Prognostic factors of patients with pulmonary large-cell neuroendocrine carcinoma after surgery: a competing risk analysis

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Abstract

Background: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare primary malignant tumor with a poor prognosis. Our aim was to determine the prognostic factors of patients with pulmonary LCNEC after surgery based on competing risk model.

Methods: Patients were identified in the Surveillance, Epidemiology, and End Results (SEER) database. For single outcome events, Kaplan-Meier method and Cox proportional risk model were used for analysis. Competing risk model was used in the analysis of multiple outcome events to adjust potential confounding factors. Competing risk model was used to calculate the cumulative incidence function of LCNEC-specific death. The Fine-Gray model was used for multivariate analysis to determine independent prognostic factors.

Results: We finally screened 614 patients with pulmonary LCNEC who underwent surgery. The univariate analysis showed that T stage, N stage, M stage, regional nodes positive (RNP), and radiotherapy were significantly associated with the cumulative incidence of LCSD ($P < 0.05$). The Fine-Gray model showed that age, T stage, M stage, RNP, radiotherapy, and chemotherapy were independent prognostic factors for patients with pulmonary LCNEC after surgery ($P < 0.05$).

Conclusion: Based on the competing risk model, we estimated a more accurate cumulative incidence of LCNEC-specific death and prognostic factors for patients with pulmonary LCNEC after surgery.

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[1, 2]. The 2015 World Health Organization standard classified LCNEC, small-cell lung carcinoma, typical carcinoid, and atypical carcinoid as neuroendocrine tumors[3]. Pulmonary LCNEC was high-grade neuroendocrine tumor with 5-year survival rate ranging from 15% to 57%[4-7]. Surgical treatment was still one of the main options for patients with pulmonary LCNEC. Previous studies had performed predictive tools for pulmonary LCNEC patients[8]. However, there were few reports about the survival of pulmonary LCNEC after surgery[9]. Therefore, it is important to accurately assess the prognosis of patients with pulmonary LCNEC after surgery to help make treatment decisions and improve follow-up monitoring.

The competing risks model was an analytical technique used to deal with competing events and has been widely used in clinical research. Traditional survival analysis methods such as Kaplan-Meier method and Cox model may had limitations because they ignored the competing risk factors between outcome events[10]. In the previous survival analysis of LCNEC, competing risk events were treated as censored, which may lead to the risk of bias[11].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[12-

14]. Analysis of the SEER database should provide useful information about prognostic factors in patients with pulmonary LCNEC after surgery.

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

Methods

Data sources

The specific database we used was 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

Pulmonary LCNEC patients were identified in the SEER database 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) received definite surgical treatment; and (4) availability of data on age at diagnosis, race, sex, year of diagnosis, laterality, grade, T stage, N stage, M stage, regional nodes positive (RNP), radiotherapy, chemotherapy, survival time, and cause of death. Patients with nonprimary tumors were excluded from the study. Patients with more than one primary tumor were also excluded. The patient inclusion and exclusion process applied to the SEER database was shown in Figure 1.

Covariates

We included the following variables: age at diagnosis, race, sex, year of diagnosis, laterality, grade, T stage, N stage, M stage, RNP, radiotherapy, and chemotherapy. All variables were categorical variables. The causes of death were divided into the following three situations: alive, LCSD, and death due to other causes. LCSD was the primary outcome that we were interested in, and death due to other causes were considered competing events.

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. Traditional survival analysis methods were used to analyzed single outcome events. The Kaplan-Meier analysis was used to estimate the cumulative incidence, and the log-rank test was used for comparison between groups. The Cox proportional riskregression model

was used for multivariate analysis, and the results were expressed as hazard ratio (HR) and 95% confidence interval (CI). The competing-risks model analyzed competing risk events to adjust potential confounding factors. For the univariate analysis, we used the cumulative incidence function for determining the cumulative morbidity at different time points, and Gray's test for comparison between groups. According to the results of univariate analysis and clinical value, selected variables into multivariate analysis. The Fine-Gray proportional subdistribution hazard model was used for the multivariate analysis to identify prognostic factors. The results of the multivariate analysis were presented as subdistribution hazard ratio (sHR) and associated 95% CI values. All analyses were performed using R software (version 3.5.1).

