Original Article

Clinical characteristics and treatments of large cell lung carcinoma: a retrospective study using SEER data

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Background: Large cell lung carcinoma (LCLC) is a rare malignancy with poor outcome, and little is known about its clinical characteristics and treatments.

Methods: The clinical information of LCLC patients was collected from the Surveillance, Epidemiology, and End Results (SEER) database between 2004 and 2015. The Kaplan-Meier method was used to determine the overall survival (OS) and lung cancer-specific survival (LCSS). Univariate and multivariate analyses were further performed to investigate the independent prognostic factors of OS. A final nomogram was built using the Cox proportional hazards model.

Results: In total, 4,099 patients diagnosed with LCLC were included. 70.2% of patients were older than 60, and more male patients were found. Besides, 60.2% of lesions were found in the upper lobe. Moreover, most patients showed poor differentiation and presented with stage III or IV. Multivariate Cox analysis revealed age, gender, marital status, laterality, tumor size, stage, chemotherapy and surgery were independent prognostic factors of LCLC. The prognosis after surgery combined with chemotherapy was better than that after surgery alone (P=0.041, HR =0.875, 95% CI: 0.771–0.993). The nomogram had good discrimination with a concordance index of 0.757.

Conclusions: LCLC is more common in the elderly and males. Most of lesions are located in the upper lobe and are diagnosed at stage III/IV with poor differentiation. Age, gender, marital status, laterality, tumor size, stage, chemotherapy and surgery were associated with OS. Surgery combined with chemotherapy may achieve a better prognosis and the nomogram accurately predicted the 1-, 3-, and 5-year OS.

Keywords: Large cell lung carcinoma (LCLC); Surveillance, Epidemiology, and End Results (SEER); treatment; prognosis

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Introduction

Lung cancer is the most common malignant tumor in the world and has the highest fatality rate (1). It consists of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Histologically, NSCLC can be further classified as adenocarcinoma, squamous cell carcinoma and large cell carcinoma with or without neuroendocrine features. In NSCLC, according to cohort demographics and classification scheme, large cell lung cancer (LCLC) only accounts for 9% of all cases and often has poor differentiation and prognosis (2-5). Based on the WHO lung cancer classification (6), LCLC is defined as an undifferentiated non-small cell

carcinoma, because it lacks the cellular and structural characteristics related to the adenocarcinoma or squamous cell carcinoma. The diagnosis of LCLC mainly depends on post-operative pathological examination rather than biopsy and cytological examination (7). There is evidence showing that LCLC is frequently found in males and smokers and often presents as a large mass with central necrosis (8-10). Furthermore, LCLC is more commonly seen in the elderly (>60), and its clinical symptoms and signs correlate with the location and the extent of invasion.

Due to its low incidence and a lack of relevant clinical data, less is known about its clinical and biological characteristics. In this retrospective study, the clinical information of patients with LCLC registered in the Surveillance, Epidemiology and End Results (SEER) database was extracted and analyzed, aiming to better understand its clinical behaviors and factors affecting the survival of patients.

Methods

Data extraction

The SEER database includes the information on cancer incidence and survival from 18 cancer registries, covering 26% of the population. Data for patients diagnosed with LCLC during 2004–2015 were extracted using the SEER*Stat software version 8.3.5. The study cohort contained patients according to the International Classification of Disease for Oncology, third edition (ICD-O-3) histology code 8012/3 (Large cell carcinoma, NOS), 8013/3 (Large cell neuroendocrine carcinoma), and 8014/3 (Large cell carcinoma with rhabdoid phenotype).Based on the 2004 WHO classification, large cell neuroendocrine carcinoma belongs to the family of large cell carcinoma. Therefore, such patients were also comprised in the cohort. The exclusion criteria were as follows: (I) patients had more than one primary tumors; (II) patients had no data on the survival; (III) the diagnosis was not pathologically confirmed; (IV) patients without clinicopathological information, including age, gender, race, marital status, primary site, laterality, grade, size, AJCC stage, chemotherapy and surgery. The clinical staging was determined according to the eighth TNM edition through the R version 3.4.3 software.

The outcomes included overall survival (OS) and lung cancer-specific survival (LCSS). The analysis cut-off date was 31 December 2015. OS was defined as the time from diagnosis to death from any cause or until the most recent follow-up. And the LCSS was defined as the time from diagnosis to either death caused by disease or last follow-up. In the SEER database, patients who survived for less than 1 month were coded with a survival time of zero. Therefore, a survival of 0.5 months was assigned to these patients following the standard epidemiological convention.

