~IIA [HR, 2.4; 95% CI, 1.505-3.828], P < 0.001), no surgery treatment (Unknown vs. NO [HR, 0.569; 95% CI, 0.443-0.731], YES vs. NO [HR, 0.467; 95% CI, 0.358-0.609], both P < 0.001), were independent indicators of poor prognosis.

Discussion

Neuroendocrine carcinoma of the cervix is a rare but highly malignant primary carcinoma of the cervix, which represents 0.9–1.5% of all cervical carcinomas.[3] The biology characteristics of NECC are different from squamous cell carcinoma or adenocarcinoma of the cervix. For example, local and distant relapses occur more frequently in NECC, and the 5-year overall survival rates for patients with NECC at early (I–IIA) and advanced stage (IIB–IVB) were 30–63% and 0–18% respectively, compared to > 65% for cervical squamous cell carcinoma and adenocarcinoma. [2–4] The management of NECC is difficult and is associated with uncertainty. Until now there is no standardized therapy for this type of malignancy based on controlled trials. Evaluating the clinical features and prognostic factors may assist gynecologic oncologists in early diagnosis and treatment decision-making, whereas those have not been explored comprehensively

In this study, clinical parameters were used for predicting OS. As discovered based on the SEER database, tumor subtype, age, marriage, race, number of regional lymph nodes, number of positive lymph nodes, radiotherapy, surgery, and FIGO stage were all factors affecting OS,[5] and multivariate analysis identified FIGO staging and surgery treatment as independent indicators. Older age was an unfavorable predictor for OS. The poor physical condition of aging patients might reduce the patient's tolerance to surgery and other treatment, and subsequently decrease the survival time. People with married status showed a better prognosis for NECCs. The reason may be that married people could get more social and economic support. However, the effect of these prognostic factors on OS was limited.

Surgery, especially in the case of primary NECCs, is the primary therapeutic option. Agreed well with those of previous study, we found that surgery significantly improves the prognosis in patients with NECCs, the median OS of which was 40 months (95% CI, 26-82), while the median OS of the non-surgery group was

11 months (95% CI, 10-23) and 22 (95% CI, 17-32) for those whose surgery status was unknown ($P < 0.001$). Currently, the most common primary treatment was radical surgery combined with either neoadjuvant or adjuvant chemotherapy. However, for patients with end-stage disease, radical hysterectomy with lymphadenectomy brings more postoperative and long-term complication, which showed negative effect on the prognosis.[6–10]

Radiotherapy can effectively improve the prognosis of NECC patients according to our result. However, another analysis of the SEER database of patients with High-Grade Neuroendocrine cancer of cervix concluded that primary treatment by radical surgery or external beam radiotherapy with or without brachytherapy yielded equally poor survival. [11] Radiotherapy is often used as an adjuvant after surgery to improve the prognosis of patients, and sometimes as an alternative to radical surgical resection for end-stage patients.[12] The reason for this conflict may be some subtypes of NECCs were low sensitive to radiotherapy[9]. And all the patients they included in the research had a higher degree of malignancy and were less sensitive to treatment.

Chemotherapy is often used to improve the prognosis of NECCs patients. In our analysis, chemotherapy had a negative prognostic impact. However, Cohen et al. reviewed 188 patients with SCNEC, chemotherapy improved the 3-year OS in patients with stages IIB–IVA and the use of chemotherapy was independent prognostic variable for improved OS.[13] The reason for this contradiction may be that no treatment guidelines are currently available due to the rarity of the disease. Many chemotherapy regimens have been described in the treatment, among them, cisplatin/carboplatin in combination with other chemotherapy regimens have been described most frequently published studies. But the exact dosage and therapy duration varied considerably. [14, 15] In addition, chemotherapeutic drugs are cytotoxic, causing pain and relatively high mortality in patients. Nevertheless, future clinical trials should continue to explore the role of chemotherapy in NECC patients.