Results

Patient Characteristics

A total of 614 patients with pulmonary LCNEC who underwent surgery were included in the cohort. Demographic and tumor characteristics were shown in Table 1. There were 265 patients with LCSD, and 93 patients died due to other causes. The median survival times in patient with LCSD and total-patient groups were 23.7 and 43.5 months, respectively. In all patients, patients aged 60-74 account for about half (51.6%). There were 588 patients (95.8%) with grade □-□, 534 patients (87%) with T stage 1-2, 446 patients (72.6%) with N0, and 571 patients (93%) with M0. In the results of regional lymph node examination, patients with positive lymph nodes accounted for 24.9%. There were 99 and 257 patients received radiotherapy and chemotherapy, respectively.

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

Variable	Total (%)	LCNEC-specific death (%)	Death due to other causes (%)
n	614	265	93
Age (years)			
<60	190 (30.9)	79 (29.8)	17 (18.3)
60-74	317 (51.6)	132 (49.8)	51 (54.8)
≥75	107 (17.4)	54 (20.4)	25 (26.9)
Race			
White	524 (85.3)	226 (85.3)	82 (88.2)
Black	66 (10.7)	26 (9.8)	8 (8.6)
Other	24 (3.9)	13 (4.9)	3 (3.2)
Sex			
Male	317 (51.6)	139 (52.5)	51 (54.8)
Female	297 (48.4)	126 (47.5)	42 (45.2)
Year of diagnosis			
2004-2009	272 (44.3)	141 (53.2)	49 (52.7)
2010-2015	342 (55.7)	124 (46.8)	44 (47.3)
Laterality			
Left	274 (44.6)	116 (43.8)	43 (46.2)
Right	340 (55.4)	149 (56.2)	50 (53.8)
Grade			
	3 (0.5)	0 (0.0)	1 (1.1)
	23 (3.7)	14 (5.3)	3 (3.2)
	455 (74.1)	196 (74.0)	67 (72.0)
	133 (21.7)	55 (20.8)	22 (23.7)
T			
T1	235 (38.3)	83 (31.3)	45 (48.4)
T2	299 (48.7)	129 (48.7)	38 (40.9)
T3	40 (6.5)	27 (10.2)	3 (3.2)
T4	40 (6.5)	26 (9.8)	7 (7.5)
N			
N0	446 (72.6)	161 (60.8)	75 (80.6)
N1	97 (15.8)	62 (23.4)	9 (9.7)
N2	68 (11.1)	40 (15.1)	9 (9.7)
N3	3 (0.5)	2 (0.8)	0 (0.0)
M			
M0	571 (93.0)	233 (87.9)	89 (95.7)
M1	43 (7.0)	32 (12.1)	4 (4.3)
Regional nodes positive			
0	461 (75.1)	170 (64.2)	75 (80.6)
1	69 (11.2)	33 (12.5)	9 (9.7)
2	37 (6.0)	24 (9.1)	5 (5.4)
≥3	47 (7.7)	38 (14.3)	4 (4.3)
Radiotherapy			
No	515 (83.9)	199 (75.1)	88 (94.6)
Yes	99 (16.1)	66 (24.9)	5 (5.4)

Chemotherapy			
No/Unknown	357 (58.1)	148 (55.8)	69 (74.2)
Yes	257 (41.9)	117 (44.2)	24 (25.8)

Abbreviations: LCNEC, large-cell neuroendocrine carcinoma.

Univariate analysis

The estimated cumulative incidence of LCSD at 1 year, 3 years, and 5 years in patients with pulmonary LCNEC after surgery was shown in Table 2. The Gray test and log-rank test showed that T stage, N stage, M stage, positive lymph nodes, and radiotherapy were significantly associated with the cumulative incidence of LCSD. The cumulative incidence curves of LCSD and competing events were shown in Figure 2.

