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Surgical resection of small cell lung carcinoma: prognostic factors and the tumor microenvironment

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Abstract

Background—Surgery in small cell lung cancer (SCLC) is limited to very early stages, but several reports suggest a potential broader role. Little is known of the influence of microenvironment on the biology of SCLC.

Methods—We assessed the clinical prognostic factors in a large series of resected SCLC patients. The prognostic value of Programmed cell Death Ligand-1 (PD-L1) expression in tumor cells and tumor infiltrating lymphocytes (TILs), and the percentage of CD3, CD20, CD45 and CD68 positive cells, were also investigated.

Results—205 SCLC cases were resected between 2005 and 2015 and the median follow-up was 29 months (range: 2-135 months). Median survival of all patients was 69 months, and 5-year survival rates were 63.8%, 65.5%, 34.9%, and 0% for pathological stages I, II, III, and IV, respectively. By multivariate analysis complete resection, cigarette index (CI), lymph node metastatic rate (LNR), percentage of CD3 positive cells and PD-L1 expression in tumor cells and TILs were independent prognostic factors. High PD-L1 expression was present in 3.2% and 33.5% of all tumor samples in tumor cells and TILs, respectively. High PD-L1 expression in tumor cells or TILs correlated with shorter survival, whereas high expression of CD3, CD20 and CD45 correlated with better survival.

Conclusions—Resected stage II SCLC patients have similar survival as stage I, suggesting that surgery could be extended to patients with hilar lymph node involvement. Survival was better in tumors with a higher percentage of T cells and B cells, whereas PD-L1 expression in tumor cells and TILs correlated with worse survival, which suggests a potential role of immunotherapy in resected SCLC.

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Keywords

small cell lung cancer; prognosis; surgery; ratio of metastatic lymph nodes; PD-L1

Introduction

Lung cancer is the leading cause of cancer death in the world. In 2015, 733,300 cases were newly diagnosed with lung cancer in China and 610,200 died[1]. Small cell lung cancer (SCLC) accounts for 15-20% of all lung cancer cases[2], is associated with smoking, and its incidence has been steadily decreasing in Europe and North America as a result of smoking control. However, its incidence has not decreased in China, where tobacco control has not been implemented to the same extent. Compared to NSCLC, SCLC is characterized by a shorter tumor doubling time, and higher rates of early distant metastases. Although chemotherapy combined with radiotherapy can improve survival in patients with limited disease, and potentially cure 20-25% of patients, local recurrence rate is still as high as 28%~47%. Despite its exquisite chemosensitivity, drug resistance invariably occurs, and long-term survival is less than 10%[2]. SCLC is clinically staged into limited disease and extensive disease, according to the Veterans Administration Lung Cancer Study Group (VALCSG) staging system revised by the International Association for Study of Lung Cancer (IASLC) in 1989. In 2009, IASLC enacted the 7th edition of UICC TNM Classification for Lung Cancer, and recommended using the TNM classification for SCLC staging. Chemotherapy combined with radiotherapy is the standard therapeutic approach for patients with limited disease stage SCLC (Stage I-III). A limited role for surgery has been recognized. The National Comprehensive Cancer Network guidelines and the latest American College of Chest Physicians guidelines limit the use of surgery to treat Stage I (T1-2N0M0)[3],[4] however, in the European Society for Medical Oncology guidelines, surgery is considered for both stage I and II (T1-2N0-1M0)[5]. Large retrospective population-based databases suggest a broader role of surgery and in selected cases it might actually be preferred to chemo-radiation[6, 7].

Besides stage, ratio of metastatic lymph nodes (LNR), and examined lymph nodes (ELN) have been shown to be independent prognostic factors in resected non-small cell lung cancer (NSCLC)[8], but no data are available in resected SCLC.

Immune escape mechanisms are important in tumor development and progression. Upregulation of Programmed Death Ligand −1 (PD-L1) on tumor cells and down regulation of the immune check-point Programmed Death 1 (PD-1) on the membrane of T cells, are crucial mechanisms by which tumors evade the immune system. Immune-checkpoints have recently been successfully targeted with antibodies, with activity demonstrated in a large number of tumors. PD-L1 expression is upregulated in many tumor types and expression of PD-L1 on tumor cells but also on TILs has been shown to be predictive of outcome in several studies[9–11].

In NSCLC patients, meta-analyses showed that PD-L1 expression in tumors is associated with poor differentiation and shorter overall survival[12]. Expression of PD-L1 on tumor cells

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has been shown to be a predictor of response to anti-PD-1 and anti-PD-L1 antibodies[9]. Limited and conflicting data have been reported in SCLC[7].

