Nomogram to predict survival of pulmonary large-cell neuroendocrine carcinoma after surgery

Qian Huang
Henan University
Jie Liu
Henan University
Huifang Cai
Henan University
Qi Zhang
Henan University
Lina Wang (wanglinatg@163.com)
Henan University

Research article

Keywords: pulmonary large-cell neuroendocrine carcinoma, prediction model, prognostic factors, nomogram, Surveillance, Epidemiology and End Results program

Posted Date: March 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17339/v1

Abstract

Background Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare primary malignant tumor with a poor prognosis, and surgery is the main treatment. However, there are no effective predictive tools to assess the prognosis of postoperative patients. Our aim is to identify prognostic factors and construct nomogram to accurately assess prognosis.

Methods Patients were identified in the Surveillance, Epidemiology, and End Results (SEER) database. Based on the results of Cox regression analysis, construct nomogram for predicting 1-, 3-, and 5-year survival. The predictive performance of nomogram was evaluated using the consistency index (C-index), the area under the receiver operating characteristics curve (AUC), and calibration plots.

Results We finally screened 903 patients with pulmonary LCNEC who underwent surgery. The Cox regression analysis showed that age, SEER stage, T stage, N stage, M stage, tumor size, and chemotherapy were independent prognostic factors for overall survival ($P<0.05$). The C-index of the nomogram is 0.681 on the training cohort and 0.675 on the validation cohort. The AUC and calibration plots show that the nomogram has good performance.

Conclusion We constructed and validated nomogram for predicting 1-, 3-, and 5-year survival of patients with pulmonary LCNEC after surgery. Our nomogram provides reference information for assessing the overall survival of these patients.

Introduction

Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare and highly invasive subtype of lung cancer that accounts for fewer than 3% of cases[1, 2]. The 2015 World Health Organization (WHO) standard classifies LCNEC, small-cell lung carcinoma, typical carcinoid, and atypical carcinoid as neuroendocrine tumors[3]. Pulmonary LCNEC is high-grade neuroendocrine tumor with 5-year survival rate ranging from 15–57%[4–7]. Surgical treatment is still one of the main options for patients with pulmonary LCNEC. Previous studies have performed predictive tools for pulmonary LCNEC patients[8]. However, there are few reports about the survival of pulmonary LCNEC after surgery and there is no effective prediction tool[9]. Therefore, it is important to accurately assess the prognosis of patients with pulmonary LCNEC after surgery.

Nomogram is a predication tool based on statistical data obtained from a population with the same disease characteristics. Many nomograms suitable for various types of tumors have been established to help clinicians to make rational decisions regarding diagnoses, treatments, and prognoses[10–12]. Moreover, a large-sample study of rare diseases can be conducted by utilizing a population-based cancer database, and the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute covers approximately 34.6% of the U.S. population[13–15]. Analysis of the SEER database should provide useful information about prognostic factors in patients with pulmonary LCNEC after surgery.

This study obtained data from the SEER database and constructed nomogram to predict survival in patients with pulmonary LCNEC after surgery. Our aim was to determine independent prognostic factors for patients with pulmonary LCNEC after surgery and to predict their overall survival at 1-, 3-, and 5-year.

Methods

Data sources

The specific database we used is designated “the Incidence – SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying).” All data on patients with pulmonary LCNEC were obtained using version 8.3.5 of the SEER*Stat software (www.seer.cancer.gov/seerstat). Since all information in the SEER database has been de-identified, no institutional review board approval or informed consent was required for this study.

Patients

Patients were identified in the SEER database as having pulmonary LCNEC by applying the International Classification of Disease—Oncology, Third Edition (ICD-O-3) site code: Lung and Bronchus. The ICD-O-3 histology code: 8013/3. The inclusion criteria for this study were as follows: (1) diagnosed between 2004 to 2015; (2) diagnosis confirmed by microscopy; (3) receiving definite surgical treatment; and (4) availability of data on age at diagnosis, race, sex, marital status, year of diagnosis, laterality, grade, SEER stage, T stage, N stage, M stage, tumor size, radiation, chemotherapy, and survival time. Patients with nonprimary tumors were excluded from the study. The patient inclusion and exclusion process applied to the SEER database is shown in Fig. 1.

Covariates

We included the following variables: age at diagnosis, race, sex, marital status, year of diagnosis, laterality, grade, SEER stage, T stage, N stage, M stage, tumor size, radiation, and chemotherapy. The age at diagnosis was continuous variable while the other variables were categorical variables. Unmarried patients included those who were widowed, single, unmarried, living with a domestic partner, divorced, or separated.

Statistical analysis and nomogram construction

All tests were two-sided and $P < 0.05$ was considered indicative of statistical significance. Categorical variables are expressed as percentages. Continuous variables that conformed to a normal distribution are expressed as mean and standard-deviation values, while other continuous variables (i.e., those conforming to a skewed distribution) are presented by median and interquartile-range values. Cox regression models were used for univariate and multivariate analysis, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI) values. Based on the results of multivariate analysis, construct nomogram in patients with pulmonary LCNEC after surgery. All analyses were performed using R software (version 3.5.1).

Nomogram validation and performance evaluation

We validated the models in both the training and validation cohorts. The predictive performance of nomogram was evaluated using the consistency index (C-index) and the area under the receiver operating characteristics curve (AUC). The value of the C index ranges from 0.5 to 1.0, 0.5 means no discrimination, and 1.0 means excellent discrimination[16]. The consistency between the predicted and actual results was evaluated using calibration plots. The discrimination performance and calibration were evaluated using bootstrap with 500 resamples.

Results

Patient Characteristics

A total of 903 patients with pulmonary LCNEC who underwent surgery were included in the cohort. Demographic and tumor characteristics are shown in Table 1. There are 632 patients in the training cohort and 271 patients in the validation cohort. At the end of follow up, 565 patients died. The median follow-up time was 27 months.