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

Variables	LCNEC-specific death (%)			Gray test	LCNEC-specific death (%)			log-rank test
	1-Year	3-Year	5-Year	*P*-value	1-Year	3-Year	5-Year	*P*-value
Age (years)				0.283				0.072
<60	13.7%	36.2%	40.5%		14.0%	37.5%	42.3%	
60-74	13.3%	34.7%	42.9%		13.7%	36.8%	46.3%	
≥75	17.8%	45.7%	53.2%		18.7%	50.8%	60.2%	
Race				0.518				0.613
White	13.8%	36.7%	43.5%		14.2%	38.9%	46.8%	
Black	15.2%	38.1%	42.4%		16.0%	41.6%	46.6%	
Other	20.8%	42.0%	56.7%		20.8%	43.2%	58.7%	
Sex				0.549				0.420
Male	16.8%	38.3%	43.8%		17.4%	40.8%	47.2%	
Female	11.5%	35.9%	44.1%		11.8%	38.0%	47.4%	
Year of diagnosis				0.351				0.450
2004-2009	14.7%	37.6%	45.4%		15.1%	39.7%	48.5%	
2010-2015	13.8%	36.5%	41.7%		14.2%	38.9%	45.0%	
Laterality				0.627				0.581
Left	13.6%	34.1%	44.5%		13.9%	36.1%	48.0%	
Right	14.7%	39.5%	43.5%		15.2%	42.0%	46.7%	
Grade				0.259				0.159
□	-	-	-		-	-	-	
□	21.7%	50.4%	60.8%		23.8%	56.3%	68.8%	
□	13.4%	37.4%	43.5%		13.9%	39.9%	46.9%	
□	15.8%	34.2%	43.1%		16.1%	35.6%	45.7%	
T				<0.001				<0.001
T1	10.2%	28.8%	37.0%		10.5%	30.7%	40.2%	
T2	13.8%	37.2%	43.1%		14.3%	39.5%	46.1%	
T3	25.0%	59.5%	65.4%		25.4%	62.1%	68.4%	
T4	30.0%	61.2%	70.4%		30.8%	67.5%	82.0%	
N				<0.001				<0.001
N0	9.7%	30.4%	37.6%		9.9%	32.4%	40.6%	
N1	23.7%	54.3%	61.8%		24.8%	58.5%	66.8%	

N2	27.9 %	54.5%	58.3%		29.0%	57.5%	62.0 %	
N3	66.7 %	66.7%	-		66.7%	66.7%	-	
M				<0.001				<0.001
M0	13.2 %	34.6%	41.8%		13.6%	36.8%	45.0 %	
M1	27.9 %	69.1%	71.7%		28.2%	72.8%	75.9 %	
Regional nodes positive				<0.001				<0.001
0	10.2 %	31.5%	38.4%		10.5%	33.4%	41.3 %	
1	18.8 %	40.9%	46.4%		19.7%	44.1%	50.3 %	
2	21.6 %	51.9%	61.2%		23.5%	57.3%	69.0 %	
≥3	40.4 %	74.2%	79.0%		41.0%	77.0%	82.5 %	
Radiotherapy				<0.001				<0.001
No	12.5 %	33.8%	40.2%		12.9%	36.1%	43.5 %	
Yes	23.2 %	54.3%	63.1%		23.4%	55.6%	65.0 %	
Chemotherapy				0.381				0.820
No/ Unknown	14.3 %	36.9%	43.0%		14.9%	40.1%	47.4 %	
Yes	14.0 %	37.3%	45.2%		14.3%	38.5%	47.1 %	

Multivariate analysis

The Cox proportional risk model showed that T3 stage (HR = 2.048; 95% CI, 1.331-3.152; *P* = 0.001), T4 stage (HR = 2.334; 95% CI, 1.466-3.715; *P* < 0.001), M1 stage (HR = 1.626; 95% CI, 1.057-2.500; *P* = 0.027), and received radiotherapy (HR = 1.615; 95% CI, 1.187-2.199; *P* = 0.002) were independent prognostic factors for patients with pulmonary LCNEC after surgery. We used the Fine-Gray proportional subdistribution hazard model to adjust potential confounding factors. The Fine-Gray model showed that age, T stage, M stage, RNP, radiotherapy and chemotherapy were prognostic factors for patients with pulmonary LCNEC after surgery (Table 3). Older patients had a higher risk of LCSD (sHR = 1.681; 95% CI, 1.157-2.442; *P* = 0.006), compared with patients younger than 60 years. In addition, a lower risk of LCSD was observed in patients received chemotherapy (sHR = 0.659; 95% CI, 0.486-0.892; *P* = 0.007).