We conducted a retrospective analysis of a large series of resected SCLC treated at a single institution in China, and explored the PD-L1 expression in tumor cells and TILs, as well as other immune markers.

Materials and Methods

A total of 205 SCLC patients were surgically resected at the Tianjin Medical University Cancer Institute and Hospital, in Tianjin China, from January 2005 to January 2015.

Patients with a histologic diagnosis of SCLC confirmed by microscopic examination, and International Classification of Diseases for Oncology, Third Edition (ICD-0-3) codes 8041 to 8045 were included in this analysis. Each case was restaged in accordance with the 7th edition of UICC TNM Classification for Lung Cancer. Staging procedures before surgery consisted of chest CT-scan and brain CT scan and upper abdomen ultrasound. More recently PET-CT scan and brain MRI were introduced.

Two patients who died within 30 days from operation and patients with other active malignancies were excluded from this analysis. Updated survival was obtained by direct visits and/or by telephone.

We defined incomplete resections as (1) non-R0 resection (with positive bronchial resection margins either microscopically or macroscopically, R1/2 resection); (2) no lymph node dissection; (3) extranodal soft tissue invasion, and (4) involvement of blood vessels, nerves, or vital organs[13].

The examined lymph node number (ELN) was the total number of dissected lymph nodes, and lymph node ratio (LNR) was the number of lymph nodes with metastasis divided by the total number of dissected lymph nodes.

Immunohistochemistry

After independent review of all pathological slides and assessment of FFPE blocks quality, 155 cases were adequate. The remaining 50 cases could not be used for the construction of a tumor tissue microarray (TMA) or whole slide section: 35 because of poorly preserved blocks, and 15 because of insufficient or highly necrotic tumor tissue. There were no significant differences between the clinical characteristics of the whole series (205 cases) and the series in which immunohistochemistry was feasible (155 cases) (Table S1). The survival analyses were based on the 205 cases database, unless immunohistochemistry results were considered (155 cases).

A TMA was constructed using the TMA Master (3DHISTECH, Budapest, Hungary) according to the manufacturer’s protocol and cores of each sample were in triplicate and 2 mm in diameter. Blocks were sectioned at a thickness of 4 pm. In 40 cases whole slides were also used. Briefly, sections were incubated in xylene, followed by ethanol, and then washed with distilled water. For antigen retrieval, sections were boiled in 10 mM sodium citrate

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buffer for 10 min at 121 °C. After rinsing with distilled water, sections were incubated in 3% peroxidase and washed with distilled water and then with buffer. For staining, sections were incubated with the primary antibody overnight. For antigen visualization, a peroxidase-labeled secondary antibody (EnVision/HRP system, Dako, Carpinteria, CA) was applied. Subsequently, the sections were rinsed in the buffer provided in the kit and immersed in 3,3'-diaminobenzidine (DAB) stain. All primary antibodies were Ready to Use (Pre-Diluted) antibodies from Dako, including PD-L1 (clone 22C3, Pharm Dx FDA Approved), CD3 (Polyclonal), CD45 (Leukocyte Common Antigen-LCA, Clone 2B11+PD7/26), CD20 (Clone L26) and CD68 (Clone KP1).

Two independent pathologists (BK and JC) reviewed the stained slides in a blinded fashion. The percentages of tumor cells or TILs with positive staining to PD-L1 (from 0 to 100%) were used to calculate mean PD-L1 expression scores. We selected two different cutoff values for PD-L1 staining in tumor cells: 1% (⩾ 1 % vs <1%) and 50% (⩾50% vs <50%). For PD-L1 expression in TILs, we selected the optimal value as the cutoff value using ROC curve. For all other staining results of continuous variables we selected the median value as the cutoff value. Kaplan-Meier method was used to build survival curves and the log-rank test was used to compare survival curves. The overall survival (OS) was defined as the time between the operation and the date of death or the latest follow up. The 1, 3, 5-year overall survival rates were calculated from the survivorship.

Statistical considerations

Statistically significant factors identified by univariate analysis were selected for the COX proportional hazard model for multivariate analysis. Pearson's correlation analysis was performed on all statistically significant factors selected by univariate analysis, and the factors with a correlation coefficient larger than 0.7 were considered as highly correlated with each other, and would be adjusted to avoid multi-colinearity by using least absolute shrinkage and selection operator (LASSO), p values <0.05 were considered statistically significant. SPSS19.0 was used for statistical analysis of the data.