The number of regional lymph nodes, instead of the number of positive lymph nodes showed effect on overall survival rates according to our analysis. This may give us an early warning of poor survival outcomes during the treatment, as patients with cervical NECCs are more likely to have lymph node involvement, compared with those who suffer from squamous cell carcinomas or adenocarcinomas of the cervix. [16]

To our knowledge, this study is the first to offer a comprehensive analysis of the first diagnosed Neuroendocrine carcinoma of the cervix cases available in the SEER database. Altogether, 250 NECC patients complied with the standard. We included demographic characteristics, FIGO stage, and treatment strategies in our analysis. As a result, our data have good generalizability and do not need to be limited by race, age, and marriage. Moreover, our data were tested by ROC analysis, K-M analyses, and Cox proportional-hazards model, to predict the survival of NECC patients.

The present study has several limitations. Firstly, although the SEER-Medicare linked database provides a large sample size with diverse demographic data, most patients from the SEER database were white race, so there was potential racial heterogeneity that could not be extrapolated to other human species.

Secondly, some important data associated with patients' prognosis are missing, such as resection mode, chemotherapy strategy, and radiotherapy dose, the effectiveness of the therapies in White patients with NECCs cannot be fully elucidated. Thirdly, it has all the limitations inherent in retrospective studies, which have a lower level of evidence than prospective studies. Finally, as the pathogenesis of the disease continues to be explored, and new treatment options continue to be improved, such as the application of targeted drugs like Bevacizumab the prognosis of patients will certainly change. The information data of this nomogram would also need to be updated. In the future, more important variables would be collected and incorporated into the nomogram.

In conclusion, NECC is a rare disease with highly aggressive features and poor survival. Despite the lack of more prospective randomized clinical trials, our retrospective investigation based on the SEER database shows that for patients with NECC surgery and radiotherapy seems to be the effective treatment, while chemotherapy has a negative prognostic impact. We hope that our study can deepen people's understanding of this rare disease and inspires more studies to help define optimal local management for NECC.

Declarations

Author Contribution

All authors contributed to the study conception and design. Pro. Xiumin Huang: proposed the project and designed the study. Material preparation, data collection and analysis were performed by Dr. Ziran Yin. The first draft of the manuscript was written by Dr. Ziran Yin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors, Dr. Ziran Yin and Pro. Xiumin Huang, declare that they have no conflict of interest.

Ethical approval statement

The data are public and do not involve the privacy of patients, so the review and consent of the ethics committee are not required.

Informed consent

The data are public and do not involve the privacy of patients, so no individual consent is required to be included in this study.