Statistical analysis

Categorical variables were analyzed with the Chi-square test. To adjust for the bias between surgical patients with or without chemotherapy, the propensity-matched (PSM) analysis was adopted. The PSM module was based upon age, gender, race, marital status, primary site, laterality, grade, size, and stage. Cumulative survival curves were determined using the Kaplan-Meier method and compared using the log-rank test. To perform univariate and multivariate analyses, Cox proportional hazards model was employed. Only variables that were significantly associated with the survival in univariate Cox analysis were included in the multivariate Cox analysis. Hazard ratio (HR) and 95% confidence interval (CI) were presented. And the nomogram was delineated based on the results of multivariate Cox analysis by using R version 3.4.3 software. The prediction error was estimated with 1000 bootstrap samples. A value of two-sided $P<0.05$ was considered statistically significant. Statistical analysis was performed with the software R version 3.4.3 and SPSS 25.0 (SPSS, Chicago, IL). GraphPad Prism 5.0 (GraphPad Software, San Diego, CA) was used to delineate the survival curve.

Results

Clinical characteristics

As shown in *Table 1*, a total of 4,008 patients were diagnosed with LCLC between 2004 and 2015, and 70.2% of patients were older than 60 years. Slightly more than half of the patients were male (57.6%). In addition, the majority (53.9%) was married and 58.1% of tumors located in the right lung (41.4% in the left lung). Interestingly, the upper lobe was the most common site of lesions (60.2%), followed by the lower lobe (24.9%). And 97.8% of tumors showed poor differentiation or undifferentiation. Correspondingly, stage III/IV tumors accounted for 57.4%, while 20.1% and 12.5% of tumors were diagnosed at stage I and II,

Table 1 Characteristics of 4,008 patients with LCLC

Characteristics	Number of cases (%)
Total	4,008
Age	
≤60	1,196 (29.8)
>60	2,812 (70.2)
Gender	
Female	1,699 (42.4)
Male	2,309 (57.6)
Race	
White	3,273 (81.7)
Black	538 (13.4)
Other (American Indian/AK Native, Asian/Pacific Islander)	197 (4.9)
Marital Status	
Married	2,161 (53.9)
Single	566 (14.1)
Other (Separated/Divorced/Widowed)	1281 (32)
Primary site	
Main bronchus	159 (4)
Upper lobe, lung	2,411 (60.2)
Middle lobe, lung	188 (4.7)
Lower lobe, lung	998 (24.9)
Overlapping lesion	56 (1.4)
Lung, NOS	196 (4.9)
Laterality	
Left	1,658 (41.4)
Right	2,328 (58.1)
Bilateral	22 (0.5)
Grade	
Well/Moderate	89(2.2)
Poor/Undifferentiated	3,919(97.8)
Tumor size (cm)	
≤3	1,327 (33.1)
3–5	1,174 (29.3)
5–7	718 (17.9)
≥7	789 (19.7)
Stage	
I	807 (20.1)
II	501 (12.5)
III	966 (24.1)
IV	1,734 (43.3)
Chemotherapy	
No/Unknown	2,181 (54.4)
Yes	1,827 (45.6)
Surgery	
No/Unknown	2,364 (59)
Yes	1,644 (41)

respectively. Moreover, the size of most tumors (62.4%) was less than 5 cm.

Treatments

Table 2 shows the relevant treatments of LCLC. Only 26.1% of patients received surgery alone, while 15.0% of cases accepted surgery combined with chemotherapy. There were meaningful differences in the age, marital status, tumor size and stage between surgical patients with or without chemotherapy ($P<0.05$ for all). Neither distribution of gender, race, primary site, laterality nor grade differed significantly between objects who selected surgery or surgery plus chemotherapy. Furthermore, the results of the correlational analysis presented that with the improvement of size and stage, patients were more inclined to choose comprehensive treatment.