Results

A total of 205 surgery cases were analyzed. See Table 1 for patient characteristics. Most patients had a lobectomy and a radical dissection. Lymph node dissection was not performed in 10.2% of the patients, including 9 stage IV patients. A median of 19 lymph nodes were dissected per patient. Among them an average number of 2.4 were metastatic (by H&E stain). The median metastasis rate (number of lymph nodes involved in cases with positive lymph nodes divided by total number of resected lymph nodes) was 21.4%. In total, 1498 lymph node stations were dissected (7 per patient on average), including 698 stations from N1 regions among which 84 were metastatic, 1498 stations from N2 regions among which 108 were metastatic.

Neoadjuvant and adjuvant chemotherapy was a platinum-based doublet in 97.1% of patients (cisplatin-etoposide in 78.6%). Adjuvant chemotherapy was given in 68.3% of patients and postoperative chest radiotherapy was with doses between 50Gy/25f and 60Gy/30f. Eighteen patients (8.8%), received prophylactic cranial irradiation (PCI), mostly as 30Gy/10f (61.1%).

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Ten cases of combined small cell carcinoma are reported in detail elsewhere[14].

In total, 68.2% of the patients received adjuvant chemotherapy, 67.1% (51/76) and 73.9% (34/46) of patients in stage I and stage II respectively. There was a borderline survival influence of chemotherapy for all resected SCLC patients (p=0.04). But there was no significant difference in OS for stage I (median OS for patients who did and did not receive chemo were 108 months and NR, p=0.237) and stage II (median OS for patients did and did not receive chemo were 120 months and 61 months respectively, p=0.346). For all p-stage, there was no difference between patients who did and did not receive adjuvant radiotherapy (p=0.945). For p-stage I, the median OS for patients who received or did not receive radiotherapy were NR and 108 months, respectively (p=0.506); for p-stage II, the median OS were 69 months and 120 months, respectively (p=0.467). There was no survival difference in stage FII patients who did/did not receive radiotherapy.

PD-L1 and other markers in tumor cells and TILs

The mean PD-L1 expression in tumor cells and TIFs was 3.0% and 3.3%, respectively. Only 5 cases (3.2%) showed PD-L1 positive tumor cells when 50% was used as the cutoff value, whereas 20 cases (12.9%) were positive with a PD-L1 expression cut-off value of 1%. There was no difference in the rate of PD-L1 expression positivity in the different pathological stages (p=0.628). Positive PD-L1 expression in TIFs was observed in 52 cases (33.5%). PD-L1 expression in tumor cells was highly correlated with PD-L1 expression in TIFs (Pearson test r=0.564, p<0.001) (Figure S1A).

The mean expression of CD3, CD20, CD45 and CD68 positive cells in whole slides or cores were 10.3%, 5.8%, 16.2% and 5.6%, respectively. Most cases showed a diffuse staining for CD3 positive cells, whereas CD20 positive cells appeared mainly as clusters of cells in between tumor cells (Figure S2). The expression of CD3, CD20, and CD45 positive cells were significantly correlated with each other (p<0.001). Compared with PD-L1 expression in tumor cells, PD-L1 expression in TILs had a stronger positive correlation with the expression of CD3, CD20 and CD45 (p<0.001) (Table 2). CD3 and CD45 expression had a weak negative correlation with the maximum tumor diameter (Spearman test rho=−0.234, p=0.003; rho=−0.200, p=0.014, respectively), and CD3 has also a weak negative correlation with pathological stage (Spearman test rho=−0.202, p=0.016)(Figure S1B–D).

Survival

The median follow-up time was 29 months (range: 2-135 months). Median OS of all 205 patients was 69 months, and 1, 3 and 5 years survival rates were 84.8%, 60.0% and 51.1%, respectively, OS was significantly different between stage I and III and between stage II and III (median 108, 88, and 40 months respectively, p<0.05), whereas there was no significant difference between stage I and II. Stage I and II combined had a median survival of 88 months (95%CI 62.9-113.1)(Figure 1A–B).

Younger age (<60 years old), cigarette index (CI) less than 400, ELN greater than 19, LNR less than 21.4%, lobectomy, R0 and complete resection, postoperative chemotherapy, and pathological stage I and II had a significantly longer overall survival than their respective counterparts, by univariate analysis (Table S2; Figure 2). Furthermore, higher PD-L1

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expression in tumor cells, using both 1% and 50% cutoff values, and higher PD-L1 expression in TILs (≥8%) correlated with poorer OS. Median OS of cases with high PD-L1 expression in tumor cells (using 50% as cutoff value) was much shorter than that of cases with lower expression (12 months, 95%CI, 7.7-16.3 vs 57 months, 95%CI, 36.3-77.7; p=0.007). High PD-L1 expression in TILs was also associated with shorter survival (median OS 26 months 95%CI, 20.1-31.9 vs 69 months, 95%CI, 34.2-103.8; p=0.011). On the other hand, high expression of CD3, CD20 and CD45 was associated with longer OS (Table S3; Figure 3). CD68 positivity and tumor biomarker levels, including neuron-specific enolase (NSE), carcinoembryonic antigen (CEA) and fragments of cytokeratin-19 (Cyfra21-1) did not have prognostic value.

