

Prognostic factors for pulmonary large-cell neuroendocrine carcinoma: a competing-risks analysis

Qian Huang

Henan University

Jie Liu

Henan University

Qiao Huang

Wuhan University Zhongnan Hospital

Huifang Cai

Henan University

Qi Zhang

Henan University

Lina Wang (✉ wanglinatg@163.com)

Henan University

Research article

Keywords: Cumulative incidence function for the prognostic factors, (A) sex, (B) primary site, (C) laterality, (D) AJCC stage, (E) T stage, (F) N stage, (G) M stage, (H) lymph nodes status, (I) surgery, (J) chemotherapy

Posted Date: July 26th, 2019

DOI: <https://doi.org/10.21203/rs.2.11951/v1>

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Abstract

Background Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare and highly invasive subtype of lung cancer that accounts for fewer than 3% of cases. The prognostic factors for pulmonary LCNEC are unclear in the literature. Methods Patients diagnosed with pulmonary LCNEC between 2004 and 2015 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. The CumIncidence function was used for the univariate analysis. Multivariate analysis was performed using Cox regression analysis, subdistribution hazard function analysis, and cause-specific hazard function analysis. Results We finally screened 1246 patients diagnosed with pulmonary LCNEC, among whom 796 died of LCNEC and 141 died from other causes. The univariate analysis showed that sex, primary site, laterality, American Joint Committee on Cancer (AJCC) stage, T stage, N stage, M stage, lymph-node status, surgery, and chemotherapy were significant prognostic factors for pulmonary LCNEC ($P < 0.05$). The multivariate analysis demonstrated that sex, AJCC stage, TNM stage T4, TNM stage N3, lymph-node status, surgery, and chemotherapy were independent risk factors for the prognosis ($P < 0.05$). Conclusion We have conducted a competing-risks analysis of patients with pulmonary LCNEC in the SEER database. The results showed that sex, AJCC stage, TNM stage T4, TNM stage N3, lymph-node status, surgery, and chemotherapy are independent prognostic factors for pulmonary LCNEC patients. The reported data represent reference information that can be used for accurate assessments of the prognosis of pulmonary LCNEC 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]. LCNEC was first reported as a solitary pulmonary neuroendocrine tumor in 1991[3]. The World Health Organization (WHO) subsequently recognized LCNEC as a variant of large-cell carcinoma and a type of neuroendocrine tumor and non-small-cell lung cancer[4, 5]. However, the 2015 WHO standard classifies LCNEC, small-cell lung carcinoma, typical carcinoid, and atypical carcinoid as neuroendocrine tumors[6]. The low incidence of pulmonary LCNEC has resulted in there being few prognostic studies of pulmonary LCNEC, and moreover the findings of these studies have been controversial.

Previous studies have performed survival analyses of pulmonary LCNEC patients. However, the application of traditional survival analysis methods that are widely used to identify prognostic factors has limitations[7], such as overestimating the risk of disease by failing to allow for competing risk factors for death. The competing-risks model is an analytical technique used to deal with competing events and is being increasingly used in clinical research[8–10]. 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. Analyzing the SEER database should provide useful information on the prognostic factors for pulmonary LCNEC.

This study considered other causes of death as competing events for LCNEC-specific death (LCSD). We used a competing-risks model to analyze the survival of pulmonary LCNEC patients in the SEER database in order to screen prognostic factors and provide reliable evidence for clinical treatment decisions.

Methods

2.1. *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).” The SEER Research Data Agreement was signed for accessing the information in the SEER database using reference number 11075-Nov2018. 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.

2.2. *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 C34.0-C34.9 and the ICD-O–3 histology code 8013/3. The inclusion criteria for this study were as follows: (1) aged ≥ 18 years and diagnosed between 2004 to 2015; (2) diagnosis confirmed by microscopy; and (3) availability of data on age at diagnosis, race, sex, marital status, year of diagnosis, primary site, laterality, grade, American Joint Committee on Cancer (AJCC) stage, T stage, N stage, M stage, lymph-node status, surgery, radiotherapy, chemotherapy, survival time, and cause of death. Patients with nonprimary tumors were excluded from the study. The patient inclusion and exclusion process applied to the SEER database is shown in Figure 1.