Survival

The median OS and LCSS were 35 months (95% CI: 30.61–39.40) and 55 months (95% CI: 43.29–66.71), respectively. *Figure 1* show the OS and LCSS curves. Meanwhile, the overall 1-, 3- and 5-year survival rates were 45.6%, 24.8%, and 19.0%. Correspondingly, the 1-, 3-, and 5-year of LCSS were 49.1%, 28.8% and 24.1%, respectively. In addition, the median survival time was 34 months (range: 28.59–39.41 months) in patients

Table 2 Surgically treated patients with or without chemotherapy

Characteristics	Chemotherapy		P value
	No/unknown (n=1,045)	Yes (n=599)	
Age			<0.01
≤60	250 (23.9)	279 (46.6)	
>60	795 (76.1)	320 (53.4)	
Gender			0.744
Female	478 (45.7)	269 (44.9)	
Male	567 (54.3)	330 (55.1)	
Race			0.474
White	886 (84.8)	506 (84.5)	
Black	101 (9.7)	66 (11)	
Other (American Indian/AK Native, Asian/Pacific Islander)	58 (5.6)	27 (4.5)	
Marital status			0.014
Married	582 (55.7)	372 (62.1)	
Single	124 (11.9)	73 (12.2)	
Other (separated/divorced/widowed)	339 (32.4)	154 (25.7)	
Primary site			0.348
Main bronchus	9 (0.9)	5 (0.8)	
Upper lobe, lung	667 (63.8)	400 (66.8)	
Middle lobe, lung	56 (5.4)	21 (3.5)	
Lower lobe, lung	281 (26.9)	150 (25)	
Overlapping lesion	15 (1.4)	14 (2.3)	
Lung, NOS	17 (1.6)	9 (1.5)	
Laterality			0.835
Left	462 (44.2)	268 (44.7)	
Right	583 (55.8)	331 (55.3)	
Bilateral	0	0	
Grade			0.442
Well + moderate	37 (3.5)	17 (2.8)	
Poor + undifferentiated	1,008 (96.5)	582 (97.2)	
Tumor size (cm)			<0.01
≤3	573 (54.8)	201 (33.6)	
3–5	282 (27)	216 (36.1)	
5–7	112 (10.7)	95 (15.9)	
≥7	78 (7.5)	87 (14.5)	
Stage			<0.01
I	594 (56.8)	110 (18.4)	
II	211 (20.2)	184 (30.7)	
III	153 (14.6)	225 (37.6)	
IV	87 (8.3)	80 (13.4)	

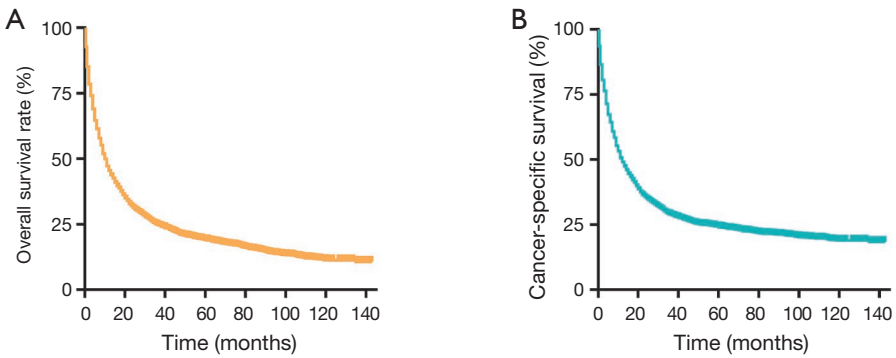

Figure 1 Kaplan Meier curve of (A) overall survival and (B) cancer-specific survival.

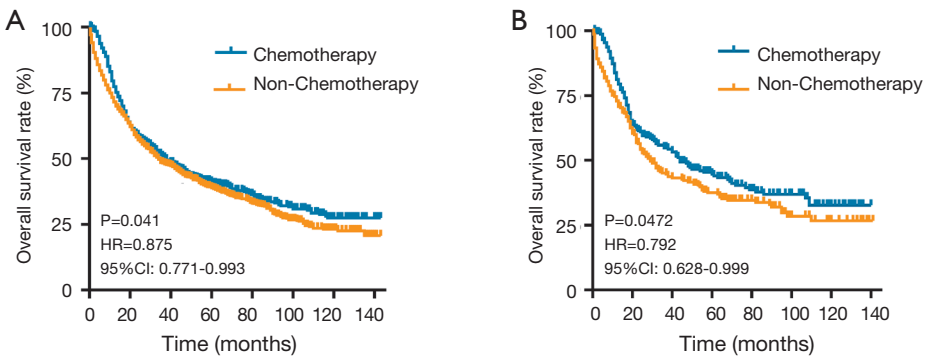

Figure 2 Kaplan-Meier curve of overall survival in surgically treated patients with/without chemotherapy before (A) and after (B) propensity score matching.

undergoing surgery alone and 38 months (range: 31.04–44.99 months) in those receiving surgery plus chemotherapy (*Figure 2A*). Moreover, in patients with surgery alone and those with surgery combined with chemotherapy, the 1-year survival rate was 71.7% and 77.5%; the 3-year survival rate was 48.3 and 50.7%; and the 5-year survival rate was 38.8% and 41.0%, separately. As shown in *Figure 2B*, the OS in patients receiving surgery with chemotherapy was better than in patients undergoing surgery alone (P=0.041, HR =0.875, 95% CI: 0.771–0.993).