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

Variables	Fine-Gray model				Cox model			
	Coefficient	sHR	95%CI	*P*-value	Coefficient	HR	95%CI	*P*-value
Age (years)								
<60	Reference				Reference			
60-74	0.228	1.256	0.938-1.682	0.125	0.141	1.152	0.873-1.520	0.320
≥75	0.519	1.681	1.157-2.442	0.006	0.342	1.407	0.959-2.065	0.081
T								
T1	Reference				Reference			
T2	0.149	1.161	0.863-1.561	0.324	0.134	1.143	0.849-1.539	0.380
T3	0.743	2.101	1.332-3.314	0.001	0.717	2.048	1.331-3.152	0.001
T4	0.980	2.664	1.652-4.295	<0.001	0.847	2.334	1.466-3.715	<0.001
N								
N0	Reference				Reference			
N1	0.589	1.802	0.793-4.096	0.160	0.617	1.854	0.779-4.414	0.160
N2	0.146	1.157	0.517-2.590	0.723	0.169	1.184	0.513-2.736	0.690
N3	-0.067	0.935	0.206-4.255	0.931	0.097	1.102	0.091-13.326	0.940
M								
M0	Reference				Reference			
M1	0.589	1.802	1.204-2.698	0.004	0.486	1.626	1.057-2.500	0.027
Regional nodes positive								
0	Reference				Reference			
1	0.027	1.027	0.444-2.379	0.950	-0.130	0.878	0.366-2.107	0.770
2	0.556	1.743	0.733-4.142	0.209	0.344	1.411	0.584-3.409	0.440
≥3	1.020	2.774	1.235-6.231	0.014	0.831	2.296	0.981-5.375	0.055
Radiotherapy								
No	Reference				Reference			
Yes	0.398	1.489	1.078-2.057	0.016	0.480	1.615	1.187-2.199	0.002
Chemotherapy								
No/Unknown	Reference				Reference			
Yes	-0.418	0.659	0.486-0.892	0.007	-0.301	0.740	0.546-1.004	0.053

Abbreviations: sHR, subdistribution hazard ratio; HR, hazard ratio; CI, confidence interval.

Discussion

Pulmonary LCNEC is a rare primary malignant tumor with a poor prognosis[15, 16]. The clinical and biological characteristics of pulmonary LCNEC were similar to small cell lung carcinoma, but standard treatment management has not yet been established. Recent reports showed that surgery remains a reliable option for patients with pulmonary LCNEC[17-21]. We used competing risks model to analyze the survival of pulmonary LCNEC patients after surgery in the SEER database. Our results indicated that age,

T stage, M stage, RNP, radiotherapy, and chemotherapy were independent prognostic factors for patients with pulmonary LCNEC after surgery. In addition, the competing risks model showed more accurate results compared to traditional survival analysis. In our study, 93 patients died due to other causes, accounting for 26% of deaths. In the traditional survival analysis, these 93 competing events will be used as censored data, which may lead to incorrect and biased results.

We found that age was an independent factor that influences the prognosis in the multivariate analysis based on Fine-Gray model. However, the Cox model showed that age was not an independent prognostic factor for patients with pulmonary LCNEC after surgery. This suggested that ignoring the competing risk between outcome events may lead to bias in results. Age has been identified as a prognostic factor for patients with pulmonary LCNEC, but the division of age is still controversial[22]. Kujtan et al.[23] concluded that patients older than 70 years have a worse prognosis, while Cao et al.[24] report that patients 65 years or older have worse survival outcomes than younger patients. For patients with pulmonary LCNEC after surgery, our results showed that patients over 75 years of age had a higher risk of LCSD. Due to the differences in the populations included in these studies and the limited number of current studies, multicenter studies were needed for validation.

The TNM stage were the important and stable indicators to predict the survival time of patients with lung cancer[25]. The prognosis of patients differed significantly between different clinical stages. Our results indicated that T stage and M stage were an independent prognostic factor for patients with pulmonary LCNEC after surgery. However, no correlation between N stage and LCNEC-specific death was observed in the Fine-Gray model and Cox model. 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 were adverse factors for survival[14]. Our results also showed a similar phenomenon. Patients with distant metastases had a worse prognosis than patients without metastases, and the greater the number of positive regional lymph nodes, the worse the prognosis. Positive lymph nodes had a predictive role in the prognosis of lung cancer. Previous study had reported that patients with lymph node positive non-small cell lung cancer had a higher risk of recurrence[26]. In addition, the positive-to-resected lymph node ratio predicted survival in many cancers[27, 28]. Therefore, positive lymph node assessment may be a way to predict survival outcomes in patients with pulmonary LCNEC.

