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ORIGINAL ARTICLE

Clinicopathological characteristics and prognostic factors of pulmonary large cell neuroendocrine carcinoma: A large population-based analysis

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Keywords
Clinicopathological characteristic; metastasis; prognostic factor; pulmonary large cell neuroendocrine carcinoma; SEER.

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Abstract

Background: The study was conducted to compare the clinicopathological characteristics, survival outcomes, and metastatic patterns between pulmonary large cell neuroendocrine carcinoma (LCNEC) and other non-small cell lung cancer (ONSCLC), and to identify the prognostic factors of LCNEC.

Methods: Data of patients diagnosed with LCNEC and ONSCLC from 2004 to 2014 were obtained from the Surveillance, Epidemiology, and End Results dataset. Pearson's chi-square tests were used to compare differences in clinicopathological characteristics. The Kaplan–Meier method was used for survival analysis. A propensity score was used for matching and a Cox proportional hazards model was used for multivariate and subgroup analyses.

Results: A total of 2368 LCNEC cases and 231 672 ONSCLC cases were identified. LCNEC incidence increased slightly over time. Except for marital status, LCNEC patients had obviously different biological features to ONSCLC patients. Survival analysis showed that LCNEC had poorer outcomes than ONSCLC. Multivariate analysis revealed that female gender, black race, surgery, radiation, and chemotherapy were protective factors for LCNEC. Matched subgroup analysis further demonstrated that most subgroup factors favored ONSCLC, especially in early stage. Early-stage LCNEC patients had a higher risk of lung cancer-specific death than early-stage ONSCLC patients. Moreover, metastatic patterns were different between LCNEC and ONSCLC. LCNEC patients with isolated liver metastasis or combined invasion to other organs had poorer survival rates.

Conclusions: LCNEC has totally different clinicopathological characteristics and metastatic patterns to ONSCLC. LCNEC also has poorer survival outcomes, primarily because of isolated liver metastasis or combined invasion to other organs. Most subgroup factors are adverse factors for LCNEC.

Introduction

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare but aggressive subtype of lung cancer, with an incidence around 3%.[1] LCNEC was first identified as a new subtype of lung cancer by Travis *et al.*[2] and was then classified by the World Health Organization as a variant of large cell carcinoma (LCC), a part of non-small cell lung cancer (NSCLC).[3] However, in 2015, LCNEC was reclassified as a subcluster of pulmonary neuroendocrine tumors (NETs), which include small cell lung cancer (SCLC), typical carcinoid (TC), and atypical carcinoid (AC).[4] LCNEC generally manifests as a high-grade malignant tumor with neuroendocrine morphology, such as organoid nesting, palisading, rosettes, and trabeculae. Resembling SCLC, LCNEC often presents with large zones of necrosis, as well as a high mitotic rate. In contrast, LCNEC might have more cytoplasm and larger cells than SCLC.[5]

Interestingly, a previous study demonstrated that LCNEC is a kind of biologically heterogeneous tumor that comprises not only a small cell carcinoma-like subset, but also a non-small cell carcinoma-like subset.[6] Consistent with this finding, the clinical treatment for LCNEC remains controversial.[7]

Despite numerous efforts to compare clinicopathological characteristics and survival between LCNEC and SCLC, only a few studies with small sample sizes have provided limited information about the clinical relationship between LCNEC and other non-small cell lung cancer (ONSCLC). The aim of this study was to compare clinicopathological characteristics and survival outcomes between LCNEC and ONSCLC, and to investigate the effect of different metastatic patterns and treatments on survival using the Surveillance, Epidemiology, and End Results (SEER) dataset.

Methods

Patient selection and covariates

The SEER dataset used in the current study was released in November 2017. This dataset includes cancer cases from 18 population-based cancer registries (1973–2015) and covers approximately 27.8% of the American population.[8] We included eligible patients based on the following criteria: LCNEC and ONSCLC cases diagnosed during 2004 and 2014, tumor located in the lung and bronchus, only one primary tumor, and diagnosis was not made by death certificate or autopsy. The histology codes of all cases were identified according to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). We only included cases from 2004 to 2014 because most covariates were exactly recorded from 2004, and at least 12 months' follow-up was guaranteed. The covariates included year of diagnosis; age; gender; race; marital status; laterality; tumor grade; tumor size; regional node status; surgery; radiation; chemotherapy; American Joint Committee on Cancer (AJCC) N-stage; AJCC M-stage; survival months; SEER cause-specific death classification; vital status recode; and metastasis to the bone, brain, liver, and lung (metastasis to these four sites were only available for 2010+ diagnoses). SEER*Stat software version 8.3.5 was used to select eligible patients. All patients with unknown diagnostic information were excluded. The study design is presented in Figure 1.

Outcome measurement

In order to conduct cancer-specific survival analysis and identify cancer-specific prognostic factors, lung cancer-specific survival (LCSS) was used as the primary outcome in this study. LCSS was defined as the interval from diagnosis to death as a result of lung cancer. Patients who were alive or had died as a result of other reasons at the last follow-up were regarded as censored cases in survival analysis. We also analyzed overall survival (OS), which was defined as the interval from diagnosis to death as a result of any cause. Patients who were still alive at the last follow-up were considered censored cases. The final follow-up date was 31 December 2015.