Furthermore, the PSM analysis was done in surgical patients with or without chemotherapy based on the age, gender, race, marital status, primary site, laterality, grade, tumor size, and stage. In the analysis, 244 patients received chemotherapy and 244 subjects had no chemotherapy (1:1). There were no significant differences in the clinical characteristics between them (*Table S1*). OS curves and Log-rank analysis indicated that patients receiving chemotherapy enhanced the survival (P=0.047, HR=0.7924, 95% CI: 0.628–0.999).

Variables potentially influencing OS were further investigated using the univariate Cox proportional hazards analysis. *Table 3* displays the potential factors (P<0.01) associated with the prognosis except for the race (P=0.18). Further multivariate Cox analysis was performed to identify the independent prognostic elements. Results showed age (P<0.01), gender (P=0.01), marital status (P=0.004), laterality (P=0.015), tumor size (P<0.01), stage (P<0.01), chemotherapy (P<0.01) and surgery (P<0.01) were able to predict the survival of LCLC patients. The pathological grade correlated with the stage, thus it could exclude. Moreover, a nomogram (*Figure 3*) was plotted based on the risk factors identified by the multivariate analysis for predicting 1-, 3-, and 5-year OS. And according to the internal bootstrap resampling validation, the calibration plot (*Figure 4*) was illustrated. The C-index for prediction

Table 3 Univariate and multivariate Cox proportional hazard analyses of clinical characteristics for overall survival rate of LCLC patients

Independent variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age		<0.01		<0.01
≤60	1.00 (reference)		1.00 (reference)	
>60	1.252 (1.159–1.353)		1.264 (1.166–1.371)	
Gender		<0.01		0.01
Female	1.00 (reference)		1.00 (reference)	
Male	1.184 (1.103–1.270)		1.101 (1.023–1.186)	
Race		0.18		
White	1.00 (reference)			
Black	1.04 (0.939–1.152)	0.446		
Other (American Indian/AK Native, Asian/Pacific Islander)	0.875 (0.744–1.029)	0.106		
Marital Status		<0.01		0.004
Married	1.00 (reference)		1.00 (reference)	
Single	1.192 (1.074–1.322)	0.001	1.136 (1.021–1.264)	0.019
Other (separated/divorced/widowed)	1.126 (1.043–1.216)	0.002	1.125 (1.038–1.219)	0.004
Primary site		<0.01		
Main bronchus	1.00 (reference)			
Upper lobe, lung	0.588 (0.497–0.695)	<0.01		
Middle lobe, lung	0.613 (0.490–0.769)	<0.01		
Lower lobe, lung	0.631 (0.529–0.752)	<0.01		
Overlapping lesion	0.504 (0.354–0.718)	<0.01		
Lung, NOS	1.147 (0.923–1.426)	1.147		
Laterality		0.004		0.015
Left	1.00 (reference)		1.00 (reference)	
Right	0.974 (0.908–1.045)	0.463	0.903 (0.841–0.969)	0.005
Bilateral	2.037 (1.310–3.169)	0.002	0.822 (0.527–1.283)	0.388
Grade		0.012		
Well + moderate	1.00 (reference)			
Poor + undifferentiated	1.37 (1.072–1.752)			
Tumor size (cm)		<0.01		<0.01
≤3	1.00 (reference)		1.00 (reference)	
3–5	1.332 (1.218–1.457)	<0.01	1.081 (0.983–1.188)	0.107
5–7	1.62 (1.463–1.794)	<0.01	1.134 (1.015–1.267)	0.026
≥7	2.186 (1.981–2.412)	<0.01	1.346 (1.208–1.500)	<0.01

Table 3 (*continued*)

Table 3 (*continued*)

Independent variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Stage		<0.01		<0.01
I	1.00 (reference)		1.00 (reference)	
II	1.277 (1.110–1.469)	0.001	1.386 (1.192–1.611)	<0.01
III	2.052 (1.829–2.301)	<0.01	1.858 (1.619–2.132)	<0.01
IV	4.831 (4.348–5.367)	<0.01	3.454 (3.018–3.953)	<0.01
Chemotherapy		<0.01		<0.01
No/unknown	1.00 (reference)		1.00 (reference)	
Yes	0.852 (0.794–0.913)		0.504 (0.467–0.543)	
Surgery		<0.01		<0.01
No/unknown	1.00 (reference)		1.00 (reference)	
Yes	0.282 (0.261–0.305)		0.411 (0.373–0.453)	

of OS was 0.757 (95% CI: 0.749–0.765), which indicated a sufficient level of discrimination.