Table 1

Baseline characteristics of the patients

Variable	Total (n = 903)	Training Cohort (n = 632)	Validation Cohort (n = 271)
Age, median (IQR)	66 (59–73)	66 (59–73)	67 (59–73)
Race			
White	769 (85.2)	539 (85.3)	230 (84.9)
Black	95 (10.5)	69 (10.9)	26 (9.6)
Other	39 (4.3)	24 (3.8)	15 (5.5)
Sex			
Male	471 (52.2)	331 (52.4)	140 (51.7)
Female	432 (47.8)	301 (47.6)	131 (48.3)
Marital status			
Married	512 (56.7)	364 (57.6)	148 (54.76)
Unmarried	356 (39.4)	242 (38.3)	114 (42.1)
Unknown	35 (3.9)	26 (4.1)	9 (3.3)
Year of diagnosis			
2004–2009	398 (44.1)	283 (44.8)	115 (42.4)
2010–2015	505 (55.9)	349 (55.2)	156 (57.6)
Laterality			
Left	395 (43.7)	273 (43.2)	122 (45.0)
Right	507 (56.1)	359 (56.8)	148 (54.6)
Bilateral	1 (0.1)	0 (0.0)	1 (0.4)
Grade			
	8 (0.9)	6 (0.9)	2 (0.7)
	36 (4.0)	26 (4.1)	10 (3.7)
	660 (73.1)	461 (72.9)	199 (73.4)
	199 (22.0)	139 (22.0)	60 (22.1)
SEER stage			

Abbreviations: IQR, interquartile range.

Variable	Total (n = 903)	Training Cohort (n = 632)	Validation Cohort (n = 271)
Localized	412 (45.6)	289 (45.7)	123 (45.4)
Regional	398 (44.1)	278 (44.0)	120 (44.3)
Distant	93 (10.3)	65 (10.3)	28 (10.3)
T			
T1	350 (38.8)	243 (38.4)	107 (39.5)
T2	413 (45.7)	294 (46.5)	119 (43.9)
T3	52 (5.8)	34 (5.4)	18 (6.6)
T4	83 (9.2)	60 (9.5)	23 (8.5)
Tx	5 (0.6)	1 (0.2)	4 (1.5)
N			
N0	658 (72.9)	455 (72.0)	203 (74.9)
N1	129 (14.3)	89 (14.1)	40 (14.8)
N2	107 (11.8)	81 (12.8)	26 (9.6)
N3	6 (0.7)	5 (0.8)	1 (0.4)
Nx	3 (0.3)	2 (0.3)	1(0.4)
M			
M0	831 (92.0)	582 (92.1)	249 (91.9)
M1	71 (7.9)	49 (7.8)	21 (7.7)
Mx	2 (0.2)	1 (0.2)	1 (0.4)
Tumor size (mm)			
< 20	465 (51.5)	315 (49.8)	150 (55.4)
20–49	276 (30.6)	192 (30.4)	84 (31.0)
> 50	153 (16.9)	119 (18.8)	34 (12.5)
Unknown	9 (1.0)	6 (0.9)	3 (1.1)
Radiation			
No/Unknown	751 (83.2)	527 (83.4)	224 (82.7)
Yes	152 (16.8)	105 (16.6)	47 (17.3)

Abbreviations: IQR, interquartile range.

Variable	Total (n = 903)	Training Cohort (n = 632)	Validation Cohort (n = 271)
Chemotherapy			
No/Unknown	544 (60.2)	376 (59.5)	168 (62.0)
Yes	359 (39.8)	256 (40.5)	103 (38.0)
Abbreviations: IQR, interquartile range.			

Prognostic factors for OS

Univariate analysis of the training cohort showed that age (P < 0.001, HR = 1.033, 95% CI = 1.023–1.044), SEER stage (regional, P < 0.001, HR = 1.462, 95% CI = 1.177–1.817; distant, P < 0.001, HR = 3.153, 95% CI = 2.318–4.288), T stage (T2, P < 0.001, HR = 0.965, 95% CI = 0.771–1.207; T3, P < 0.001, HR = 1.600, 95% CI = 1.045–2.449; T4, P < 0.001, HR = 2.440, 95% CI = 1.754–3.394; Tx, P < 0.001, HR = 6.557, 95% CI = 0.910-47.217), N stage (N1, P < 0.001, HR = 1.770, 95% CI = 1.347–2.326; N2, P < 0.001, HR = 1.960, 95% CI = 1.478-2.600; N3, P < 0.001, HR = 4.830, 95% CI = 1.795–12.998; Nx, P < 0.001, HR = 0.780, 95% CI = 0.109–5.583), M stage (M1, P < 0.001, HR = 2.135, 95% CI = 1.543–2.956; Mx, P < 0.001, HR = 13.548, 95% CI = 1.871–98.088), tumor size (> 50, P = 0.013, HR = 1.453, 95% CI = 1.081–1.953; Unknown, P = 0.010, HR = 3.240, 95% CI = 1.313–7.997), and radiation (P = 0.001, HR = 1.516, 95% CI = 1.179–1.950) were prognostic factors, as shown in Table 2. Multivariate analysis showed that age (P < 0.001, HR = 1.034, 95% CI = 1.023–1.046), SEER stage (distant, P = 0.007, HR = 2.700, 95% CI = 1.296–5.624), T stage (T2, P = 0.047, HR = 0.726, 95% CI = 0.528–0.997), N stage (N1, P < 0.001, HR = 2.024, 95% CI = 1.442–2.840; N2, P < 0.001, HR = 2.228, 95% CI = 1.557–3.189), M stage (Mx, P = 0.023, HR = 11.076, 95% CI = 1.380-88.911), tumor size (20–49, P = 0.039, HR = 1.342, 95% CI = 1.013–1.778; >50, P = 0.004, HR = 1.752, 95% CI = 1.190–2.580), and chemotherapy (P < 0.001, HR = 0.549, 95% CI = 0.423–0.713) were independent prognostic factors (Table 3).