Statistical analysis

In this study, the Pearson's chi-square test was used to compare the differences in clinicopathological characteristics between LCNEC and ONSCLC. Survival curves were plotted using the Kaplan–Meier method, and differences between each curve were determined by the log-rank test. To analyze prognostic factors affecting LCSS and OS, multivariate analysis and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model.

MatchIt package (Rx64, version 3.4.4) designed for propensity score matching was used to match each LCNEC case with four ONSCLC cases for further survival analysis. The following predetermined factors were considered: year of diagnosis, gender, age, race, laterality, tumor grade, tumor size, marital status, regional node status, and distant metastasis. To perform subgroup analysis, an unadjusted Cox proportional hazard model was used to calculate HRs with 95% CIs of matched groups. We then displayed the effect of each prognostic factor on LCSS by forest plot.

To analyze the differences in metastatic patterns between the groups, we included all cases between 2010 and 2014 for study. The HR of each metastasis pattern was calculated using an unadjusted Cox proportional hazard model to identify potential prognostic factors for LCSS.

A two-sided P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristic comparison between large cell neuroendocrine carcinoma and other non-small cell lung cancer

Overall, 234 040 NSCLC patients were enrolled, including 2368 LCNEC patients and 231 672 ONSCLC patients. LCNEC cases accounted for 0.92% of all NSCLC patients during 2004–2009, and the proportion increased to 1.11% during 2010–2014. Baseline clinicopathological characteristics were compared between LCNEC and ONSCLC. As shown in Table 1, considerable differences were observed.

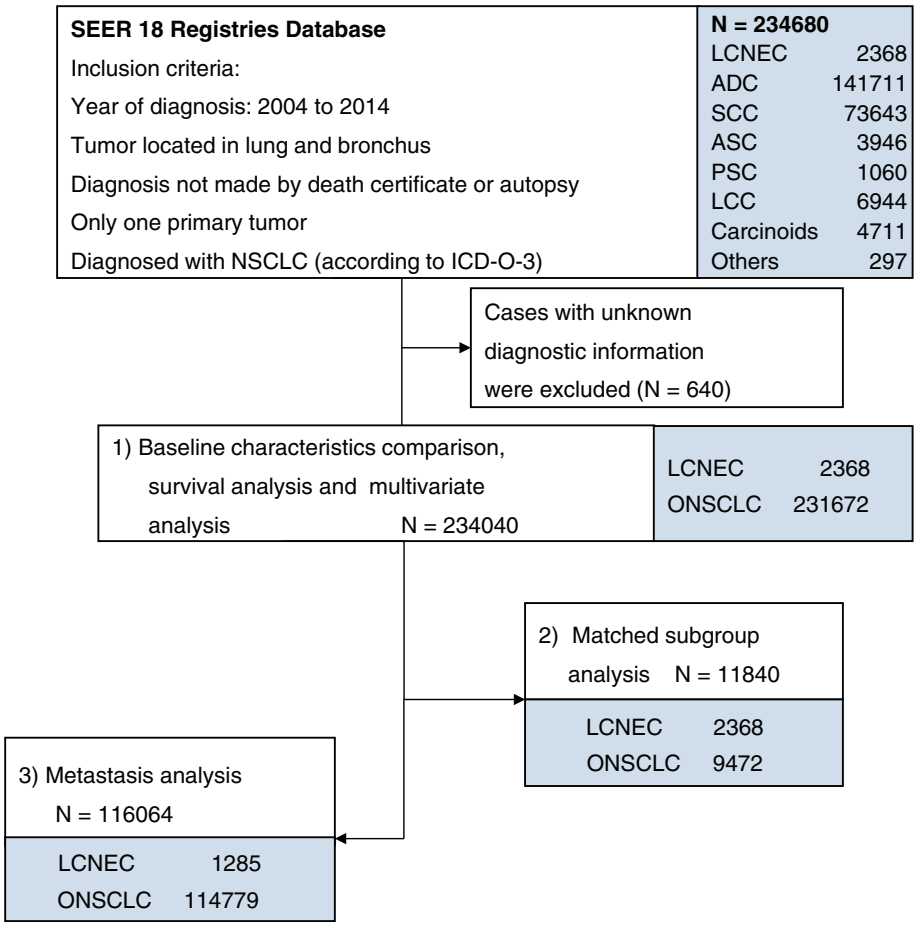

Figure 1 A flowchart of patient selection and study design. ADC, adenocarcinoma; ASC, adenosquamous carcinoma; ICD-O-3, International Classification of Diseases for Oncology, 3rd Edition; LCC, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; NSCLC, non-small cell lung cancer; ONSCLC, other non-small cell lung cancer; PSC, pulmonary sarcomatoid carcinoma; SCC, squamous cell carcinoma; SEER, the Surveillance, Epidemiology, and End Results dataset.