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Figures

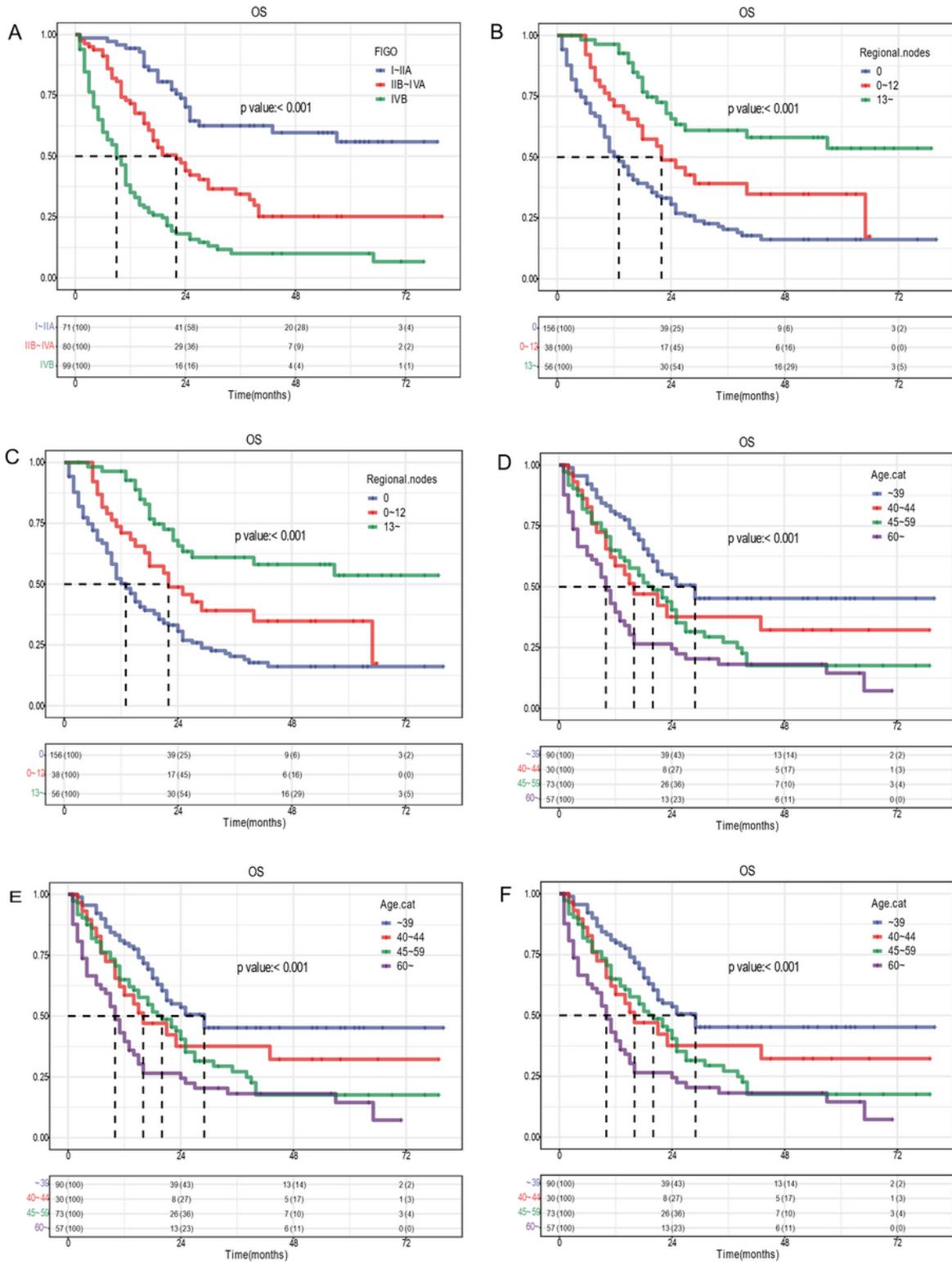


Figure 1

Kaplan-Meier analysis of overall survival (OS) among patients with cancer of the cervical neuroendocrine carcinomas. **(A)** Overall survival (OS) stratified by FIGO staging. **(B)** Overall survival (OS) stratified by the number of regional lymph nodes. **(C)** Overall survival (OS) stratified by the number of positive lymph

nodes. (D) Overall survival (OS) stratified by age. (E) Overall survival (OS) stratified by marital status. (F) Overall survival (OS) stratified by histological grade of the cervical carcinoma.