Discussion

According to the 2004 lung cancer classification (11), LCLC is a poorly differentiated tumor and accounts for about 10% of NSCLC. However, with the emergence of 2015 lung cancer classification (6), basaloid carcinoma is classified as squamous cell carcinoma, the large cell neuroendocrine carcinoma and compound large cell neuroendocrine carcinoma are classified as neuroendocrine tumors, the lymphoepithelioma-like carcinoma is categorized as other or unclassified cancer, finally, the clear cell carcinoma and LCLC with rhabdoid phenotype are not comprised. Thus, the incidence of LCLC is likely to be lower than 10%, based on the new classification (9).

In our series, LCLC was more common in males and ~~in~~ the elderly at the time of diagnosis. In addition, lesions predominated on upper lobe, which was consistent with previous findings (12-14). Cao *et al.* also reported that large cell neuroendocrine carcinoma frequently observed in men and old people (15). Cao *et al.* (15) and Oshiro *et al.* (16) held that most of large cell neuroendocrine carcinoma was pathologically high-grade. In our study, 97.8% of patients showed poor differentiation at the time of diagnosis. Previous researches appeared that LCLC formed a large mass (13,17). During our research, nearly half of the neoplasms was smaller than 5 cm in diameter.

Early diagnosis and early treatment are crucial for the survival of LCLC patients because of the poor prognosis. A prospective study on large cell neuroendocrine carcinoma showed that postoperative chemotherapy could achieve a better prognosis as compared to surgery alone (18). In addition, Kujtan *et al.* found that the survival time of patients with stage IA large cell neuroendocrine carcinoma who received surgery combined with chemotherapy was significantly longer than in those receiving surgery alone (19). Hanagiri *et al.* presented that the 5-year survival rate in patients receiving surgery for large cell carcinoma was 61.5% (13). However, the 5-year survival rate was only 38.8% in our study. This might be ascribed to the small sample size (57 patients). Moreover, our results showed the 5-year survival rate of patients receiving surgery combined with chemotherapy was 41%, which was better than that of patients receiving surgery alone. Some studies had also recommended a combination of surgery and chemotherapy for the treatment of LCLC, and post-operative cisplatin/pemetrexed may achieve a better prognosis than post-operative cisplatin/gemcitabine (10.4 *vs.* 6.7 months, respectively) (20).

There were also several limitations in our study. First, we carried out the research according to the 2004 lung cancer classification, which is different from the 2015 lung