The LCNEC group had a significantly lower percentage of patients aged > 70 years (37.75% vs. 46.47%; $P < 0.001$) and a significantly higher percentage of patients with grade III or IV disease (34.08% vs. 27.61% and 11.02% vs. 1.52%, respectively; $P < 0.001$) than the ONSCLC group. The LCNEC group also had a significantly higher amount of regional node-positive (19.64% vs. 13.70%; $P < 0.001$) and distant metastasis cases (52.23% vs. 47.67%; $P < 0.001$) than the ONSCLC group. Moreover, the proportion of men was higher in the LCNEC than in the ONSCLC group (56.38% vs. 53.37%; $P = 0.004$), and the proportion of white race showed similar results (83.57% vs. 80.06%; $P < 0.001$). No significant difference was observed in marital status.

Survival and multivariate analyses

The median follow-up duration was nine months in the LCNEC group and 11 months in the ONSCLC group. Kaplan–Meier survival analysis suggested that LCSS was poorer in the LCNEC group than in the ONSCLC group ($P < 0.001$) (Fig 2a). The median LCSS (mLCSS) was 10.0 months (95% CI 9.3–10.7) in the LCNEC group compared to 13.0 months (95% CI 12.9–13.1) in the ONSCLC group. The HR for death was 1.160 (LCNEC vs. ONSCLC, 95% CI 1.107–1.216; $P < 0.001$). Similarly, LCNEC patients had poorer OS than ONSCLC patients ($P < 0.001$) (Fig 2b). The median OS (mOS) in the LCNEC group was 9.0 months (95% CI 8.4–9.6) compared to 11.0 months (95% CI 10.9–11.1) in the ONSCLC group. The HR was 1.133 (LCNEC vs. ONSCLC, 95% CI 1.085–1.185; $P < 0.001$).

To further investigate the effect of clinicopathological characteristics and treatments (including surgery, radiation, and chemotherapy) on survival, we conducted multivariate analysis using the Cox proportional hazards model. All factors were associated with ONSCLC survival (both endpoints). In contrast, the year of diagnosis, marital status, and tumor grade were not associated with LCNEC survival (Table 2, Table S1). Multivariate analysis revealed that female gender, black race, surgery, radiation, and chemotherapy were protective factors for LCNEC, while older age, male gender, white race, larger tumors, regional node infiltration, and distant metastasis were adverse factors for prognosis.

Table 1 Baseline clinicopathological characteristics of LCNEC and ONSCLC patients

Characteristic	LCNEC, N = 2368 (%)	ONSCLC, N = 231 672 (%)	Total, N = 234 040 (%)	*P*
Year of diagnosis				
2004–2009	1083 (45.73)	116 893 (50.46)	117 976 (50.41)	< 0.001
2010–2014	1285 (54.27)	114 779 (49.54)	116 064 (49.59)	
Age at diagnosis (years)				
< 60	663 (28.00)	53 957 (23.29)	54 620 (23.34)	< 0.001
60–69	811 (34.25)	70 062 (30.24)	70 873 (30.28)	
≥ 70	894 (37.75)	107 653 (46.47)	108 547 (46.38)	
Gender				
Female	1033 (43.62)	108 018 (46.63)	109 051 (46.60)	0.004
Male	1335 (56.38)	123 654 (53.37)	124 989 (53.40)	
Race				
White	1979 (83.57)	185 473 (80.06)	187 452 (80.09)	< 0.001
Black	288 (12.16)	27 858 (12.02)	28 146 (12.03)	
Others	101 (4.27)	18 341 (7.92)	18 442 (7.88)	
Marital status				
Married	1218 (51.44)	119 230 (51.47)	120 448 (51.46)	0.485
Not married	1064 (44.93)	102 918 (44.42)	103 982 (44.43)	
Unknown	86 (3.63)	9524 (4.11)	9610 (4.11)	
Laterality				
Left	903 (38.13)	91 013 (39.29)	91 916 (39.27)	0.041
Right	1336 (56.42)	130 423 (56.30)	131 759 (56.30)	
Others	129 (5.45)	10 236 (4.41)	10 365 (4.43)	
Tumor grade				
I–II	37 (1.56)	63 981 (27.62)	64 018 (27.35)	< 0.001
III	807 (34.08)	63 963 (27.61)	64 770 (27.67)	
IV	261 (11.02)	3532 (1.52)	3793 (1.62)	
Unknown	1263 (53.34)	100 196 (43.25)	101 459 (43.35)	
Tumor size (cm)				
≤ 3	783 (33.07)	74 029 (31.95)	74 812 (31.97)	< 0.001
3–5	537 (22.68)	53 746 (23.20)	54 283 (23.19)	
5–7	300 (12.67)	30 293 (13.08)	30 593 (13.07)	
> 7	312 (13.18)	23 645 (10.21)	23 957 (10.24)	
Unknown	436 (18.41)	49 959 (21.56)	50 395 (21.53)	
Regional nodes				
Negative	516 (21.79)	42 984 (18.55)	43 500 (18.59)	< 0.001
Positive	465 (19.64)	31 746 (13.70)	32 211 (13.76)	
Unknown	1387 (58.57)	156 942 (67.75)	158 329 (67.65)	
Distant metastasis				
No/Unknown	1131 (47.76)	121 226 (52.33)	122 357 (52.28)	< 0.001
Yes	1237 (52.23)	110 446 (47.67)	111 683 (47.72)	

LCNEC, large cell neuroendocrine carcinoma; ONSCLC, other non-small cell lung cancer.