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[19-21]. However, the use of radiotherapy and chemotherapy remains controversial[29]. Our study showed that radiotherapy and chemotherapy were an independent prognostic factor for patients with pulmonary LCNEC after surgery. Iyoda et al.[30] analyzed 79 patients with pulmonary LCNEC and showed that platinum-based adjuvant chemotherapy after surgery may reduce tumor recurrence. Tang et al.[31] reported that cisplatin combined with pemetrexed is effective and safe in patients with pulmonary LCNEC. Furthermore, a

retrospective study[32] 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 had some limitations. First, since the study had a retrospective design, inherent selection bias might have been present. Second, the SEER database did not contain all clinical factors, so some factors that may affected the survival of patients were not included, such as smoking status, comorbidities, and weight. 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

Based on the competing risk model, we estimated the cumulative incidence of LCNEC-specific death at 1 year, 3 years, and 5 years in patients with pulmonary LCNEC after surgery. In addition, we found that age, T stage, M stage, RNP, radiotherapy and chemotherapy were independent prognostic factors for patients with pulmonary LCNEC after surgery.

Abbreviations

LCNEC, large-cell neuroendocrine carcinoma; SEER, Surveillance, Epidemiology, and End Results; LCSD, LCNEC-specific death; ICD-O-3, International Classification of Disease—Oncology, Third Edition; RNP, regional nodes positive; HR, hazard ratio; CI, confidence interval; sHR, subdistribution hazard ratio.

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.

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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.