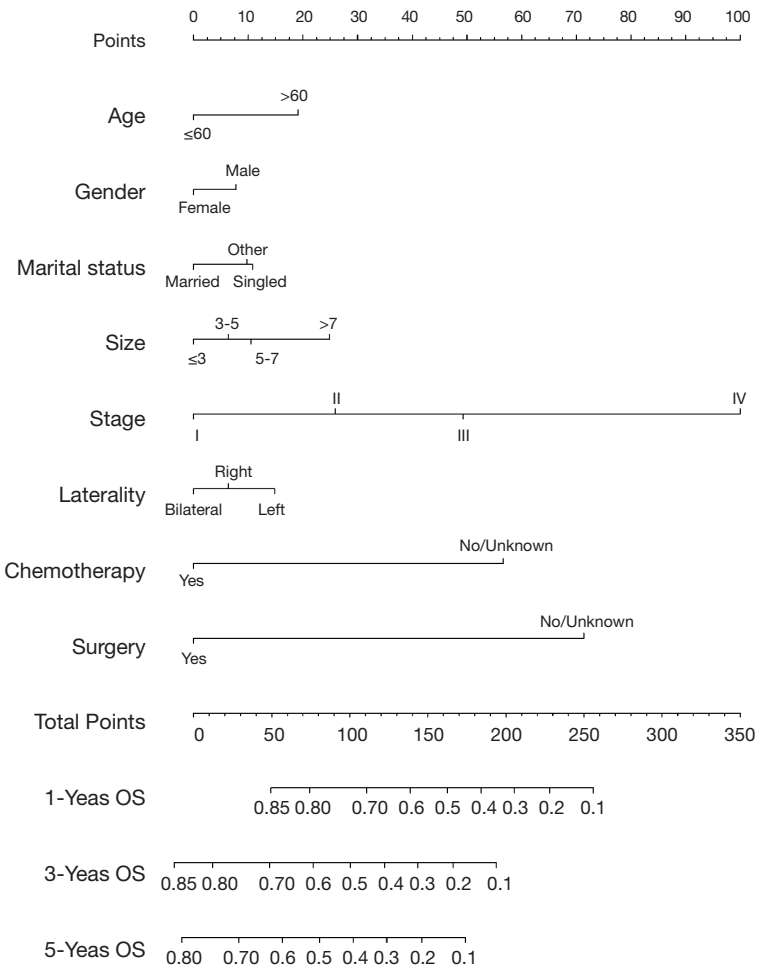

Figure 3 Nomogram to predict 1-, 3-, 5-year overall survival of patients with large cell lung cancer.

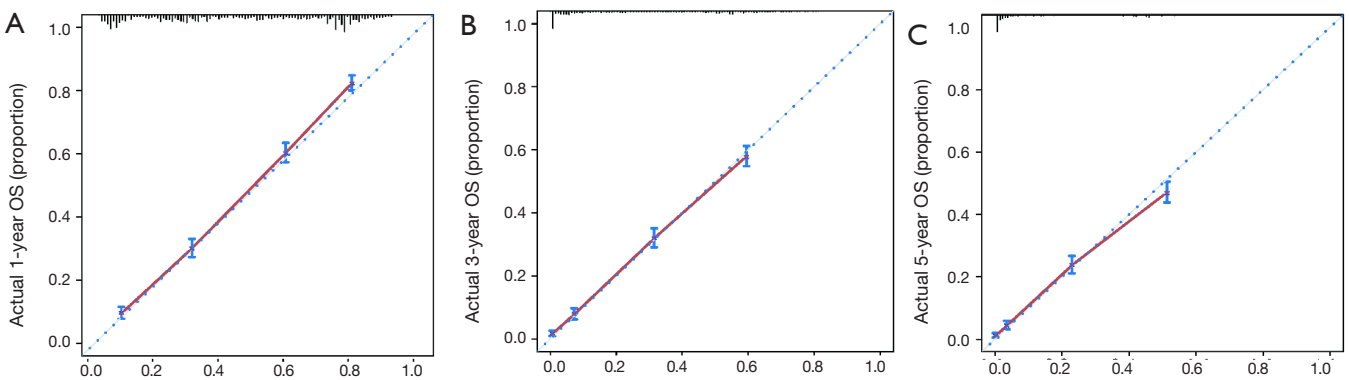

Figure 4 Calibration plots of the nomogram prediction of (A) 1-, (B) 3-, (C) 5-year overall survival of large cell lung cancer patients.

cancer classification. Second, patients were divided into two groups according to whether they received chemotherapy or not, but the specific regimens for chemotherapy were unknown. At last, for patients diagnosed with LCLC, more prospective clinical studies are needed to elucidate the prognostic factors and further investigate the efficacy of available treatments.

In conclusion, LCLC is more common in the elderly (>60 years) and mainly located in the upper lobe. The majority of tumors are diagnosed at stage III/IV. Surgery combined with chemotherapy is beneficial for the prognosis of LCLC patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.40). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

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Supplementary

Table S1 Characteristics of 488 patients after PSM analysis

Characteristics	Non-chemotherapy (n=244)	Chemotherapy (n=244)	P value
Age			1
≤60	69	69	
>60	175	175	
Gender			1
Female	98	98	
Male	146	146	
Race			1
White	228	228	
Black	11	11	
Other (American Indian/AK Native, Asian/Pacific Islander)	5	5	
Marital Status			1
Married	175	175	
Single	14	14	
Other (separated/divorced/widowed)	55	55	
Primary site			1
Main bronchus	0	0	
Upper lobe, lung	174	174	
Middle lobe, lung	9	9	
Lower lobe, lung	59	59	
Overlapping lesion	1	1	
Lung, NOS	1	1	
Laterality			1
Left	112	112	
Right	132	132	
Bilateral	0	0	
Grade			1
Well + moderate	0	0	
Poor + undifferentiated	244	244	
Tumor size (cm)			1
≤3	83	83	
3–5	96	96	
5–7	37	37	
≥7	28	28	
Stage			1
I	80	80	
II	95	95	
III	55	55	
IV	14	14	