Survival analysis of matched groups

To exclude the effect of clinicopathological characteristic biases on survival analysis, we performed a 1:4 (LCNEC: ONSCLC) matched case-control analysis. A total of 2368 cases of LCNEC and 9472 cases of ONSCLC were included. No significant difference in baseline clinicopathological characteristics was discovered between the groups (Table S2). Kaplan–Meier survival analysis showed that both LCSS and OS were poorer in the LCNEC group than in the matched ONSCLC group (both $P < 0.001$). The mLCSS were 10.0 (95% CI 9.3–10.7) and 12.0 (95% CI, 11.5–12.5) months in the LCNEC and matched ONSCLC groups, respectively (HR 1.115, 95% CI 1.058–1.175; $P < 0.001$) (Fig 3a). The mOS were 9.0 (95% CI 8.4–9.6) and 10.0 (95% CI 9.5–10.5) months in the LCNEC and matched ONSCLC groups, respectively (HR 1.094, 95% CI 1.041–1.149; $P < 0.001$) (Fig 3b).

To further explore the prognostic factors affecting LCSS, we conducted subgroup analysis of matched groups (Fig 3c). As displayed in the forest plot, most subgroup factors favored matched ONSCLC. Interestingly, LCNEC patients with either right (HR 1.114, 95% CI 1.039–1.194; $P = 0.002$) or left (HR 1.159, 95% CI 1.065–1.262; $P = 0.001$) origination had a higher risk of LCS death. Regarding the analysis of treatment methods,

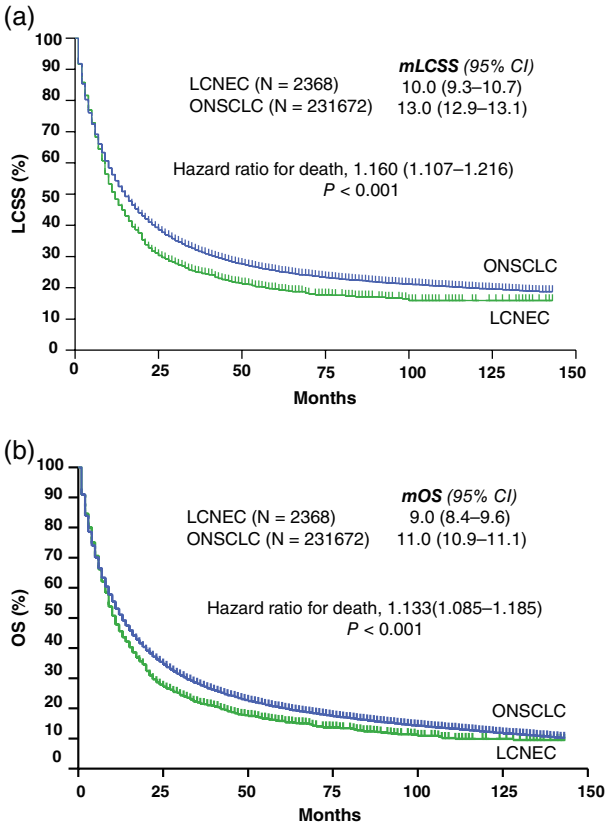

Figure 2 Kaplan–Meier curves for survival outcomes: (**a**) lung cancer-specific survival (LCSS) and (**b**) overall survival (OS). CI, confidence interval; LCNEC, large cell neuroendocrine carcinoma; m, median; ONSCLC, other non-small cell lung cancer.

chemotherapy (HR 1.099, 95% CI 1.024–1.180; $P = 0.009$) and surgery (HR 1.539, 95% CI 1.363–1.737; $P < 0.001$) favored matched ONSCLC compared to LCNEC, but no significant difference was found in HR for radiation (HR 1.059, 95% CI 0.978–1.146; $P = 0.158$). In addition, we found that LCNEC patients with unknown or without distant metastasis had higher HR (1.168) than those with distant metastasis (1.106) when compared to corresponding matched ONSCLC patients. Similarly, the HR was higher for negative regional nodes (1.338) than for positive regional nodes (1.114), and also higher for surgery (1.539) than for unknown or no surgery (1.143).

Prognostic value of metastasis

Because identification of distant metastasis to the bone, brain, liver, and lung at the time of diagnosis was not available until 2010, we only included cases diagnosed between 2010 and 2014. A total of 1285 LCNEC cases and 114 779 ONSCLC cases were identified. As shown in Figure 4a, the rates of lymph node and distant metastasis in the LCNEC group were 64.20% and 55.25%, respectively, whereas in the ONSCLC group the rates were 59.94% and 48.84%, respectively. The percentages of patients with isolated bone, brain, liver, and lung metastasis in the LCNEC group were 8.87%, 22.25%, 13.10%, and 7.60%, respectively, while in the ONSCLC group the percentages were 16.75%, 11.33%, 4.35%, and 14.71%, respectively (Fig 4b). The most common combined metastatic pattern for LCNEC was to the bone and liver (4.67%), and the least was to the brain and lung (1.17%). For ONSCLC, the most common combined metastatic pattern was to the bone and lung (2.66%), and the least was to the brain and liver (0.49%) (Fig 4c). As for three-site metastatic patterns, LCNEC had more combined metastases to the bone, brain, and liver (2.10%), but fewer to the bone, brain, and lung (0.23%). By comparison, the most common three-site metastatic combination for ONSCLC was to the bone, liver, and lung (1.11%), with the fewest to the brain, liver, and lung (0.25%) (Fig 4d). Four-site metastases of LCNEC and ONSCLC accounted for 0.39% and 0.57%, respectively.