2.3. *Covariates*

We included the following variables: age at diagnosis, race, sex, marital status, year of diagnosis, primary site, laterality, grade, AJCC stage, T stage, N stage, M stage, lymph-node status, surgery, radiotherapy, chemotherapy, and survival time. Unmarried patients included those who were widowed, single, unmarried, living with a domestic partner, divorced, or separated. The primary tumor site was divided into lung lobe, main bronchus, overlapping lesion of the lung, and not otherwise specified.

The causes of death were divided into the following three situations: alive, LCSD, and death from other causes. LCSD was the primary outcome that we were interested in, and other causes of death were considered competing events.

2.4. *Statistical analysis*

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. We used the CumIncidence function for the univariate analysis, the cumulative incidence function (CIF) for determining the cumulative morbidity at different time points, and Gray's test for testing different categories[11]. There was a competing risk between our outcomes, and so Cox regression analysis, subdistribution hazard function (SD) analysis, and cause-specific hazard function (CS) analysis were used for the multivariate analysis to identify prognostic factors[12, 13]. The results of the multivariate analysis are presented as hazard ratio (HR) and associated 95% confidence interval (CI) values. All analyses were performed using SAS statistical software (version 9.4).

Results

3.1. *Patient Characteristics*

We finally screened 1246 patients diagnosed with pulmonary LCNEC; their demographic and tumor characteristics are presented in Table 1. The median survival times in the LCSD and total-patients groups were 10 and 16 months, respectively. The 937 patients who died comprised 796 who died from LCNEC and 141 who died from other causes, which indicates that competing events constituted 15% of the deaths.

The largest age group of the diagnosed total patients comprised those aged 60–80 years, followed by patients younger than 60 years, with patients older than 80 years accounting for only a small proportion. Most of the patients who died were white (84.51%), and male deaths predominated in both the total-patient (54.98%) and LCSD (57.66%) groups. Regarding the tumor origin, in 89% of the patients it was located in a lung lobe, and only 1.36% of patients had overlapping lesions of the lung. AJCC stages I and IV accounted for 37.4% and 32.1% of the total patients, respectively. The proportions of patients with TNM stages T1 and T2 were 27.69% and 38.28%, respectively. TNM stage N0 patients accounted for 52.33%, while lymph-node-positive patients accounted for 38.84%. In addition, 56.02% and 52.17% of patients received surgery and chemotherapy, respectively, whereas only 13.88% received radiotherapy.

3.2. *Univariate analysis*

The univariate analysis revealed that the prognostic factors for pulmonary LCNEC were sex ($P = 0.0005$), primary site ($P < 0.001$), laterality ($P < 0.001$), AJCC stage ($P < 0.001$), T stage ($P < 0.001$), N stage ($P < 0.001$), M stage ($P < 0.001$), lymph-node status ($P < 0.001$), surgery ($P < 0.001$), and chemotherapy ($P = 0.007$) (Figures 2). The 6-, 12-, and 24-month CIFs are presented in Table 2.

3.3. *Multivariate analysis*

The multivariate analysis indicated that there were too few competing events to allow M-stage patients to be included in the calculations. The Cox regression analysis indicated that the independent prognostic factors for pulmonary LCNEC were sex ($P = 0.0017$, HR = 0.809, 95%CI = 0.708–0.923), AJCC stage II ($P < 0.0001$, HR = 2.629, 95%CI = 1.826–3.784), AJCC stage III ($P < 0.0001$, HR = 2.111, 95%CI = 1.560–2.856), AJCC stage IV ($P < 0.0001$, HR = 4.000, 95%CI = 3.023–5.293), TNM stage T4 ($P = 0.0043$, HR = 1.396, 95%CI = 1.111–1.756), TNM stage N3 ($P = 0.0031$, HR = 1.499, 95%CI = 1.146–1.961), lymph-node status ($P = 0.0008$, HR = 1.565, 95%CI = 1.206–2.032), surgery ($P < 0.0001$, HR = 0.569, 95%CI = 0.445–0.726), and chemotherapy ($P < 0.0001$, HR = 0.378, 95%CI = 0.323–0.441).