Table 2
Univariate Cox regression analysis for overall survival in training cohort

Characteristics	Univariate analysis	
	HR (95% CI)	P value
Age	1.033 (1.023–1.044)	< 0.001
Race		
White	Reference	
Black	1.199 (0.872–1.649)	0.263
Other	1.197 (0.735–1.950)	0.469
Sex		
Male	Reference	
Female	0.859 (0.703–1.050)	0.138
Marital status		
Married	Reference	
Unmarried	0.991 (0.803–1.223)	0.934
Unknown	0.989 (0.586–1.670)	0.968
Year of diagnosis		
2004–2009	Reference	
2010–2015	1.105 (0.896–1.364)	0.350
Laterality		
Left	Reference	
Right	0.986 (0.806–1.206)	0.890
Bilateral	-	-
Grade		
	Reference	
	1.220 (0.357–4.170)	0.750
	1.092 (0.350–3.409)	0.879
	1.117 (0.353–3.534)	0.850

Characteristics	Univariate analysis	
	HR (95% CI)	P value
SEER stage		
Localized	Reference	
Regional	1.462 (1.177–1.817)	< 0.001
Distant	3.153 (2.318–4.288)	< 0.001
T		
T1	Reference	
T2	0.965 (0.771–1.207)	< 0.001
T3	1.600 (1.045–2.449)	< 0.001
T4	2.440 (1.754–3.394)	< 0.001
Tx	6.557 (0.910-47.217)	< 0.001
N		
N0	Reference	
N1	1.770 (1.347–2.326)	< 0.001
N2	1.960 (1.478-2.600)	< 0.001
N3	4.830 (1.795–12.998)	< 0.001
Nx	0.780 (0.109–5.583)	< 0.001
M		
M0	Reference	
M1	2.135 (1.543–2.956)	< 0.001
Mx	13.548 (1.871–98.088)	< 0.001
Tumor size (mm)		
< 20	Reference	
20–49	1.203 (0.936–1.547)	0.149
> 50	1.453 (1.081–1.953)	0.013
Unknown	3.240 (1.313–7.997)	0.010
Radiation		

Characteristics	Univariate analysis	
	HR (95% CI)	P value
No/Unknown	Reference	
Yes	1.516 (1.179–1.950)	0.001
Chemotherapy		
No/Unknown	Reference	
Yes	0.828 (0.674–1.017)	0.072

Table 3
Multivariate Cox regression analysis for overall survival in training cohort

Characteristics	Multivariate analysis	
	HR (95% CI)	P value
Age	1.034 (1.023–1.046)	< 0.001
Race		
White	Reference	
Black	1.378 (0.974–1.949)	0.069
Other	1.140 (0.683–1.901)	0.614
Sex		
Male	Reference	
Female	0.985 (0.793–1.224)	0.896
Marital status		
Married	Reference	
Unmarried	0.893 (0.715–1.115)	0.320
Unknown	1.019 (0.595–1.744)	0.945
Year of diagnosis		
2004–2009	Reference	
2010–2015	1.173 (0.937–1.469)	0.162
Laterality		
Left	Reference	
Right	1.110 (0.900-1.369)	0.325
Bilateral	-	-
Grade		
	Reference	
	1.046 (0.300-3.646)	0.942
	1.197 (0.379–3.782)	0.758
	1.272 (0.396–4.082)	0.685

Characteristics	Multivariate analysis	
	HR (95% CI)	P value
SEER stage		
Localized	Reference	
Regional	1.213 (0.868–1.696)	0.256
Distant	2.700 (1.296–5.624)	0.007
T		
T1	Reference	
T2	0.726 (0.528–0.997)	0.047
T3	1.106 (0.644–1.898)	0.714
T4	1.281 (0.802–2.047)	0.298
Tx	5.206 (0.389–69.579)	0.212
N		
N0	Reference	
N1	2.024 (1.442–2.840)	< 0.001
N2	2.228 (1.557–3.189)	< 0.001
N3	3.868 (0.816–18.329)	0.088
Nx	0.203 (0.024–1.723)	0.144
M		
M0	Reference	
M1	0.947 (0.462–1.940)	0.882
Mx	11.076 (1.380-88.911)	0.023
Tumor size (mm)		
< 20	Reference	
20–49	1.342 (1.013–1.778)	0.039
> 50	1.752 (1.190–2.580)	0.004
Unknown	0.515 (0.101–2.620)	0.424
Radiation		

Characteristics	Multivariate analysis	
	HR (95% CI)	P value
No/Unknown	Reference	
Yes	1.203 (0.879–1.646)	0.246
Chemotherapy		
No/Unknown	Reference	
Yes	0.549 (0.423–0.713)	< 0.001

Construction of nomogram

The nomogram is constructed based on the independent prognostic factors of the overall survival. As shown in Fig. 2, the variables in the nomogram include age, SEER stage, T stage, N stage, M stage, tumor size, and chemotherapy. Each variable has a corresponding number of points, and the points of all variables are added up to make a total number of points. The total number of points corresponds to the 1-, 3-, and 5-year survival probabilities.

Validation of nomogram

The C-index of the nomogram is 0.681 on the training cohort and 0.675 on the validation cohort. The AUC values of 1-, 3-, and 5-year overall survival on the training cohort are 0.782, 0.715, and 0.719 (Fig. 3). The AUC values in validation cohort are 0.603, 0.634 and 0.646 (Fig. 4). The calibration curves in the training cohort (Figs. 5) and validation cohort (Figs. 6) show that the nomogram has good agreement between prediction and actual observation in the probability of 1-, 3-, and 5-year overall survival.

Discussion

Pulmonary LCNEC is a rare primary malignant tumor with a poor prognosis[17, 18]. The clinical and biological characteristics of pulmonary LCNEC are similar to small cell lung carcinoma, but standard treatment management has not yet been established. Recent reports show that surgery remains a reliable option for patients with pulmonary LCNEC[19–23]. In order to accurately assess the 1-, 3-, and 5-year survival of patients with pulmonary LCNEC undergoing surgery, we developed and validated nomogram through the SEER database. Our results indicate that age, SEER stage, T stage, N stage, M stage, tumor size, and chemotherapy are independent prognostic factors for overall survival. The nomogram constructed based on these independent risk factors has the function of predicting postoperative survival.

We found that age is an independent factor that influences the prognosis in both the univariate and multivariate analyses. In the nomogram, you can see that there are corresponding points for each age stage. The older the age, the higher the number of points. Age has been identified as a prognostic factor

for patients with pulmonary LCNEC, but the division of age is still controversial[24]. Kujtan et al.[25] concluded that patients older than 70 years have a worse prognosis, while Cao et al.[26] report that patients 65 years or older have worse survival outcomes than younger patients. Due to the differences in the populations included in the two studies and the limited number of current studies, multicenter studies are needed for validation.