We compared survival outcomes among patients with single organ metastasis (SOM) and multiple organ metastases (MOM). The results showed that isolated liver metastasis had the worst survival among all SOMs in both groups (Fig 4e,f). Surprisingly, although patients with MOM had poorer outcomes than those with SOM to the bone, brain, and lung, the difference in outcome between patients with SOM to the liver and MOM was insignificant.

LCNEC patients with distant metastasis (HR 1.179) or lymph node metastasis (HR 1.241) had a higher risk of LCS death than ONSCLC cases (Table 3). Subgroup analysis was conducted to further elucidate the prognostic value of different metastatic patterns. As shown in Table 3, HRs for isolated liver (HR 1.325) or lung (HR 1.474) metastasis and for two-site metastases (HR 1.250) were positive prognostic indicators of LCSS. There was no significant difference in HRs for other patterns of distant metastasis. In addition, all HRs of each AJCC N stage favored ONSCLC (HR 1.350 for AJCC N1 stage, HR 1.211 for N2, and HR 1.306 for N3).

Discussion

We conducted a population-based retrospective study to unravel different clinicopathological characteristics and survival outcomes between LCNEC and ONSCLC. A low incidence of LCNEC was found, at approximately 1% of all NSCLC. This incidence is similar to results of a study by Derk *et al*.,[9] but lower than other data.[1,10] The main reason for this inconsistency might be an underestimation of LCNEC, because most patients in SEER did not undergo surgery and the small sample makes identification of the neuroendocrine features of LCNEC difficult.[3,11] The

Table 2 Multivariate analysis of the effect of different variables on lung cancer-specific survival of LCNEC and ONSCLC

	LCNEC		ONSCLC	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Year of diagnosis				
2004–2009	—	—	Reference	—
2010–2014	—	—	0.896 (0.887–0.905)	< 0.001
Age at diagnosis (years)				
< 60	Reference	—	Reference	—
60–69	1.117 (0.991–1.259)	0.070	1.094 (1.079–1.109)	< 0.001
≥ 70	1.218 (1.080–1.374)	0.001	1.222 (1.207–1.238)	< 0.001
Gender				
Male	Reference	—	Reference	—
Female	0.892 (0.811–0.981)	0.018	0.811 (0.803–0.819)	< 0.001
Race				
White	Reference	—	Reference	—
Black	0.830 (0.717–0.959)	0.012	0.969 (0.955–0.984)	< 0.001
Others	0.908 (0.722–1.141)	0.407	0.757 (0.743–0.771)	< 0.001
Marital status				
Married	—	—	Reference	—
Not married	—	—	1.101 (1.089–1.112)	< 0.001
Unknown	—	—	0.918 (0.895–0.942)	< 0.001
Tumor grade				
I–II	—	—	Reference	—
III	—	—	1.293 (1.274–1.312)	< 0.001
IV	—	—	1.378 (1.324–1.434)	< 0.001
Unknown	—	—	1.166 (1.150–1.182)	< 0.001
Laterality				
Left	Reference	—	Reference	—
Right	0.995 (0.902–1.098)	0.928	1.023 (1.012–1.033)	< 0.001
Others	0.632 (0.508–0.786)	<0.001	1.040 (1.016–1.065)	0.001
Tumor size (cm)				
≤ 3	Reference	—	Reference	—
3–5	1.254 (1.095–1.436)	0.001	1.344 (1.324–1.363)	< 0.001
5–7	1.480 (1.262–1.736)	<0.001	1.627 (1.600–1.654)	< 0.001
> 7	1.788 (1.525–2.097)	<0.001	1.924 (1.890–1.959)	< 0.001
Unknown	1.459 (1.260–1.690)	<0.001	1.647 (1.622–1.671)	< 0.001
Regional nodes				
Negative	Reference	—	Reference	—
Positive	2.306 (1.873–2.839)	<0.001	2.336 (2.278–2.396)	< 0.001
Unknown	2.268 (1.826–2.816)	<0.001	2.112 (2.060–2.165)	< 0.001
Distant metastasis				
No	Reference	—	Reference	—
Yes	2.388 (2.123–2.687)	<0.001	2.118 (2.094–2.142)	< 0.001
Surgery				
No/Unknown	Reference	—	Reference	—
Yes	0.504 (0.418–0.607)	<0.001	0.389 (0.381–0.398)	< 0.001
Radiation				
No/Unknown	Reference	—	Reference	—
Yes	0.824 (0.746–0.911)	<0.001	0.947 (0.937–0.957)	< 0.001
Chemotherapy				
No/Unknown	Reference	—	Reference	—
Yes	0.494 (0.445–0.550)	<0.001	0.604 (0.598–0.611)	< 0.001