The SD model analysis showed that the independent prognostic factors were sex ($P = 0.0043$, HR = 0.793, 95%CI = 0.676–0.930), AJCC stage II ($P < 0.0001$, HR = 2.455, 95%CI = 1.615–3.730), AJCC stage III ($P = 0.0004$, HR = 1.878, 95%CI = 1.324–2.663), AJCC stage IV ($P < 0.0001$, HR = 3.495, 95%CI = 2.555–4.779), TNM stage T4 ($P = 0.0362$, HR = 1.334, 95%CI = 1.019–1.748), TNM stage N2 ($P = 0.0131$, HR = 1.403, 95%CI = 1.074–1.833), TNM stage N3 ($P = 0.0395$, HR = 1.395, 95%CI = 1.016–1.916), lymph-node status ($P = 0.0012$, HR = 1.626, 95%CI = 1.211–2.183), surgery ($P = 0.0004$, HR = 0.619, 95%CI = 0.474–0.808), and chemotherapy ($P < 0.0001$, HR = 0.521, 95%CI = 0.427–0.636).

Finally, the CS model analysis showed that the independent prognostic factors were sex ($P = 0.0012$, HR = 0.789, 95%CI = 0.683–0.911), AJCC stage II ($P < 0.0001$, HR = 2.905, 95%CI = 1.953–4.321), AJCC stage III ($P < 0.0001$, HR = 2.217, 95%CI = 1.593–3.086), AJCC stage IV ($P < 0.0001$, HR = 4.609, 95%CI = 3.390–6.265), TNM stage T2 ($P = 0.0429$, HR = 1.238, 95%CI = 1.007–1.522), TNM stage T4 ($P = 0.001$, HR = 1.518, 95%CI = 1.184–1.947), TNM stage N2 ($P = 0.012$, HR = 1.337, 95%CI = 1.066–1.677), TNM stage N3 ($P = 0.0015$, HR = 1.579, 95%CI = 1.190–2.093), lymph-node status ($P = 0.0003$, HR = 1.707, 95%CI = 1.275–2.285), surgery ($P < 0.0001$, HR = 0.544, 95%CI = 0.418–0.709), and chemotherapy ($P < 0.0001$, HR = 0.372, 95%CI = 0.314–0.440).

The results from the three types of model analysis demonstrate that sex, AJCC stage, TNM stage T4, TNM stage N3, lymph-node status, surgery, and chemotherapy are independent risk factors for the prognosis of pulmonary LCNEC (see Table 3).

Discussion

Pulmonary LCNEC is a rare primary malignant tumor with a poor prognosis. Clinical studies are urgently needed due to the current poor understanding of its biological behaviors, pathological features, and clinical effects. However, the Kaplan-Meier analysis and Cox proportional-hazards models used in most studies to detect independent prognostic factors may have limitations[7, 14].

Two widely used regression-based measurement methods have been used to analyze data affected by competing events: SD analysis and CS analysis[12, 13]. CS analysis reflects measures that are estimated when individuals exposed to competing event are censored, and adding SD analysis is worthwhile since it provides a complementary measure of risk: CS analysis might be more applicable for studying the etiology of diseases, whereas SD analysis might be more appropriate for predicting the risk that an

individual has of a particular outcome[12, 15–17]. In addition, the sample size of competing events can exert different effects on the outcomes[7]. Traditional survival analysis methods might be subject to bias when the proportion of competing events is too high. The proportion of competing events was approximately 15% in the present study, and so we used a competing-risks model to screen for independent prognostic factors for pulmonary LCNEC.

We found that sex is an independent factor that influences the prognosis in both the univariate and multivariate analyses. The results of the three model analyses further indicated that being female was a protective factor for LCSD. A series of previous reports showed that pulmonary LCNEC patients are mainly male, elderly, and heavy smokers, with at least half of these patients having a history of smoking[18–21]. Similarly, recent analyses based on the SEER database have led to consistent conclusions[22–24]. In short, the survival outcomes of LCNEC differ between men and women, but confirming whether this difference is related to smoking requires further research.

The AJCC stage is still the most important and stable indicators for predicting the survival time of patients with lung cancer. The prognosis of these patients is strongly influenced by the stage of the tumor(s) at the time of their discovery. The prognosis of patients differs significantly between different clinical stages. All three of the current model analyses showed that the risk of death is highest for stage IV patients, but lower for stage III than for stage II. Given that a higher disease stage is generally associated with a worse prognosis, we considered that this contrasting finding may be related to the small number of stage II patients. Moreover, the three models also produced different results. The SD and CS models showed that TNM stage N2 was an independent prognostic factor, while the Cox model showed no such significant effect. Similarly, only the CS model showed that TNM stage T2 was an independent prognostic factor. Therefore, in the case where the associated directions are basically the same, the competitive risk model needs to provide the results of the CS model and SD model[17]. In addition, the HR values obtained from the different models were not consistent. Table 3 indicates that the effect size was smaller for the SD model than the Cox model, while it was largest for the CS model. Because we are mainly concerned with the prognostic factors for the disease, we are more inclined to accept the results of the SD model. However, the HR values for the Cox model were all larger than those for the SD model. This suggests that the Cox model ignores the risk of competition between outcomes and overestimates the outcome, and indicates that more caution is needed when interpreting the results of traditional survival analysis.