The TNM stage are the important and stable indicators to predict the survival time of patients with lung cancer[27]. The prognosis of patients differs significantly between different clinical stages. However, pulmonary LCNEC is an aggressive malignant tumor that often leads to a poor prognosis, and there are no effective tools to assess the prognosis of patients after surgery. Cattoni et al.[9] analyzed 101 patients with pulmonary LCNEC who underwent lung resection, and the results showed that the higher the T stage, the worse the prognosis, and there was no statistical significance between N stage and survival rate. A recent study analyzed the metastasis pattern of pulmonary LCNEC and found that lymph node metastasis and distant metastasis are adverse factors for survival[15]. Our results also show a similar phenomenon, patients with distant metastases have a worse prognosis than patients with localized tumors. In addition, tumor size is also one of the prognostic factors for pulmonary LCNEC. Several studies have reported the relationship between tumor size and survival prognosis[8, 14, 15, 25]. Existing evidence suggests that tumor size over 20 mm is a sign of poor prognosis, and our results support this conclusion.

Given that we know very little about the clinicopathological and biological characteristics of pulmonary LCNEC, there is currently no uniform treatment available for reference. Previous studies have shown that surgery is very important for patients with early-stage pulmonary LCNEC[21–23]. However, the use of radiotherapy and chemotherapy remains controversial[28]. Our study shows that chemotherapy is an independent prognostic factor for patients with pulmonary LCNEC after surgery. Chemotherapy is protective factors for pulmonary LCNEC. Iyoda et al.[29] analyzed 79 patients with pulmonary LCNEC and showed that platinum-based adjuvant chemotherapy after surgery may reduce tumor recurrence. Tang et al.[30] reported that cisplatin combined with pemetrexed is effective and safe in patients with pulmonary LCNEC. Furthermore, a retrospective study[31] included 139 patients undergoing curative-intent surgery for LCNEC, of which 50 patients received adjuvant chemotherapy, radiotherapy, or concurrent chemoradiotherapy after surgery. The results of long-term follow-up showed that the 5-year overall survival rate was 53% and the disease-free survival rate was 39%. In summary, current evidence suggests that patients with pulmonary LCNEC after surgery may benefit from adjuvant therapy.

This study still has some limitations. First, since the study had a retrospective design, inherent selection bias might have been present. Second, the C-index of the nomogram is not excellent, but because primary pulmonary LCNEC is too rare, to our knowledge this is the first nomogram of pulmonary LNCEC after surgery. Third, although the SEER database is a source of high-quality data that can be used for population-based studies, it still has limitations, such as lack of detailed information on chemotherapy, surgery, and combination therapy. Fourth, small sample size of patients in some subgroups may reduce accuracy of results.

Conclusion

We constructed and validated nomogram for predicting 1-, 3-, and 5-year survival of patients with pulmonary LCNEC after surgery based on the SEER database. In addition, we found that age, SEER stage, T stage, N stage, M stage, tumor size, and chemotherapy were independent prognostic factors for patients with pulmonary LCNEC after surgery. Our nomogram provides reference information for assessing the prognosis of patients with pulmonary LCNEC after surgery.

Declarations

Ethics approval and consent to participate

Since all information in the SEER database has been de-identified, no institutional review board approval or informed consent was required for this study.

Consent for publication

All authors listed approved the publication of the manuscript.

Availability of data and materials

The datasets used and/or 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.

Funding

None.

Authors' contributions

QH and LW conceived and designed the study. HC and JL collected and analyzed data. QH and JL wrote the manuscript. QZ and LW reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgments

None.

References

1. Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2015;10(8):1133-41. doi:10.1097/jto.0000000000000589.
2. Derks JL, Hendriks LE, Buikhuisen WA, Groen HJ, Thunnissen E, van Suylen RJ et al. Clinical features of large cell neuroendocrine carcinoma: a population-based overview. The European respiratory journal. 2016;47(2):615-24. doi:10.1183/13993003.00618-2015.
3. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2015;10(9):1243-60. doi:10.1097/jto.0000000000000630.
4. Veronesi G, Morandi U, Alloisio M, Terzi A, Cardillo G, Filosso P et al. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung cancer (Amsterdam, Netherlands). 2006;53(1):111-5. doi:10.1016/j.lungcan.2006.03.007.
5. Dresler CM, Ritter JH, Patterson GA, Ross E, Bailey MS, Wick MR. Clinical-pathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. The Annals of thoracic surgery. 1997;63(1):180-5. doi:10.1016/s0003-4975(96)01058-2.
6. Jiang SX, Kameya T, Shoji M, Dobashi Y, Shinada J, Yoshimura H. Large cell neuroendocrine carcinoma of the lung: a histologic and immunohistochemical study of 22 cases. The American journal of surgical pathology. 1998;22(5):526-37. doi:10.1097/00000478-199805000-00002.
7. Iyoda A, Hiroshima K, Toyozaki T, Haga Y, Fujisawa T, Ohwada H. Clinical characterization of pulmonary large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology. Cancer. 2001;91(11):1992-2000. doi:10.1002/1097-0142(20010601)91:11<1992::aid-cncr1224>3.0.co;2-5.
8. He Y, Liu H, Wang S, Chen Y. Prognostic nomogram predicts overall survival in pulmonary large cell neuroendocrine carcinoma. PloS one. 2019;14(9):e0223275. doi:10.1371/journal.pone.0223275.
9. Cattoni M, Vallieres E, Brown LM, Sarkeshik AA, Margaritora S, Siciliani A et al. Improvement in TNM staging of pulmonary neuroendocrine tumors requires histology and regrouping of tumor size. The Journal of thoracic and cardiovascular surgery. 2018;155(1):405-13. doi:10.1016/j.jtcvs.2017.08.102.