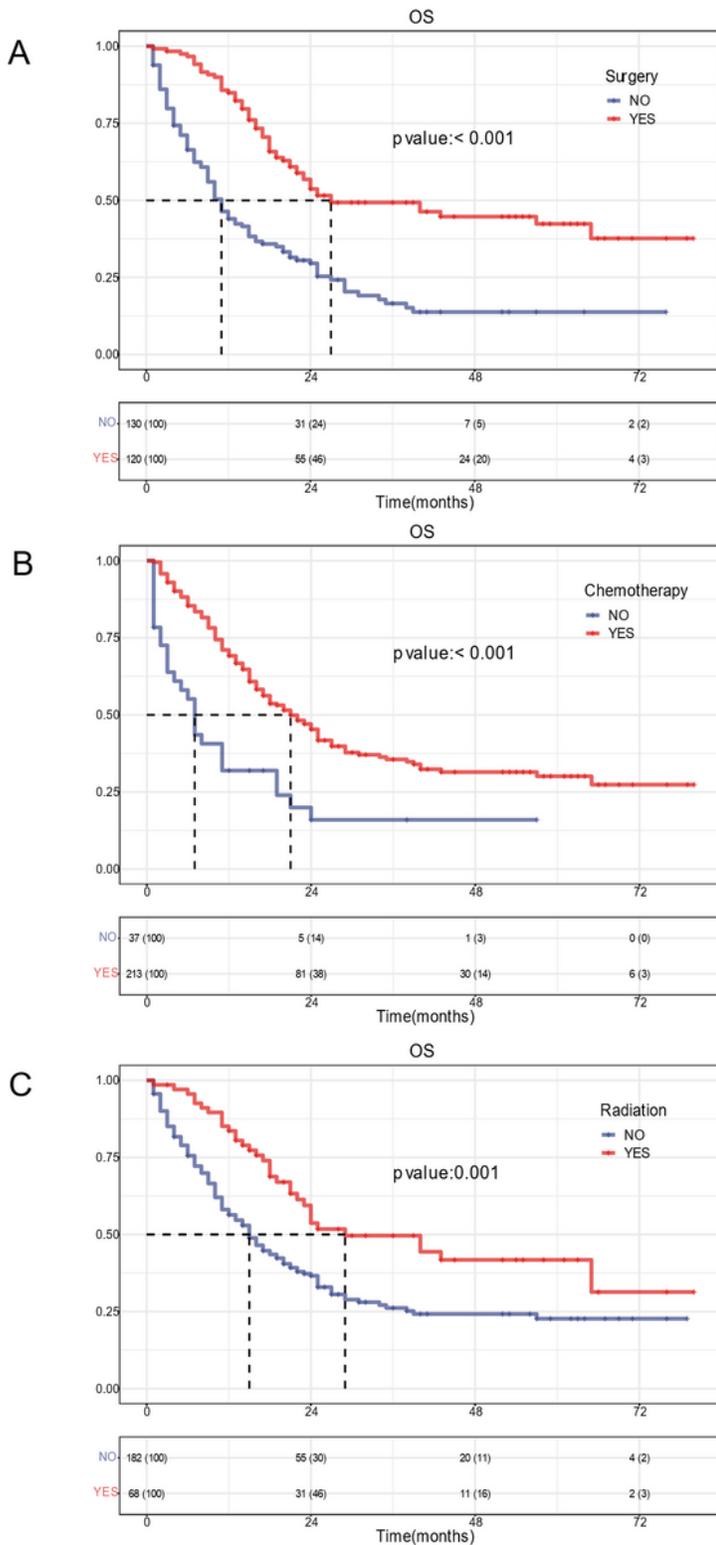


Figure 2

Kaplan-Meier analysis of overall survival (OS) among patients with cervical neuroendocrine carcinomas with respect to the factors associated with treatments. (A) Overall survival (OS) stratified by surgery

operation. (B) Overall survival (OS) stratified by chemotherapy. (C) Overall survival (OS) stratified by radiation therapy.