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 and examining the lymph nodes are very important for patients with early-stage pulmonary LCNEC[25–27]. However, the use of radiotherapy and chemotherapy remains controversial[28]. Our study showed that lymph-node status, surgery, and chemotherapy were independent prognostic factors. Patients in whom the lymph nodes were not examined or who had an unknown lymph-node status had a higher risk of death. Surgery and chemotherapy are protective factors for prognosis. Evidence is also accumulating that perioperative adjuvant chemotherapy is beneficial to the prognosis of patients with

pulmonary LCNEC and is therefore a treatment option that should be considered[29–31]. However, the most suitable treatment method for patients at a particular disease stage needs to be explored in the future.

This study was subject to some limitations. First, since the study had a retrospective design, inherent bias might have been present. Second, since cases were only included if the required data were available, selection bias might have been present. Third, although the SEER database is a source of high-quality data for use in population-based studies, a considerable amount of treatment information remains unknown (e.g., about chemotherapy and the surgical sequence), which is not conducive to determining the treatment pattern applied to particular patients. Fourth, bias was also possible due to some of the samples in subgroups being too small.

Conclusion

We have conducted a competing-risks analysis of patients with pulmonary LCNEC based on the SEER database. The results show that sex, AJCC stage, TNM stage T4, TNM stage N3, lymph-node status, surgery, and chemotherapy are independent prognostic factors for pulmonary LCNEC patients. These data provide reference information that can be utilized for accurate assessments of the prognosis of this patient population.

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

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding source

None.

Author contributions

Qian Huang: data curation, formal analysis, writing original draft, and editing.

Jie Liu: methodology, supervision, review, and editing.

Qiao Huang: Data statistics, methodology, supervision, review, and editing.

Huifang Cai: supervision, review, and editing.

Qi Zhang: methodology, review, and editing.

Lina Wang: methodology, supervision, review, and editing.

Acknowledgments

None.

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Tables

Table 1 Characteristics and demographics of patients with pulmonary large-cell neuroendocrine carcinoma.

Parameter	Classification	All(%)	LCNEC-specific death (%)
No. of patients		1246	796
Age, years			
	<60	354 (28.41)	216 (27.14)
	60-80	812 (65.17)	526 (66.08)
	>80	80 (6.42)	54 (6.78)
Race			
	White	1053 (84.51)	668 (83.92)
	Black	144 (11.56)	91 (11.43)
	Other	49 (3.93)	37 (4.65)
Sex			
	Male	685 (54.98)	459 (57.66)
	Female	561 (45.02)	337 (42.34)
Marital status			
	Married	648 (52.01)	416 (52.26)
	Unmarried	554 (44.46)	357 (44.85)
	Unknown	44 (3.53)	23 (2.89)
Year of diagnosis			
	2004-2009	512 (41.09)	348 (43.72)
	2010-2015	734 (58.91)	448 (56.28)
Primary site			
	Lung lobe	1109 (89.00)	680 (85.43)
	Main bronchus	48 (3.85)	41 (5.15)
	Overlapping lesion of lung	17 (1.36)	13 (1.63)
	NOS	72 (5.78)	62 (7.79)
Laterality			
	Left	528 (42.38)	333 (41.83)
	Right	706 (56.66)	452 (56.78)
	Other	12 (0.96)	11 (1.38)
Grade			
	I- II	46 (3.69)	31 (3.89)
	III	915 (73.43)	584 (73.37)
	IV	285 (22.87)	181 (22.74)
AJCC stage			
	I	466 (37.40)	171 (21.48)
	II	111 (8.91)	69 (8.67)
	III	269 (21.59)	195 (24.50)
	IV	400 (32.10)	361 (45.35)
T stage			
	T1	345 (27.69)	159 (19.97)
	T2	477 (38.28)	281 (35.30)
	T3	85 (6.82)	66 (8.29)
	T4	339 (27.21)	290 (36.43)