10. Zi H, Gao L, Yu Z, Wang C, Ren X, Lyu J et al. Nomograms for predicting long-term overall survival and cancer-specific survival in patients with primary urethral carcinoma: a population-based study. International urology and nephrology. 2019. doi:10.1007/s11255-019-02314-y.
11. Wang W, Hong J, Meng J, Wu H, Shi M, Yan S et al. Nomograms Predict Cancer-Specific and Overall Survival of Patients With Primary Limb Leiomyosarcoma. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2019;37(7):1649-57. doi:10.1002/jor.24298.
12. Yan P, Huang R, Hu P, Liu F, Zhu X, Hu P et al. Nomograms for predicting the overall and cause-specific survival in patients with malignant peripheral nerve sheath tumor: a population-based study. Journal of neuro-oncology. 2019;143(3):495-503. doi:10.1007/s11060-019-03181-4.
13. Kinslow CJ, May MS, Saqi A, Shu CA, Chaudhary KR, Wang TJC et al. Large-Cell Neuroendocrine Carcinoma of the Lung: A Population-Based Study. Clinical lung cancer. 2019. doi:10.1016/j.cllc.2019.07.011.
14. Wang J, Ye L, Cai H, Jin M. Comparative study of large cell neuroendocrine carcinoma and small cell lung carcinoma in high-grade neuroendocrine tumors of the lung: a large population-based study. Journal of Cancer. 2019;10(18):4226-36. doi:10.7150/jca.33367.
15. Yang Q, Xu Z, Chen X, Zheng L, Yu Y, Zhao X et al. Clinicopathological characteristics and prognostic factors of pulmonary large cell neuroendocrine carcinoma: A large population-based analysis. Thoracic cancer. 2019;10(4):751-60. doi:10.1111/1759-7714.12993.
16. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology (Cambridge, Mass). 2009;20(4):555-61. doi:10.1097/EDE.0b013e3181a39056.
17. Righi L, Gatti G, Volante M, Papotti M. Lung neuroendocrine tumors: pathological characteristics. Journal of thoracic disease. 2017;9(Suppl 15):S1442-s7. doi:10.21037/jtd.2017.01.59.
18. Grand B, Cazes A, Mordant P, Foucault C, Dujon A, Guillevin EF et al. High grade neuroendocrine lung tumors: pathological characteristics, surgical management and prognostic implications. Lung cancer (Amsterdam, Netherlands). 2013;81(3):404-9. doi:10.1016/j.lungcan.2013.05.008.
19. Gu J, Gong D, Wang Y, Chi B, Zhang J, Hu S et al. The demographic and treatment options for patients with large cell neuroendocrine carcinoma of the lung. Cancer medicine. 2019. doi:10.1002/cam4.2188.
20. Deng C, Wu SG, Tian Y. Lung Large Cell Neuroendocrine Carcinoma: An Analysis of Patients from the Surveillance, Epidemiology, and End-Results (SEER) Database. Medical science monitor : international medical journal of experimental and clinical research. 2019;25:3636-46. doi:10.12659/msm.914541.
21. Eichhorn F, Dienemann H, Muley T, Warth A, Hoffmann H. Predictors of survival after operation among patients with large cell neuroendocrine carcinoma of the lung. The Annals of thoracic surgery. 2015;99(3):983-9. doi:10.1016/j.athoracsur.2014.10.015.
22. Sakurai H, Asamura H. Large-cell neuroendocrine carcinoma of the lung: surgical management. Thoracic surgery clinics. 2014;24(3):305-11. doi:10.1016/j.thorsurg.2014.05.001.

23. Kinoshita T, Yoshida J, Ishii G, Aokage K, Hishida T, Nagai K. The differences of biological behavior based on the clinicopathological data between resectable large-cell neuroendocrine carcinoma and small-cell lung carcinoma. Clinical lung cancer. 2013;14(5):535-40. doi:10.1016/j.cllc.2013.04.003.
24. Wu BS, Hu Y, Sun J, Wang JL, Wang P, Dong WW et al. Analysis on the characteristics and prognosis of pulmonary neuroendocrine tumors. Asian Pacific journal of cancer prevention : APJCP. 2014;15(5):2205-10. doi:10.7314/apjcp.2014.15.5.2205.
25. Kujtan L, Muthukumar V, Kennedy KF, Davis JR, Masood A, Subramanian J. The Role of Systemic Therapy in the Management of Stage I Large Cell Neuroendocrine Carcinoma of the Lung. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(5):707-14. doi:10.1016/j.jtho.2018.01.019.
26. Cao L, Zhao L, Wang M, Zhang XH, Yang ZC, Liu YP. Clinicopathological characteristics and prognosis of pulmonary large cell neuroendocrine carcinoma aged >/=65 years. PeerJ. 2019;7:e6824. doi:10.7717/peerj.6824.
27. Travis WD, Giroux DJ, Chansky K, Crowley J, Asamura H, Brambilla E et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of broncho-pulmonary carcinoid tumors in the forthcoming (seventh) edition of the TNM Classification for Lung Cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2008;3(11):1213-23. doi:10.1097/JTO.0b013e31818b06e3.
28. Rieber J, Schmitt J, Warth A, Muley T, Kappes J, Eichhorn F et al. Outcome and prognostic factors of multimodal therapy for pulmonary large-cell neuroendocrine carcinomas. European journal of medical research. 2015;20:64. doi:10.1186/s40001-015-0158-9.
29. Iyoda A, Hiroshima K, Moriya Y, Iwadate Y, Takiguchi Y, Uno T et al. Postoperative recurrence and the role of adjuvant chemotherapy in patients with pulmonary large-cell neuroendocrine carcinoma. The Journal of thoracic and cardiovascular surgery. 2009;138(2):446-53. doi:10.1016/j.jtcvs.2008.12.037.
30. Tang H, Wang H, Xi S, He C, Chang Y, Wang Q et al. Perioperative chemotherapy with pemetrexed and cisplatin for pulmonary large-cell neuroendocrine carcinoma: a case report and literature review. OncoTargets and therapy. 2018;11:2557-63. doi:10.2147/ott.s160565.
31. Kim KW, Kim HK, Kim J, Shim YM, Ahn MJ, Choi YL. Outcomes of Curative-Intent Surgery and Adjuvant Treatment for Pulmonary Large Cell Neuroendocrine Carcinoma. World journal of surgery. 2017;41(7):1820-7. doi:10.1007/s00268-017-3908-8.