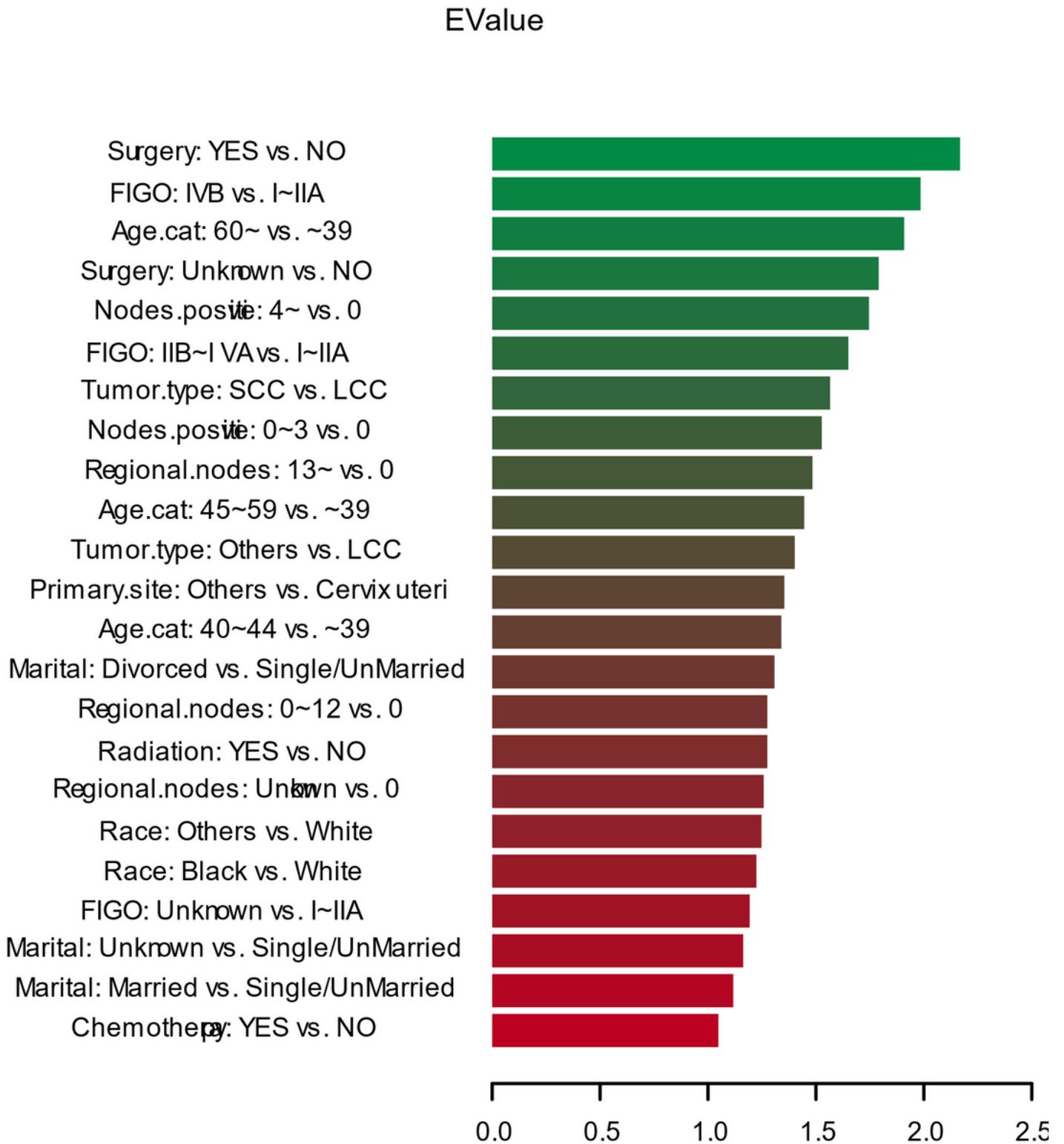


Figure 3

Expect value(E-value) for sensitivity analysis to data set of the first-diagnosed neuroendocrine carcinoma of the cervix.