N stage			
	N0	652 (52.33)	314 (39.45)
	N1	153 (12.28)	107 (13.44)
	N2	332 (26.65)	278 (34.92)
	N3	109 (8.75)	97 (12.19)
M stage			
	M0	846 (67.90)	435 (54.65)
	M1	400 (32.10)	361 (45.35)
Lns			
	positive	484 (38.84)	187 (23.49)
	negative	236 (18.94)	164 (20.60)
	No/Unknown	526 (42.22)	445 (55.90)
Surgery			
	No	548 (43.98)	475 (59.67)
	Yes	698 (56.02)	321 (40.33)
Radiotherapy			
	No	1073 (86.12)	666 (83.67)
	Yes	173 (13.88)	130 (16.33)
Chemotherapy			
	No/Unknown	596 (47.83)	348 (43.72)
	Yes	650 (52.17)	448 (56.28)
Survival months, median (IQR)		16(6-38)	10(4-20)

Abbreviations: IQR, interquartile range; LCNEC, pulmonary large-cell neuroendocrine carcinoma; Lns, lymph nodes status; NOS, not otherwise specified.

Table 2 Univariate analysis of prognostic factors in patients with pulmonary large-cell neuroendocrine carcinoma.

Prognostic factors Classification	Gray's test P-value	6-month CIF	12-month CIF	24-month CIF
Age	5.41912	0.0666		
<60			0.18927	0.32500
60-80			0.23399	0.38966
>80			0.37500	-
Race	1.75759	0.4153		
White			0.23837	0.38008
Black			0.18056	0.37672
Other			-	0.38776
Sex	12.2750	0.0005		
Male			0.27007	0.43420
Female			0.18182	0.31383
Marital status	2.76313	0.2512		
Married			0.20988	0.37570
Unmarried			0.25632	0.38996
Unknown			-	-
Year of diagnosis	0.87318	0.3501		
2004-2009			0.21289	0.35584
2010-2015			0.24251	0.39683
Primary site	88.6298	<0.001		
Lung lobe			0.19387	0.34481
Main bronchus			0.50000	0.62500
Overlapping lesion of lung			0.47059	-
NOS			0.55556	0.69444
Laterality	30.8600	<0.001		
Left			0.21023	0.36219
Right			0.23654	0.38702
Others			0.75000	-
Grade	0.24372	0.8853		
I- II			0.13043	0.36957
III			0.22951	0.37197
IV			0.24912	0.40725
AJCC stage	499.122	<0.001		
I			0.03219	0.10317
II			-	0.25225
III			0.22677	0.40520
IV			0.51250	0.72113
T stage	265.777	<0.001		
T1			0.09275	0.20000
T2			0.15933	0.30854
T3			0.24706	0.43529
T4			0.46608	0.65004
N stage	267.401	<0.001		
N0			0.11043	0.21339
N1			0.16993	0.36601

	N2			0.41867	0.60843	0.76570
	N3			0.45872	0.70151	-
M stage		426.003	<0.001			
	M0			0.09693	0.21887	0.38672
	M1			0.51250	0.72113	0.86048
Lns		342.706	<0.001			
	positive			0.06198	0.12619	0.26217
	negative			0.18220	0.36017	0.56322
	No/Unknown			0.40684	0.62239	0.78386
Surgery		420.498	<0.001			
	No			0.43978	0.65584	0.81185
	Yes			0.06590	0.16353	0.32644
Radiotherapy		3.47905	0.0622			
	No			0.23765	0.38437	0.53457
	Yes			0.18497	0.35260	0.56769
Chemotherapy		7.28393	0.0070			
	No/Unknown			0.27685	0.37094	0.49374
	Yes			0.18769	0.38830	0.58133

Abbreviations: CIF, cumulative incidence function; Lns, lymph nodes status; NOS, not otherwise specified.

Table 3 Multivariate analysis of prognostic factors in patients with pulmonary large-cell neuroendocrine carcinoma.