Figures

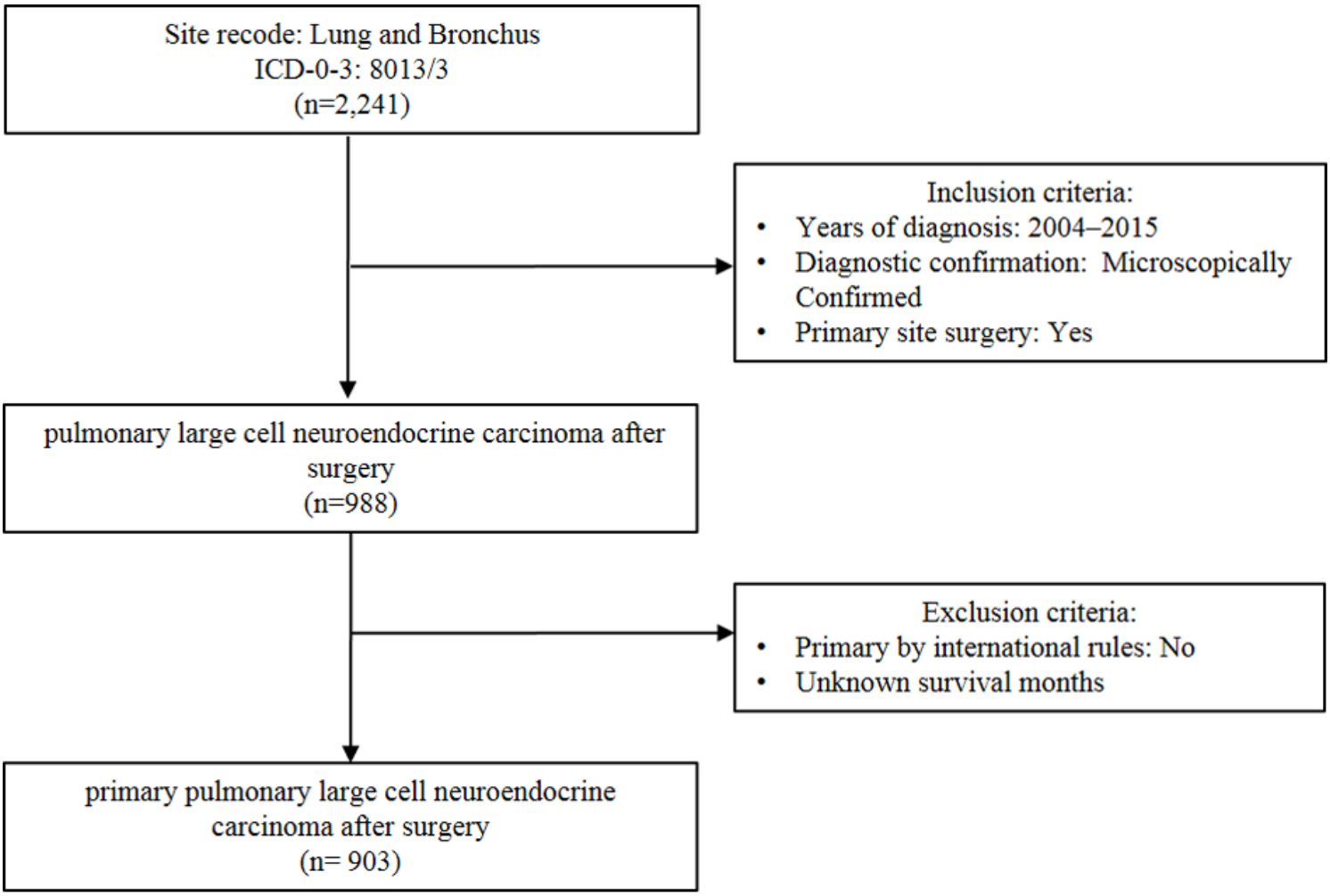

Figure 1

Patient enrollment and exclusion process of in the SEER database.

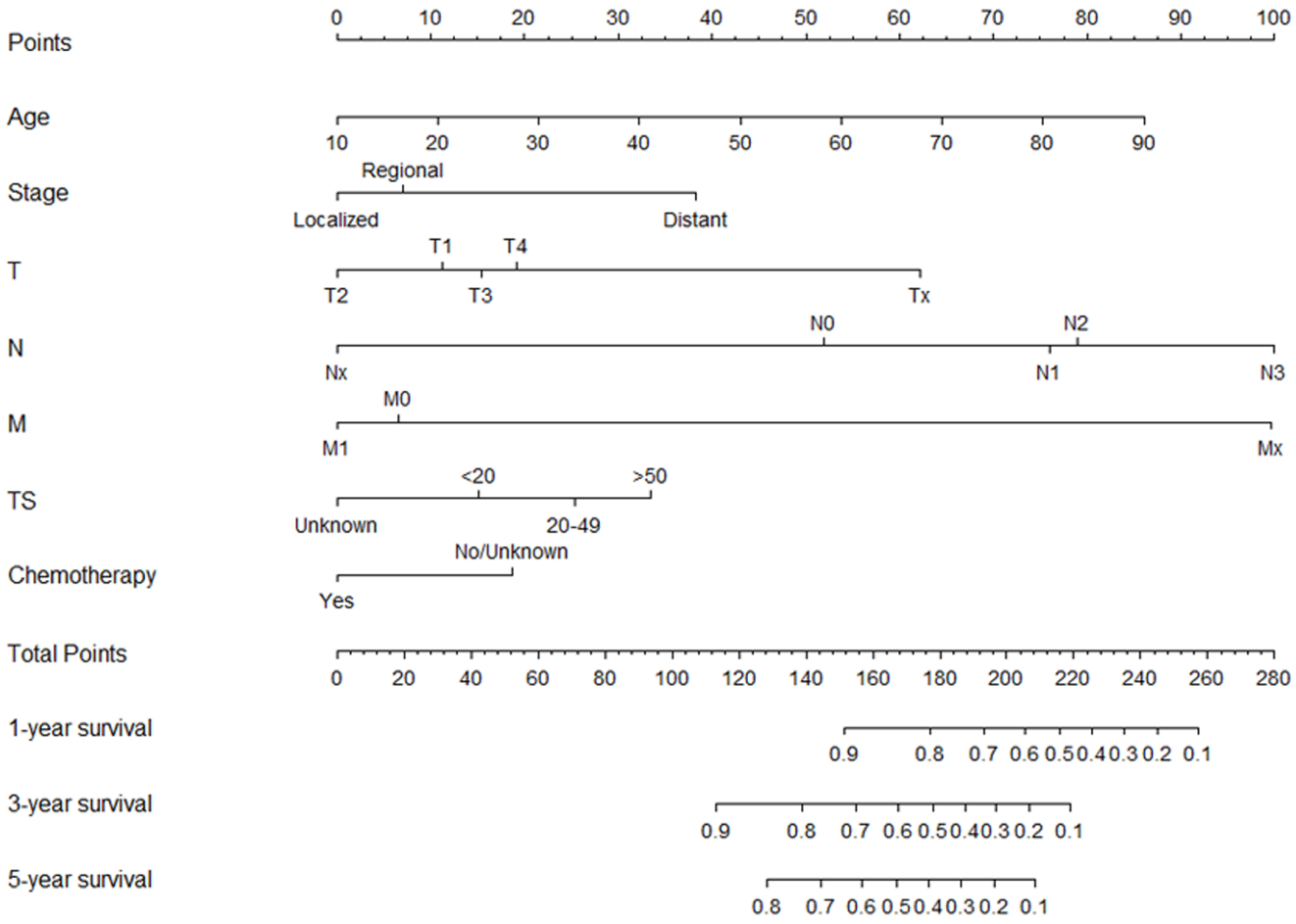

Figure 2

Nomogram predicting 1-, 3- and 5-year overall survival. Abbreviations: TS, tumor size.