Using COX proportional hazards model, PD-L1 expression in tumor cells and TILs, LNR, complete resection, CI and CD3 percentage were independent prognostic factors for OS (Table 3). Among all significant variables selected by univariate analysis, pathological stage was significantly correlated with LNR and N stage (Pearson's test r=0.806, p<0.001) (Table 2). Because of high co-linearity between pathological stage, N status and LNR, pathological stage did not play a role in the Cox proportional hazards model. Since pathological stage is one of the most important independent prognostic factors in SCLC[15], we kept it in the Cox hazard model with LASSO-COX statistic method. After this procedure, besides pathological stage, age, complete resection and cigarette index were independent factors for overall survival (Table S4; Figure S3).

Discussion

Surgery has been banned in the vast majority of patients with SCLC based on dacades old randomized studies [16, 17]. In recent years, retrospective analyses of large population databases have provided evidence for a potentially more important role of surgery in SCLC. The five-year survival for approximately 2500 resected SCLC patients was 51%, 25%, and 18% for clinical stages I, II, and IIIA, respectively, in the National Cancer Data Base (NCDB)[6]. Using an earlier NCDB cohort from 1992 to 2002, Gaspar et al[7] demonstrated a similar benefit for surgery combined with nonsurgical treatment, compared with chemoradiation therapy alone in stage I and II patients. The improved survival of potentially resectable SCLC patients treated with surgery and chemotherapy appears similar to that of NSCLC patients[18]. The 5-year survival rates were 34.6-50.3% in patients undergoing lobectomy, compared to 9.9-14.9% in patients receiving non-surgical therapy in the National Cancer Registry, the Surveillance, Epidemiology and End-Results (SEER) database[19, 20].

Our results are similar or better, with 5-year survival rates of 63.8%, 65.5% and 34.9% for pathological stage I, II and III, respectively, and suggest that surgery may also have potential benefit for stage II and some stage IIIA SCLC patients. In our study there was a relatively large number of stage III patients, which can be explained by the absence of mediastinoscopy and FDG-PET use in the preoperative staging until 2010. Since 2010, patients with clinical stage IIIA2 or stage IIIA3 by mediastinoscopy were excluded from surgery.

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Compared with several large retrospective analyses based on SEER or NCDB databases, our series had more favorable overall survival results. Other series of resected stage IIB SCLC patients who underent surgery displayed 40% 5-yrs survival rate and 34-39 months median survival[21]. A number of small institutional studies have also demonstrated 5-year OS rates of 19% to 43% for stage III patients undergoing surgery as a component of multimodality therapy for SCLC[22–24]. A report from Mayo Clinic demonstrated a 71% 3-year survival for Stage III SCLC patients who underwent surgery[25]. Better OS data for stage III SCLC surgery patients was observed in Japanese studies[21], suggesting a potential positive influence of Asian race on outcome.

Surgery is to be part of a combined modality approach, since surgery alone has inferior results[26,27]. In our study patients who underwent surgery followed by adjuvant chemotherapy had a significantly longer survival time than those who did not receive adjuvant chemotherapy (median 84 months vs 31 months, p=0.043; five-year survival rates 51.2% vs 43.8%, respectively).

The type of pulmonary resection is also an important prognostic factor[19] and in our study the median OS for patients who received a lobectomy was 84 months, compared to 69 and 21 months, respectively for pneumonectomy or wedge resection (p<0.001).

The influence of the N status on prognosis is well recognized. In our study the median OS for patients with N stage N0, N1, and N2 was 120, 28 and 40 months, with five-year survival rates of 69.4%, 40.6% and 35.7%, respectively (p<0.001). This compares favorably with the results of the SEER database[20].

PD-1, a member of the CD28 superfamily, is an important immunosuppressive molecule, mainly expressed in activated T cells and B cells and is a surface receptor of activated T cells. PD-L1, one of 2 ligands of PD-1, is present on the surface of various antigen presenting cells, stromal cells, and tumor cells. Activation of the PD-1 signaling pathway inhibits the T cell function, therefore inactivating the immune response. In some SCLC cell lines both PD-1 and PD-L1 molecules are co-expressed[28].

Although there is plenty of literature on PD-L1 expression in NSCLC and other tumor types, data in SCLC are conflicting, with PD-L1 expression ranging from 0% to 78%[29–32]. This discrepancy can be due to a number of reasons, including the way that scores were calculated and use of different cutoff values [33]. In our study we used 1% and 50% as cutoff values, which have been commonly used in NSCLC. Unlike NSCLC where PD-L1 positivity has been reported in 36%−56% of cases (using 5% as the cutoff value)[34, 35], our results show much lower (12.9%) percentages in SCLC.