Prognostic factors	Cox regression analysis			SD model analysis			CS model analysis		
	P-value	HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI
Sex									
Male (ref)	-	-	-	-	-	-	-	-	-
Female	0.0017	0.809	0.708-0.923	0.0043	0.793	0.676-0.930	0.0012	0.789	0.683-0.911
Primary site									
Lung lobe (ref)									
Main bronchus	0.2883	1.183	0.868-1.611	0.5089	0.860	0.550-1.345	0.5756	1.099	0.790-1.528
Overlapping lesion of lung	0.9199	0.972	0.556-1.698	0.1899	1.429	0.838-2.436	0.5893	1.166	0.667-2.040
NOS	0.5086	1.095	0.836-1.434	0.5321	1.116	0.790-1.577	0.5383	1.092	0.825-1.444
Laterality									
Left (ref)	-	-	-	-	-	-	-	-	-
Right	0.3510	1.065	0.933-1.215	0.6204	1.042	0.886-1.226	0.4625	1.055	0.914-1.219
Others	0.5527	1.201	0.656-2.197	0.3808	1.467	0.623-3.453	0.4910	1.248	0.665-2.343
AJCC stage									
I (ref)	-	-	-	-	-	-	-	-	-
II	<0.0001	2.629	1.826-3.784	<0.0001	2.455	1.615-3.730	<0.0001	2.905	1.953-4.321
III	<0.0001	2.111	1.560-2.856	0.0004	1.878	1.324-2.663	<0.0001	2.217	1.593-3.086
IV	<0.0001	4.000	3.023-5.293	<0.0001	3.495	2.555-4.779	<0.0001	4.609	3.390-6.265
T stage									
T1 (ref)	-	-	-	-	-	-	-	-	-
T2	0.3034	1.100	0.917-1.320	0.0611	1.217	0.991-1.494	0.0429	1.238	1.007-1.522
T3	0.3462	0.865	0.639-1.170	0.4128	1.184	0.791-1.772	0.9480	0.989	0.716-1.367
T4	0.0043	1.396	1.111-1.756	0.0362	1.334	1.019-1.748	0.0010	1.518	1.184-1.947
N stage									
N0 (ref)	-	-	-	-	-	-	-	-	-
N1	0.8745	0.976	0.725-1.315	0.7904	0.949	0.647-1.393	0.8749	1.026	0.749-1.404
N2	0.1349	1.179	0.950-1.464	0.0131	1.403	1.074-1.833	0.0120	1.337	1.066-1.677
N3	0.0031	1.499	1.146-1.961	0.0395	1.395	1.016-1.916	0.0015	1.579	1.190-2.093
Lns									
Positive (ref)	-	-	-	-	-	-	-	-	-
negative	0.1659	1.222	0.920-1.623	0.2793	1.198	0.863-1.664	0.1364	1.265	0.928-1.723
No/Unknown	0.0008	1.565	1.206-2.032	0.0012	1.626	1.211-2.183	0.0003	1.707	1.275-2.285
Surgery									
No (ref)	-	-	-	-	-	-	-	-	-
Yes	<0.0001	0.569	0.445-0.726	0.0004	0.619	0.474-0.808	<0.0001	0.544	0.418-0.709
Chemotherapy									
No/Unknown (ref)	-	-	-	-	-	-	-	-	-
Yes	<0.0001	0.378	0.323-0.441	<0.0001	0.521	0.427-0.636	<0.0001	0.372	0.314-0.440

Abbreviations: SD, subdistribution hazard function; CS, cause-specific hazard function; Lns, lymph nodes status; NOS, not otherwise specified; ref, reference; CI, confidence interval; HR, hazard ratio.

Figures

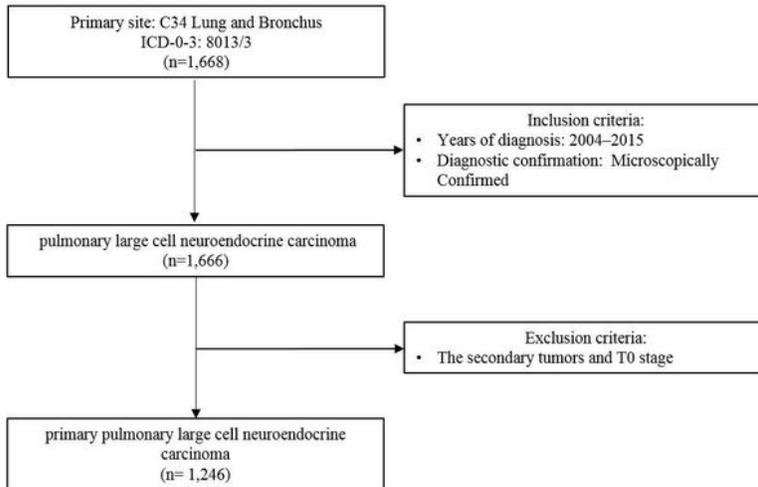


Figure 1

Patient enrollment and exclusion process of in the SEER database.