CI, confidence interval; HR, hazard ratio; LCNEC, large cell neuroendocrine carcinoma; ONSCLC, other non-small cell lung cancer.

incidence of LCNEC increased with time, which may be the result of new insights into the molecular characteristics of LCNEC and its reclassification.[3,4,12,13] Previous SCLC cases might be reclassified as LCNEC cases according to the new and comprehensive recognition of LCNEC. The baseline clinicopathological characteristics of LCNEC, except for marital status, were significantly different from those of ONSCLC in this study. Compared to ONSCLC,

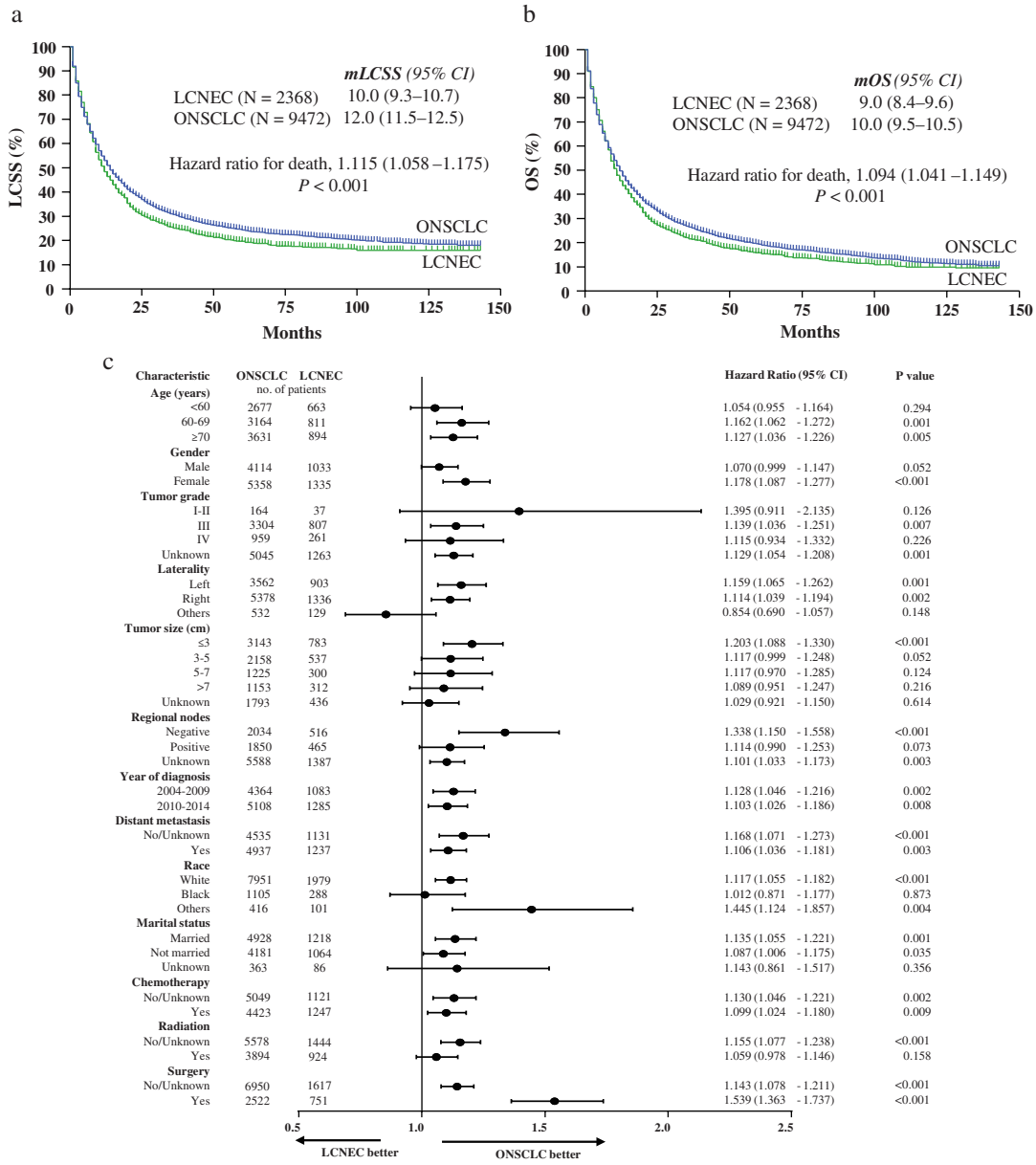

Figure 3 Kaplan–Meier curves for matched groups' survival outcomes and forest plot of hazard ratios (HRs) for lung cancer-specific survival (LCSS). Survival curves of (**a**) LCSS and (**b**) overall survival (OS) between matched groups. (**c**) Forest plot of HRs for large cell neuroendocrine carcinoma (LCNEC) versus matched other non-small cell lung cancer (ONSCLC) in subgroup analysis. The circle and line segments represent the HRs and 95% confidence intervals (CIs) of each subgroup. HR > 1.000 indicates a higher risk of LCS death in patients with LCNEC.