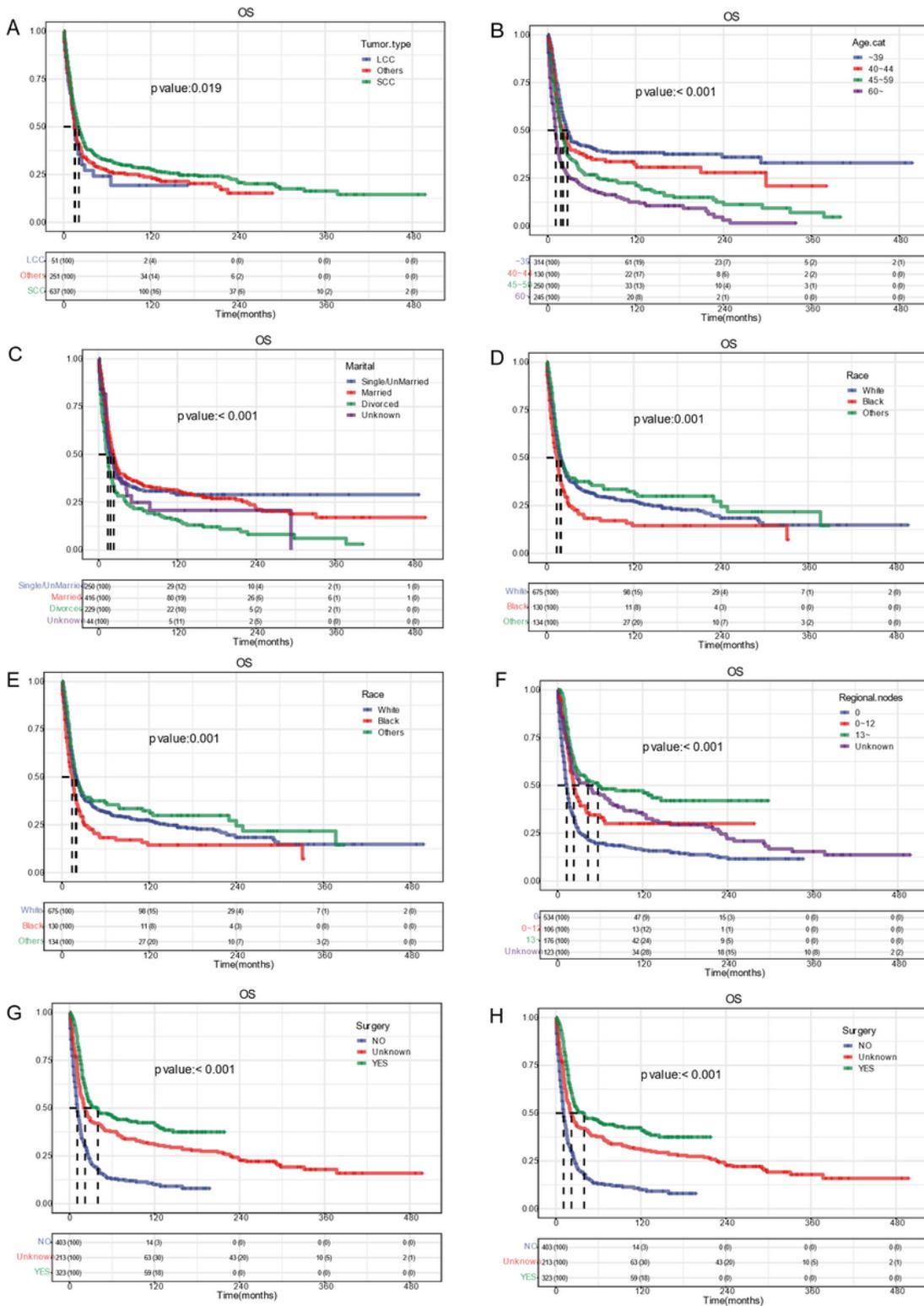


Figure 4

Median survival time and Kaplan-Meier analysis of overall survival (OS) among patients with cancer of the cervical neuroendocrine carcinomas after sensitivity analysis. **(A)** Overall survival (OS) stratified by histological grade of the cervical carcinoma. **(B)** Overall survival (OS) stratified by age. **(C)** Overall survival (OS) stratified by marital status. **(D)** Overall survival (OS) stratified by race. **(E)** Overall survival (OS) stratified by FIGO staging. **(F)** Overall survival (OS) stratified by the number of regional lymph nodes.

(G) Overall survival (OS) stratified by surgery operation. (F) Overall survival (OS) stratified by radiation therapy.