Miao et al.[31] and Chang et al.[30] reported PD-L1 positivity in 51.8% and 78% of the cases respectively in SCLC, using a scoring system based on intensity of staining and percentage of stained cells. The former study used the SP66 monoclonal antibody against PD-L1 and tumors were positive when over 5% of the tumor cells had PD-L1 expression. The latter study used a less well established rabbit polyclonal antibody that has been, and positive cases had at least 5% of the tumor cells stained with moderate or strong intensity. Two other studies found very low (5.8%)[29] or zero expression[32] in tumor cells. In a recent phase II

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study of pembrolizumab in extensive disease SCLC using the FDA approved 22C3 antibody to select patients who had at least 1% of PD-L1-positive tumor and associated inflammatory cells or stroma [36] only 31.7% of screened cases were positive. A lower degree of positivity for PD-L1 expression in SCLC than in NSCLC has also been noted with the antibody clone 28-8 used in clinical studies of nivolumab, where PD-L1 positivity in at least 1% of tumor cells was 13%−24% and in at least 5% of cells was 3%−6%[37]. The antibody 22C3 that we used is approved by FDA and used to select NSCLC patients for pembrolizumab treatment with cut-off values of 1% and 50%.

PD-L1 expression on tumor cells and TILs has been proposed as predictive biomarker for response to PD-1 and PD-L1 inhibitors in NSCLC. However the use of different antibodies and platforms has made comparisons of studies very challenging. In a study of 98 limited stage SCLC samples the antibodies SP142 and 28-8 gave 14.7-19.4% tumor cell positivity when ≥1% was the cutoff value, and results were similar between the 2 antibodies and in extensive stage cases[38].

In our study, we showed that higher PD-L1 expression either in tumor cells or in TILs correlates with poorer survival. This finding is in agreement with the study by Chang et al.[30] and in line with reports showing that high PD-L1 expression is associated with higher stage disease[30,39]. However, opposite results were reported by two other studies [40,41]. Reasons for this discrepancy may be the use of different antibodies, cut-off points and an unusually high level of described positivity[38] and small sample size.

We also showed that higher expression of CD3, CD20 and CD45, the classic surface biomarkers on TILs, correlated with a better survival, suggesting that tumor infiltration by TILs leads to stronger anti-tumor efficacy.

In conclusion, our study suggests that extending surgery to stage II SCLC patients may be beneficial, in addition to adjuvant chemotherapy. Although the PD-L1 expression in SCLC is lower than in NSCLC, a subset of SCLC has high PD-L1 expression and poorer survival. Recently, a large randomized study in extensive disease SCLC showed improved overall survival and progression-free survival of chemotherapy combined with the PD-L1 inhibitor atezolizumab, compared to chemotherapy alone [42]. This study and phase II studies demonstrating activity of nivolumab (a PD-1 inhibitor) in refractory patients with SCLC, definitely support the use of immune checkpoint inhibitors in this disease. Our data warrant the investigation of these agents in the adjuvant setting in addition to chemotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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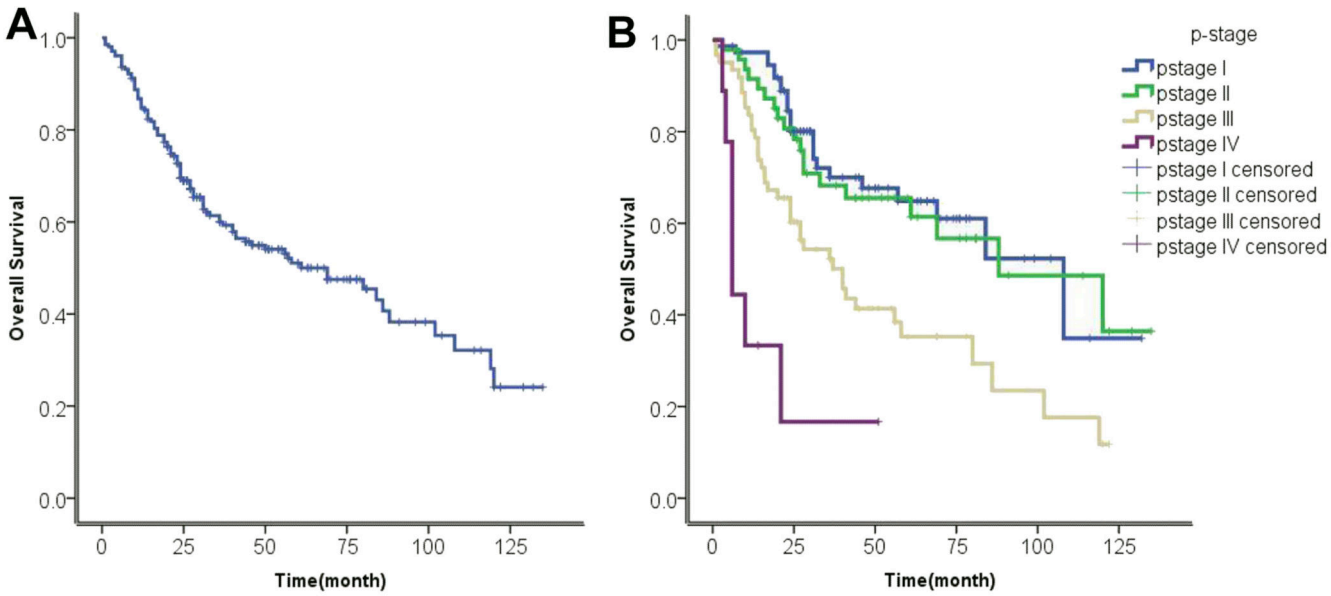