LCNEC presented a higher proportion of younger patients, with higher tumor grade, regional node infiltration, and distant metastases. On the other hand, previous studies showed significant differences in clinicopathological characteristics between LCNEC and SCLC, SQCC, ADC, and LCC.[3,9]

Dismal survival LCSS and OS outcomes were found in LCNEC compared to ONSCLC. After balancing the clinicopathological characteristics, the LCNEC survival outcomes remained inferior to ONSCLC. By contrast, LCNEC survival was superior to that of SCLC.[3,9] Limited by insufficient follow-up, we did not estimate the long-term survival rate. By reviewing previous studies, we found that the five-year OS and disease-free survival rates of LCNEC varied remarkably in different clinical trials and retrospective studies.[1,14,15] Thus, more studies are warranted to accurately evaluate the long-term survival rate of LCNEC.

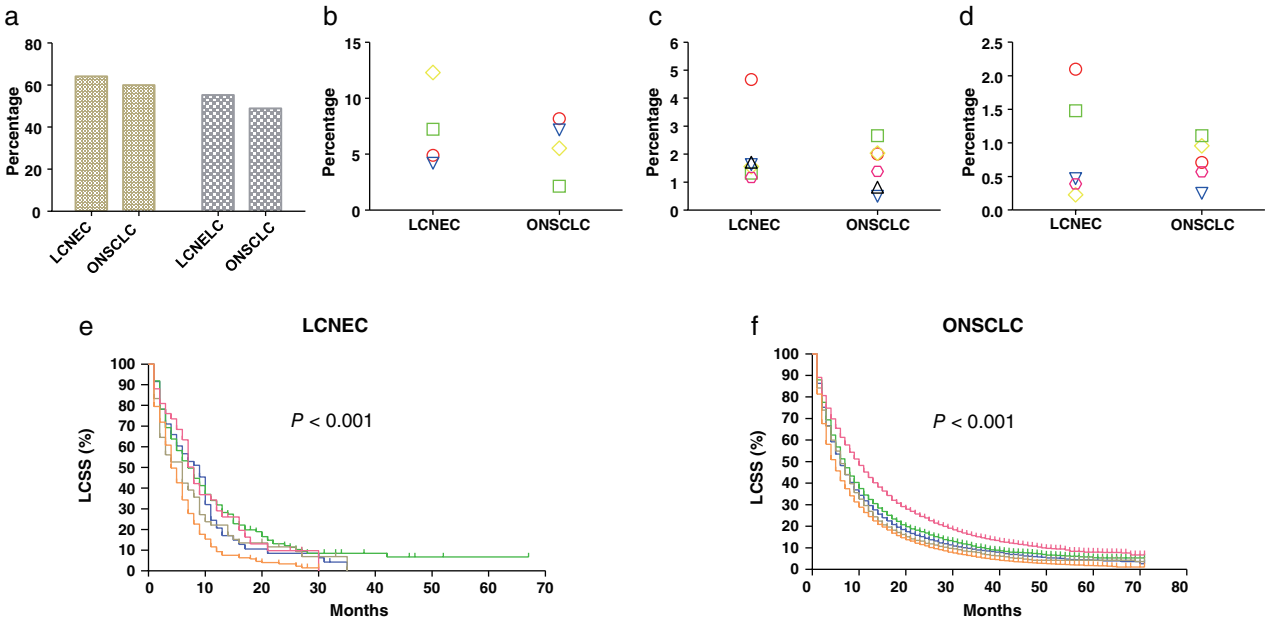

Figure 4 Metastasis distribution and survival analysis for lung cancer-specific survival (LCSS). (**a**) Lymph node and distant metastasis rates. (▨) Lymph node metastasis and (▩) Distant metastasis. (**b**) Isolated-site metastatic rates. (○) Bone, (◇) Brain, (□) Liver, and (▽) Lung. (**c**) Two-site metastatic rates. (○) Bone + Liver, (◇) Bone + Brain, (□) Bone + Lung, (▽) Brain + Liver, (○) Brain + Lung, and (△) Liver + Lung. (**d**) Three and four-site metastatic rates. (○) Bone + Brain + Liver, (◇) Bone + Brain + Lung, (□) Bone + Liver + Lung, (▽) Brain + Liver + Lung, (○) Bone + Brain + Liver + Lung. (**e**) Survival curves for LCSS of large cell neuroendocrine carcinoma (LCNEC). (——) Bone, (——) Brain, (——) Liver, (——) Lung, and (——) MO and (**f**) other non-small cell lung cancer (ONSCLC) with single organ and multiple organ (MO) metastases. (——) Bone, (——) Brain, (——) Liver, (——) Lung, and (——) MO.

Table 3 Hazard ratios of different metastatic patterns

Characteristic	HR (95% CI)	*P*
Distant metastasis	1.179 (1.091–1.275)	< 0.001
Isolated bone	1.013 (0.777–1.321)	0.922
Isolated brain	1.034 (0.873–1.224)	0.700
Isolated liver	1.325 (1.068–1.644)	0.011
Isolated lung	1.474 (1.103–1.970)	0.009
Two-site	1.250 (1.062–1.473)	0.007
Three and four-site	1.223 (0.943–1.585)	0.128
LN metastasis	1.241 (1.151–1.338)	< 0.001
N1	1.350 (1.093–1.666)	0.005
N2	1.211 (1.095–1.339)	< 0.001
N3	1.306 (1.125–1.517)	< 0.001

CI, confidence interval; HR, hazard ratio; LN, lymph node.