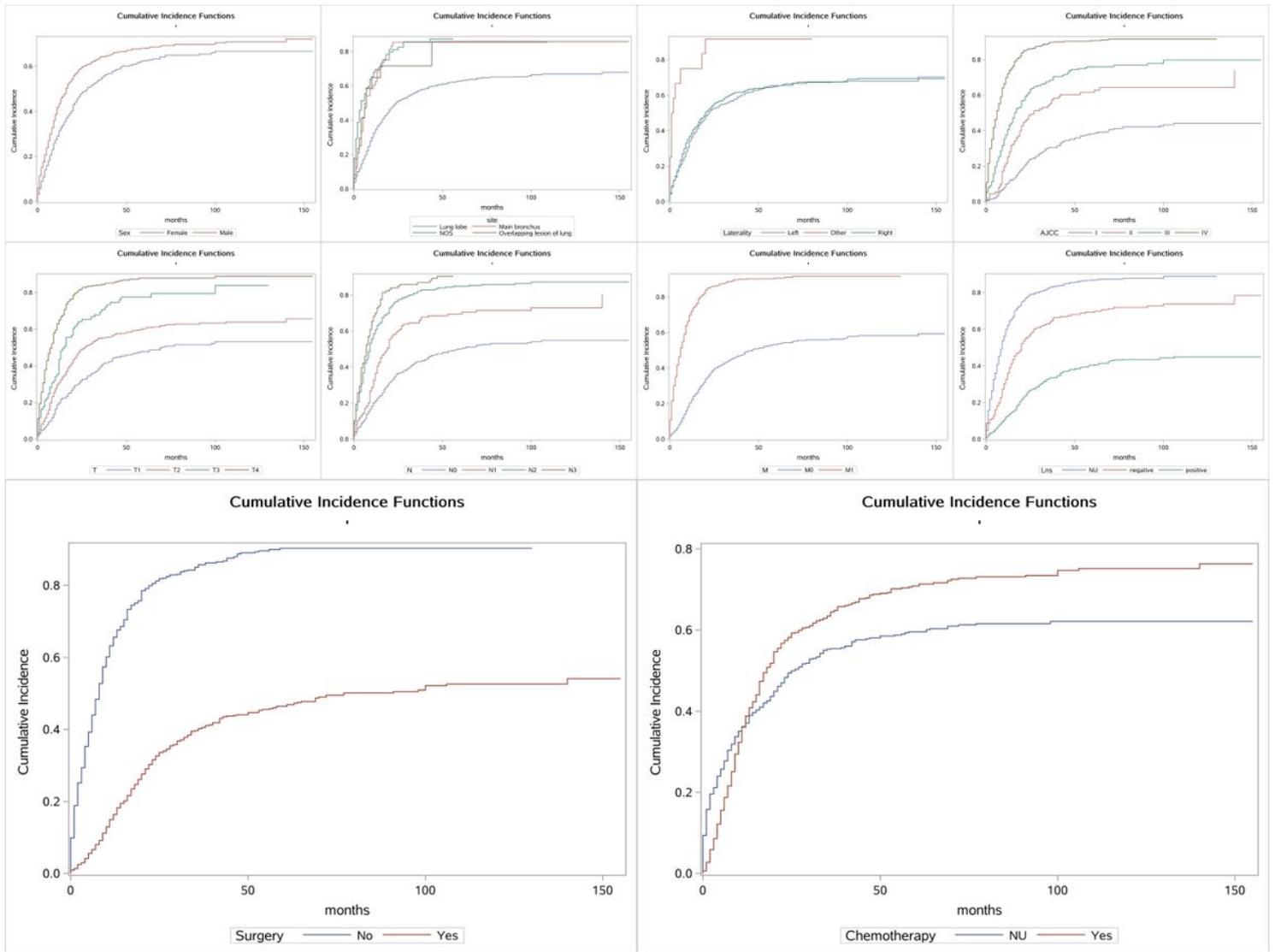


Figure 2

Cumulative incidence function for the prognostic factors. (A) sex; (B) primary site; (C) laterality; (D) AJCC stage; (E) T stage; (F) N stage; (G) M stage; (H) lymph nodes status; (I) surgery; (J) chemotherapy.

Abbreviations: Lns, lymph nodes status; NU, No/Unknown; NOS, not otherwise specified.