Figure 1.

Overall survival curves for (A) all 205 resected SCLC patients; (B) by pathological stage (blue, stage I; green, stage II; brown, stage III; purple, stage IV).

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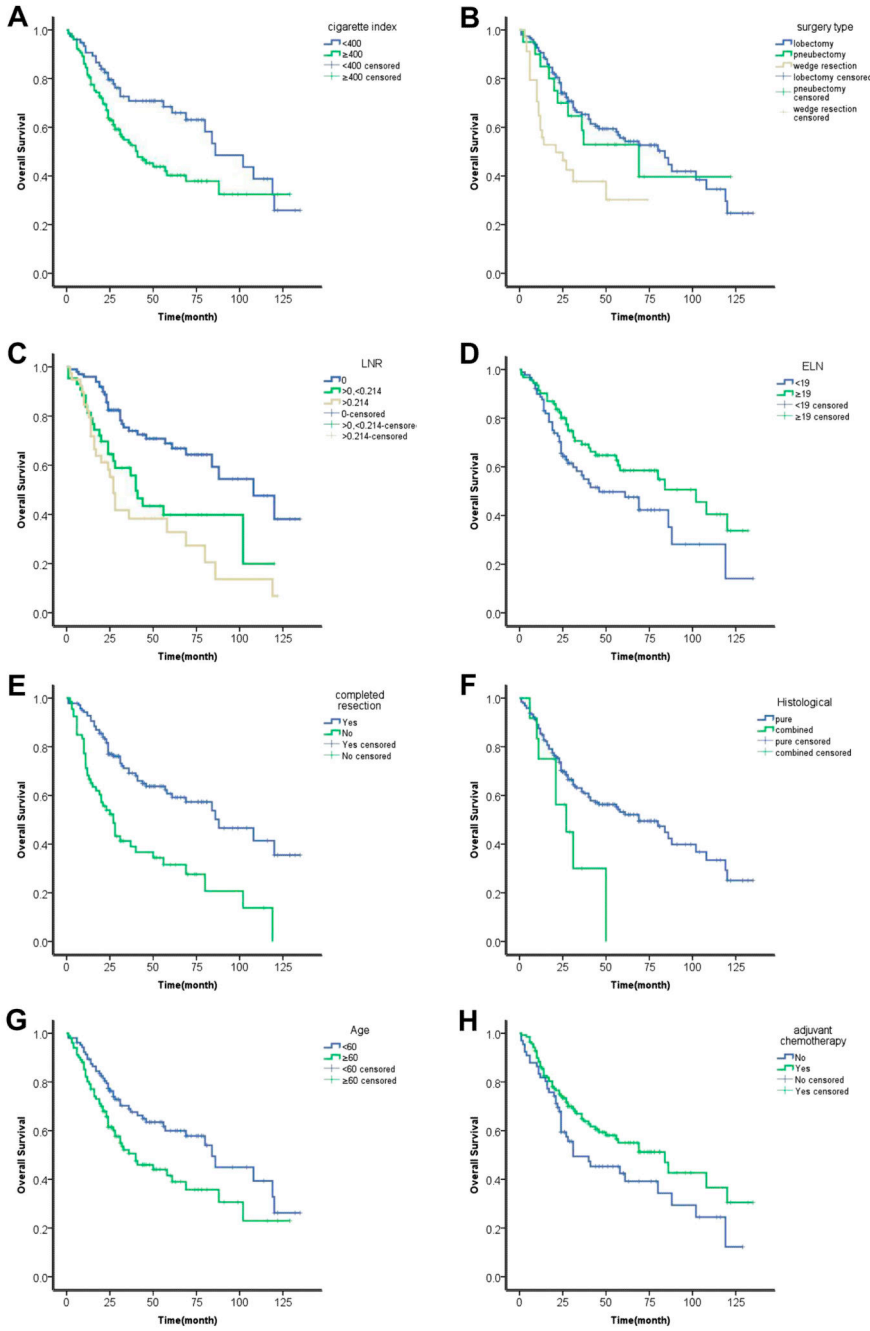

Figure 2.