The results of multivariate analysis of LCNEC suggested that possible factors contributing to poor survival outcomes were: younger age, male gender, white race, larger tumors, regional node infiltration, distant metastasis, and no/unknown treatment. Surprisingly, tumor grade had no effect on survival outcomes, which may have resulted from the high proportion of cases in unknown tumor grade. In addition, a slightly higher proportion (1.56%) of grade I–II cases might also produce a misleading result because LCNEC was identified as a high-grade NEC of lung cancer.[3] Further matched subgroup analysis indicated that LCNEC was an independent factor predicting poor LCSS in most subgroups. Moreover, we found that the HRs for negative regional nodes, no/unknown distant metastasis, and surgery were higher than their counterparts, suggesting that the survival differences were much more obvious between matched groups in early-stage than in advanced-stage patients.

Because LCNEC is rare, available data are insufficient to perform a research study or formulate a standard treatment plan. Based on previous studies, primary surgery remains the best treatment option for operable patients (tumor node metastasis stages I and II).[1] However, a study showed that stage I patients who underwent surgery alone had a very low five-year OS rate at approximately 29.5%, suggesting that surgery alone is not sufficient and adjuvant therapy is important for early-stage LCNEC.[16] In adjuvant and palliative settings, NSCLC platinum-based chemotherapy and an SCLC regimen including etoposide are generally recommended.[17–20] For advanced LCNEC, SCLC-like chemotherapy appears to be the best treatment option, with a good response rate but poor OS (8–16 months in different case series).[1] Prophylactic cranial irradiation (PCI) might be an effective treatment to improve LCNEC survival, as the brain was the most common metastatic site of LCNEC in our study. A previous retrospective study

demonstrated that PCI improved survival outcomes in stage III and IV patients, showing a trend of improvement of progression-free survival (20.5 vs. 6.4 months; $P = 0.09$) and OS (33.4 vs. 8.6 months; $P = 0.05$).[21] Likewise, PCI could significantly improve the prognosis of limited and extensive stage SCLC.[22] In contrast, previous studies showed that PCI did not effectively improve NSCLC survival.[23,24] Some studies have reported the use of targeted therapies in LCNEC. A prospective phase II study demonstrated that the combination of everolimus with carboplatin and paclitaxel could yield improved clinical benefit.[25] Immunotherapy has provided promise for the treatment of lung cancer,[26,27] but the role of immunotherapy for the treatment of LCNEC remains unknown. A retrospective study showed that 17 out of 76 LCNEC patients expressed positive tumor PD-L1,[28] therefore LCNEC patients might benefit from immunotherapy, especially anti-PD-1/PD-L1 therapy, which deserves further exploration.

Several studies have focused on the different metastatic patterns of LCNEC and their prognostic value. A paper using data based on the Netherlands Cancer Registry reported a high rate of liver metastasis (47%) in LCNEC, followed by metastasis to the bone (32%), brain (23%), and lung (14%).[9] In this study, we identified a higher overall metastasis rate in LCNEC than in ONSCLC. The most common isolated metastasis sites were the brain, bone, and liver for LCNEC, ONSCLC, and SCLC, respectively,[29] while the least common sites were the lung, liver, and lung, respectively. By parallel comparison, a higher proportion of isolated brain metastasis was found in LCNEC than in ONSCLC, consistent with previous findings.[16,30] However, isolated brain metastasis was not a risk factor to affecting survival outcome between LCNEC and ONSCLC. Furthermore, we found that LCNEC cases had a markedly higher proportion of isolated liver metastasis than ONSCLC, and a higher proportion of liver metastasis in combination with other organs. In addition, HR for isolated liver metastasis favored ONSCLC. Thus, we speculate that metastasis to the liver alone and in combination with other organs might be the main causes for the poor survival of LCNEC patients.

There are several limitations to the current study. First, some basic clinicopathological characteristics are not included in the SEER dataset, such as smoking status,[6] weight loss, performance score, and driver mutations,[31] which may provide more insight into the biological features of tumors. Second, no details of treatment regimens were presented in the dataset, and the follow-up duration was not sufficient in our study. Finally, sampling bias may exist as a result of random matching using the propensity score method.

In conclusion, this population-based retrospective study reveals that the clinicopathological characteristics and metastatic distribution of LCNEC are significantly different from ONSCLC. Most subgroup factors are adverse factors for LCNEC, and metastasis to the liver alone and in combination with other organs are the leading causes. Based on the differences between LCNEC and ONSCLC and previous reports about the different clinical features between LCNEC and SCLC, we further propose that LCNEC is an aggressive and heterogeneous subtype of pulmonary malignant tumor.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1. Multivariate analysis of the effect of different variables on overall survival of large cell neuroendocrine carcinoma (LCNEC) and other non-small cell lung cancer (ONSCLC). CI, confidence interval; HR, hazard ratio.
Table S2. Clinicopathological characteristics of matched groups. LCNEC, large cell neuroendocrine carcinoma; ONSCLC, other non-small cell lung cancer.