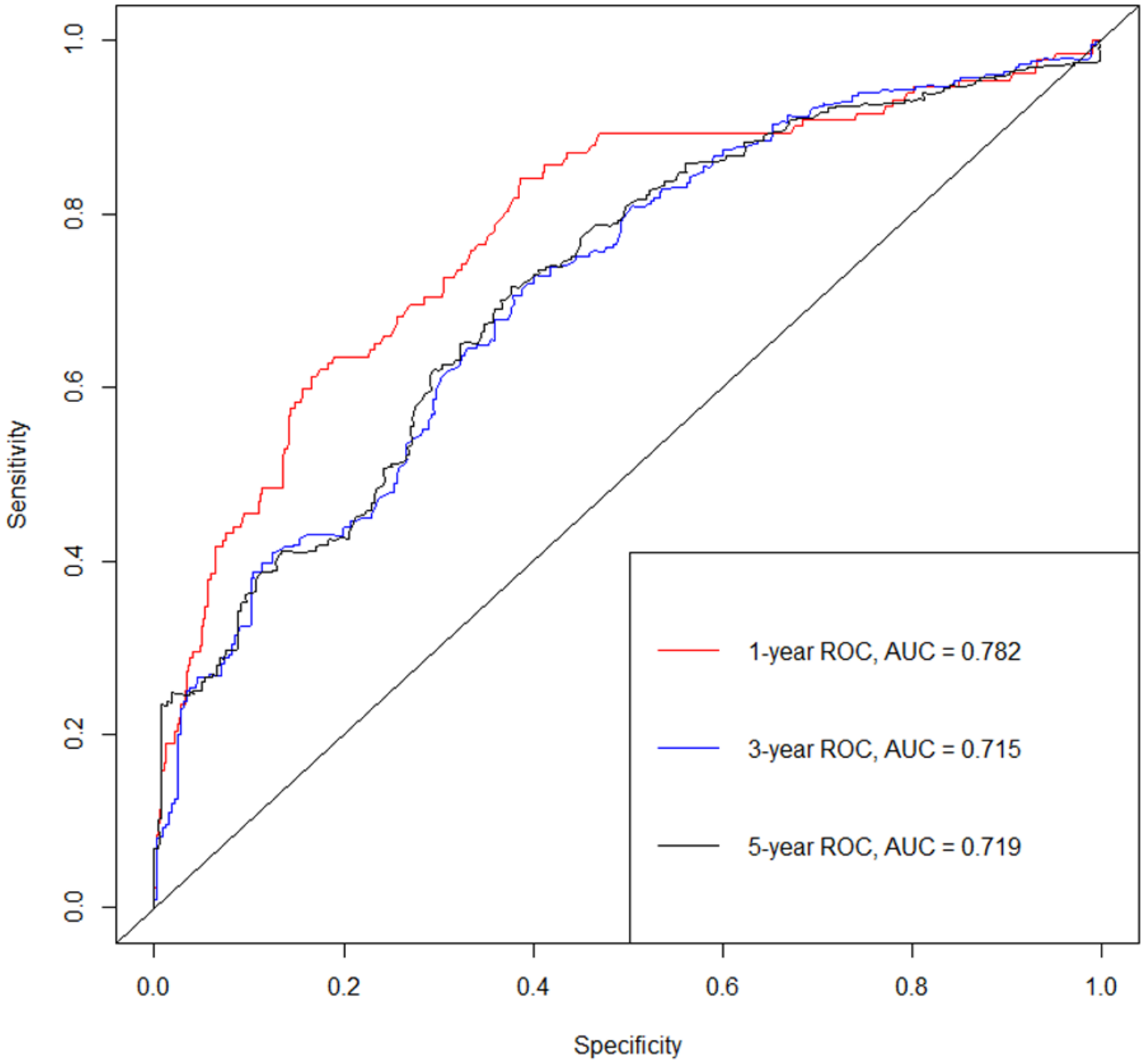

Figure 3

ROC curve of overall survival in training cohort.