Overall survival curves by: (A) cigarette index; (B) surgery type; (C) LNR; (D) ELN; (E) complete resection/R0 resection; (F) histology; (G) age; and (H) adjuvant chemotherapy. All $p<0.05$.

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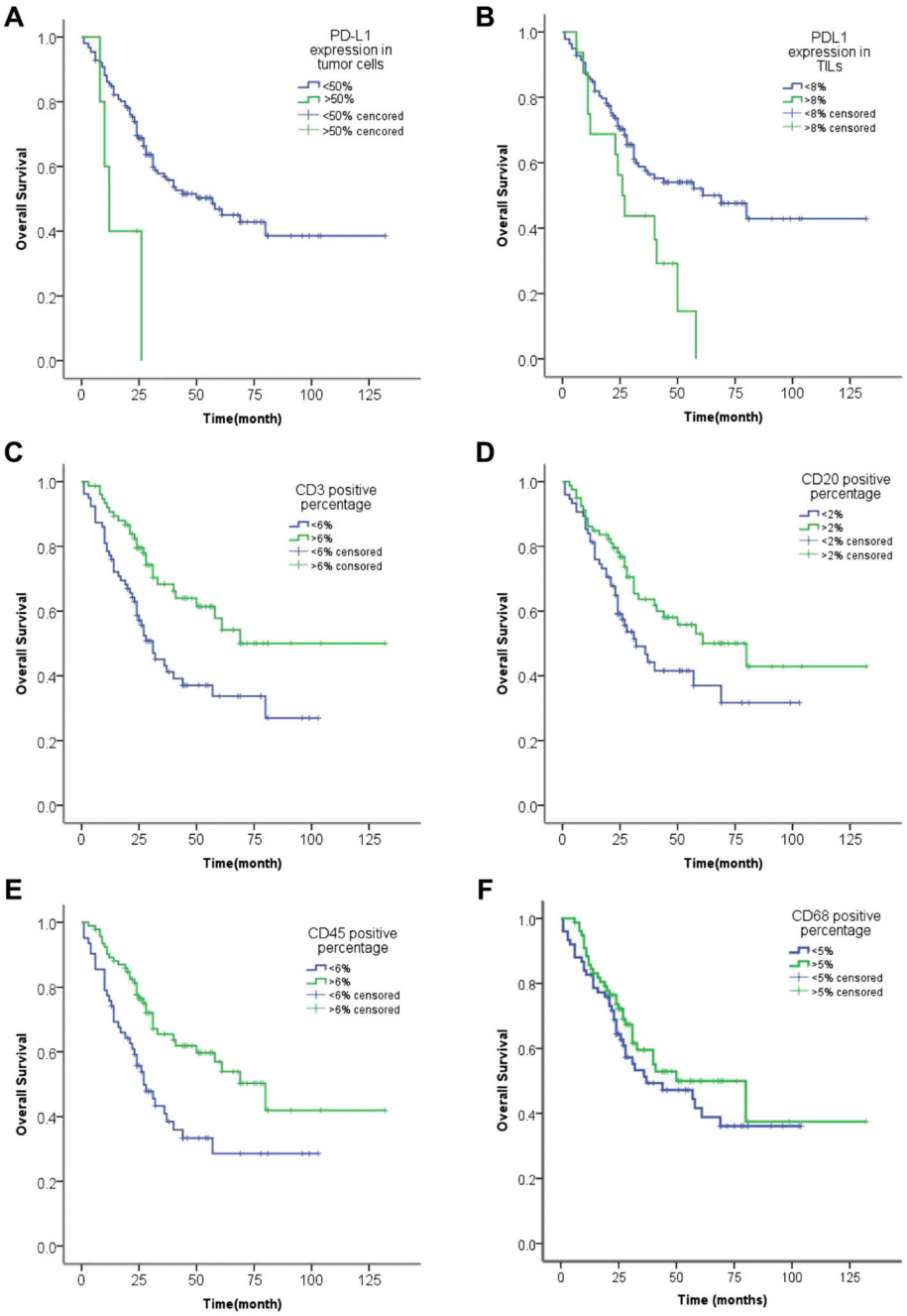

Figure 3.