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Figures

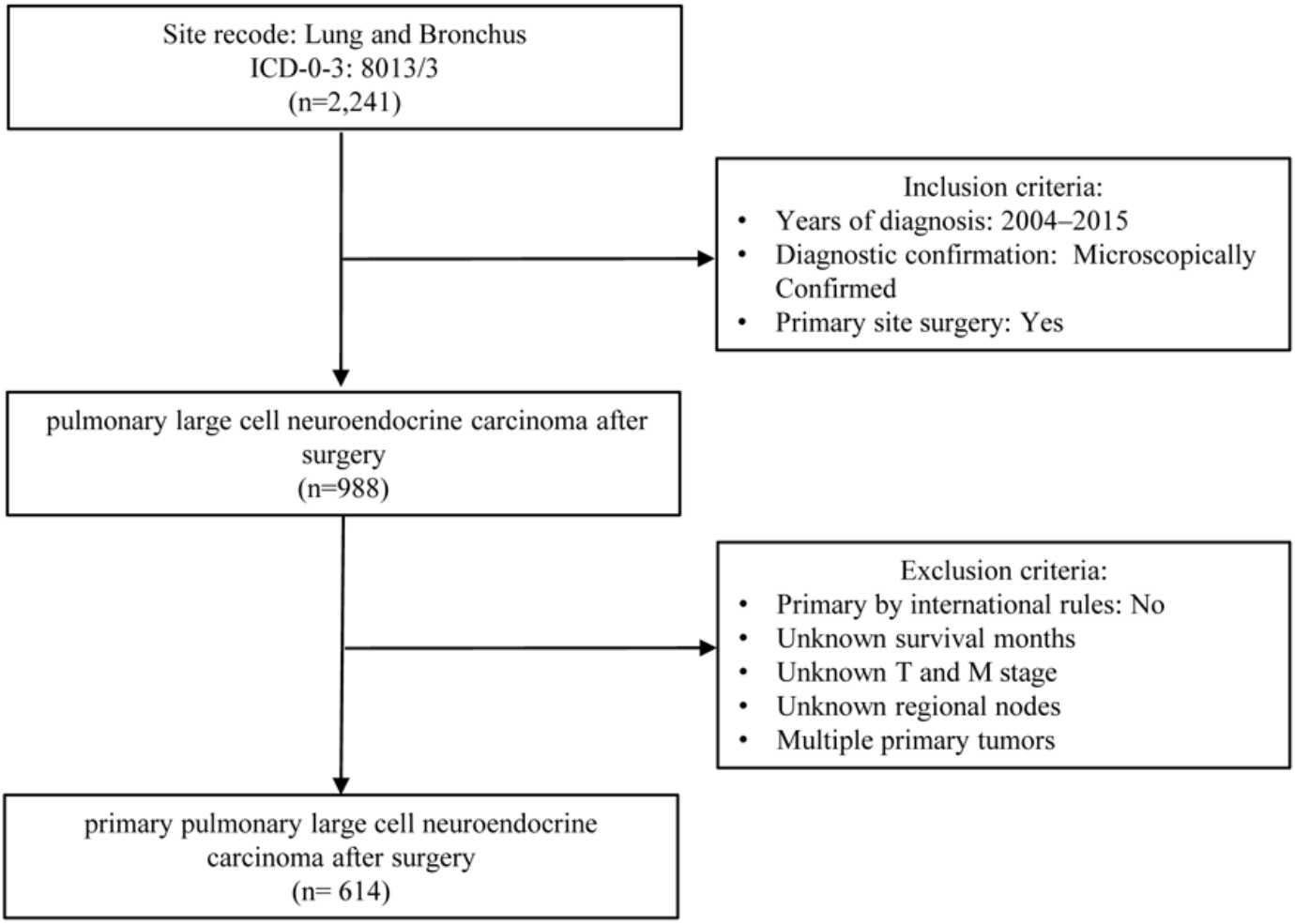

Figure 1

Patient enrollment and exclusion process of in the SEER database.

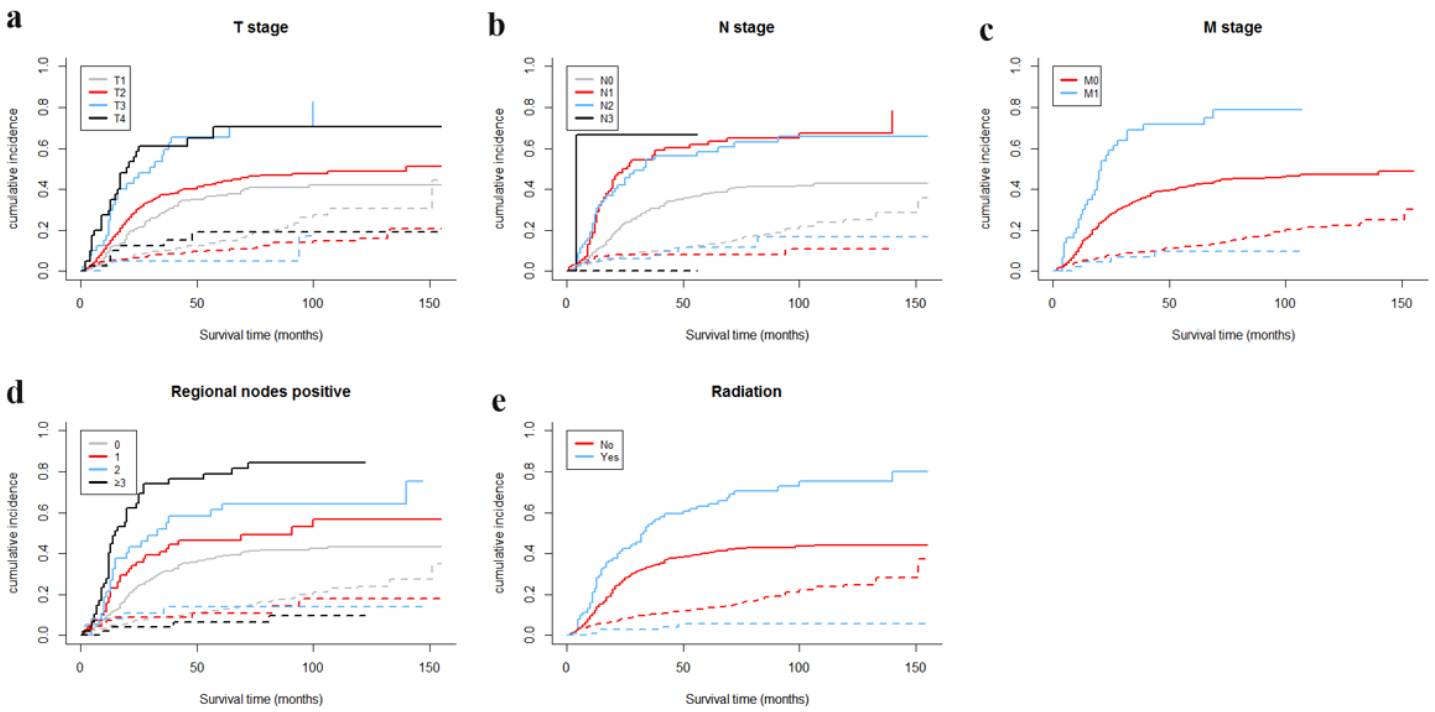

Figure 2

The cumulative incidence curves of LCSD and competing events. The solid line indicates LCSD, and the dotted line indicates competing events. LCSD, large-cell neuroendocrine carcinoma-specific death.