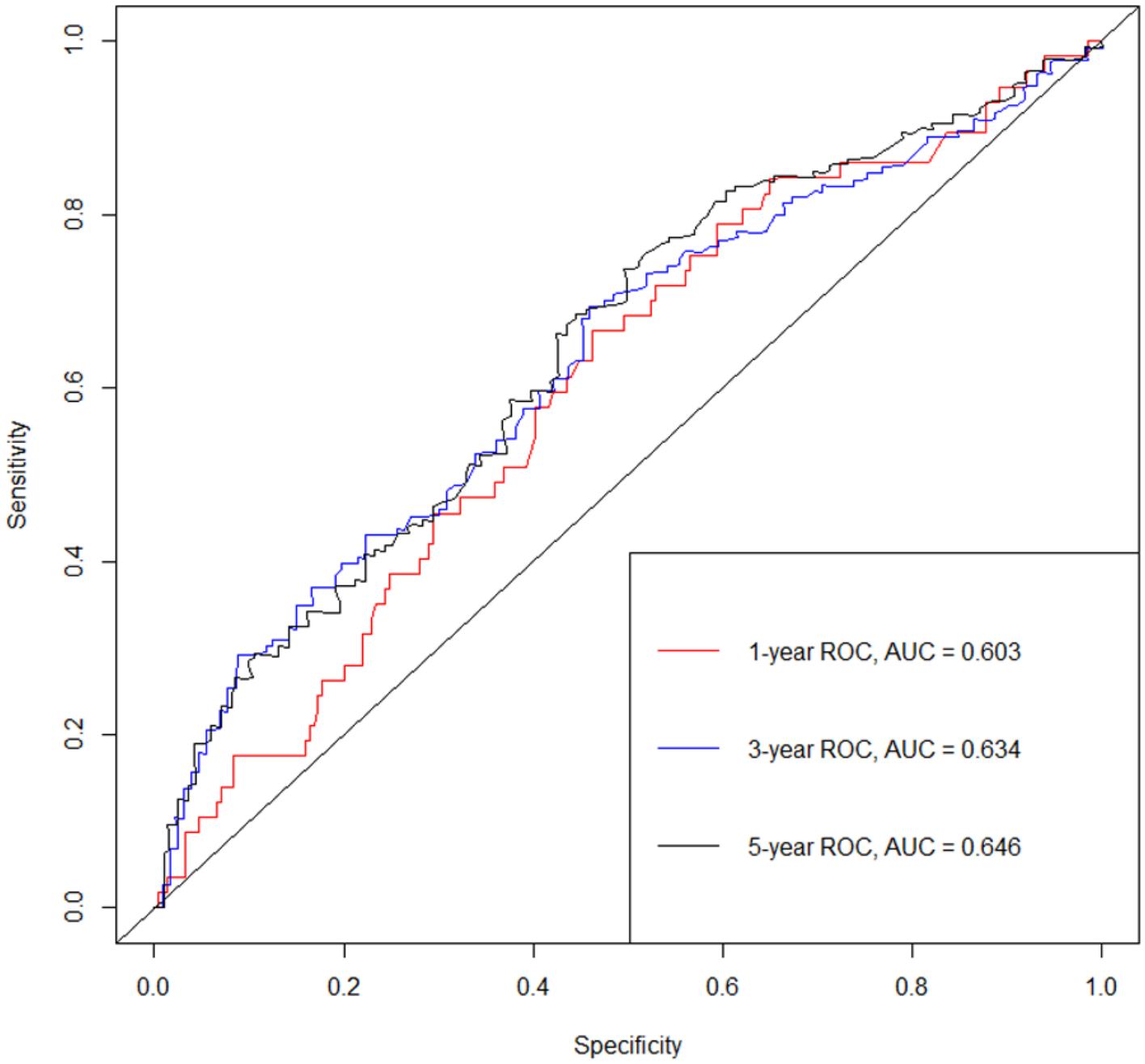

Figure 4

ROC curve of overall survival in validation cohort.

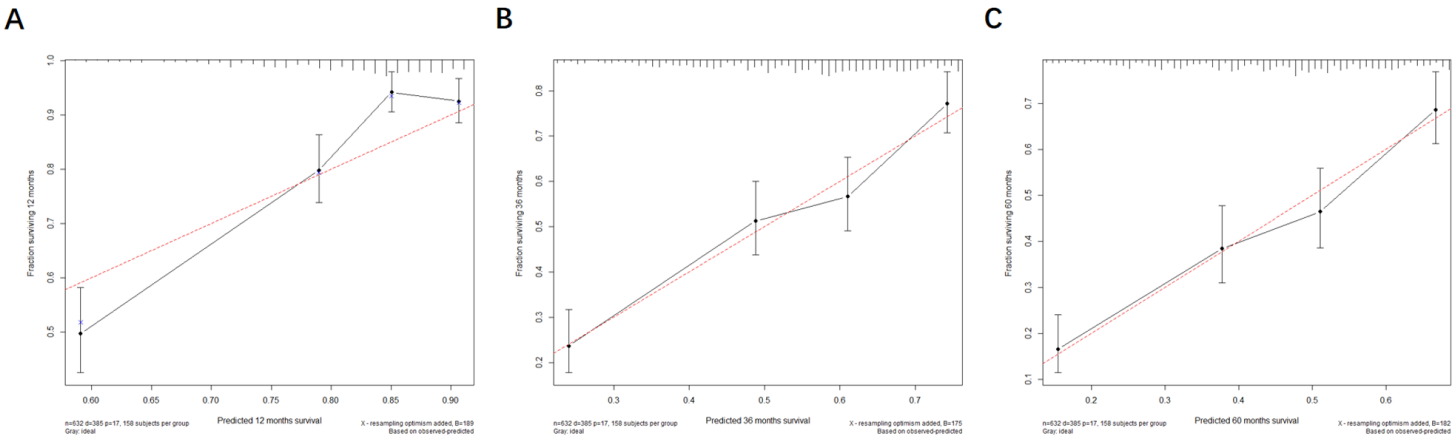

Figure 5

Calibration plots for (A) 1-, (B) 3- and (C) 5-year prediction of overall survival in training cohort.

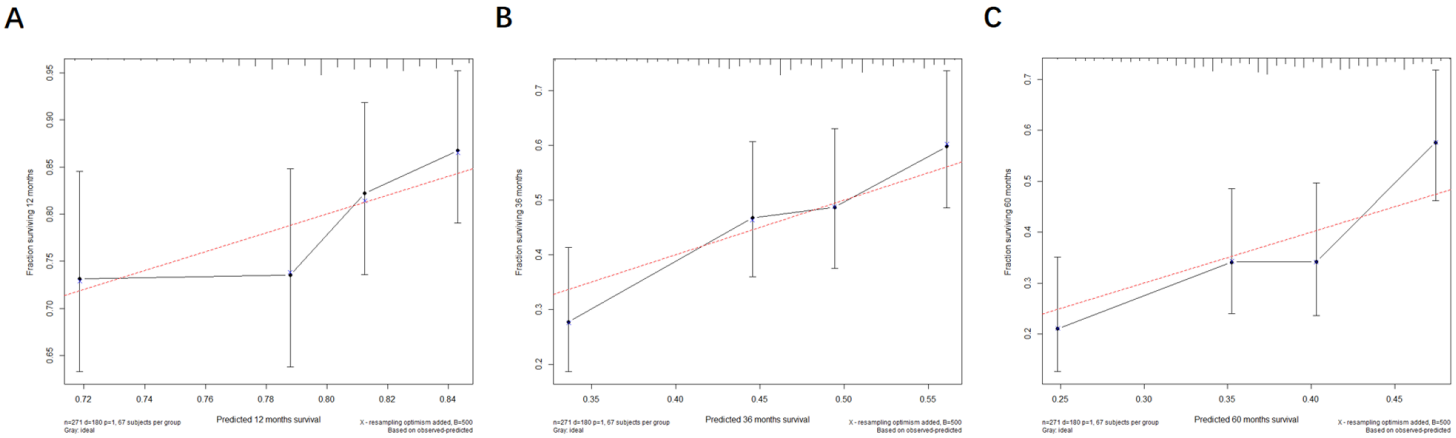

Figure 6

Calibration plots for (A) 1-, (B) 3- and (C) 5-year prediction of overall survival in validation cohort.