Overall survival curves by (A) PD-L1 expression in tumor cells (using 50% as the cut-off value); (B) PD-L1 expression in TILs; (C) CD3 positive percentage; (D) CD20 positive percentage; (E) CD45 positive percentage; (F) CD68 positive percentage. All $p<0.05$ except CD68 ($p=0.229$).

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Table 1.

Patient characteristics (n=205)

Factor	Number	Percentage (%)
Gender		
Male	164	80.0
Female	41	20.0
Age, years		
⩽60	104	50.7
>60	101	49.3
Symptom duration		
>30 days	58	28.3
⩽30 days	147	71.7
Smoking index		
<400	76	37.1
⩾400	129	62.9
Lung		
left	102	49.6
right	103	50.4
NSE		
normal	118	57.6
elevated	87	42.4
CEA		
normal	147	71.7
elevated	58	28.3
Cyfra 21–1		
normal	163	79.5
elevated	42	20.5
Surgery type		
lobectomy	151	73.7
pneumonectomy	20	9.8
Wedge resection	34	16.6
Radical resection		
Yes	139	67.8
No	66	32.2
Neoadjuvant chemotherapy		
Yes	23	11.2
No	182	88.8
PCI		
Yes	18	8.8
No	187	91.2
Histological type		
Pure SCLC	193	94.1

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Factor	Number	Percentage (%)
combined	12	5.9
T stage		
T0	3	1.5
T1	119	58.0
T2	79	38.5
T3	4	2.0
N stage		
N0	102	55.4
N1	22	12.0
N2	58	31.5
N3	2	1.1
Pathological stage		
I	79	38.5
II	42	20.5
III	61	29.8
IV	9	4.4
NA[#]	14	6.8
Lymph node dissection number		
<19	90	49.5
⩾ 19[*]	92	50.5
Ratio of metastastic lymph nodes		
0	100	54.9
>0, ⩽=0.214[*]	43	23.6
>0.214	39	21.4
Postoperative radiotherapy		
Yes	46	22.4
No	159	77.6
Adjuvant chemotherapy		
Yes	140	68.3
No	65	31.7

[*] The median number was used as the cut-off value.

[#] The pathological stage could not be estimated because of lack of information on the LN status.

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Table 2.

Correlation Coefficient between All Overall Survival Related Clinic-Pathological Factors

	age	**CD3 percentage**	**CD20 percentage**	**CD45 pencentage**	**PDL1***	**PDL1inTILs**	**smoking**	**surgery type**	**LN dissection number**	**Metastasis Rate**	**Stage**	**complete resection**	**adjuvant chemotherapy**	**N stage**
age	1	0.154	0.056	0.13	0.187	0.12	0.14	−0.007	−0.051	−0.046	−0.079	−0.011	−0.173	−0.143
CD3 percentage	0.154	1	0.394	0.774	0.091	0.056	0.015	−0.02	−0.126	−0.14	−0.143	−0.071	0.111	−0.181
CD20 percentage	0.056	0.394	1	0.498	−0.097	0.177	−0.088	0.012	−0.052	−0.037	0.061	0.054	−0.059	0.027
CD45 percentage	0.13	0.774	0.498	1	0.049	0.07	−0.023	−0.042	−0.055	−0.073	−0.029	0.017	0.067	−0.05
PDL1*	0.187	0.091	−0.097	0.049	1	0.227	0.033	−0.052	−0.089	0.059	0.059	−0.103	0.028	0.036
PDL1inTILs	0.12	0.056	0.177	0.07	0.227	1	0.039	−0.101	−0.148	0.012	0.184	−0.035	−0.074	0.203
smoking	0.14	0.015	−0.088	−0.023	0.033	0.039	1	0.043	−0.026	0.022	0.064	−0.003	0.134	0.036
surgery type	−0.007	−0.02	0.012	−0.042	−0.052	−0.101	0.043	1	−0.246	0.072	−0.013	0.503	−0.024	−0.026
LN dissection number	−0.051	−0.126	−0.052	−0.055	−0.089	−0.148	−0.026	−0.246	1	−0.005	−0.025	−0.157	0.037	0.002
Metastasis Rate	−0.046	−0.14	−0.037	−0.073	0.059	0.012	0.022	0.072	−0.005	1	0.745	0.217	−0.034	0.777
stage	−0.079	−0.143	0.061	−0.029	0.059	0.184	0.064	−0.013	−0.025	0.745	1	0.187	0.048	0.909
complete resection	−0.011	−0.071	0.054	0.017	−0.103	−0.035	−0.003	0.503	−0.157	0.217	0.187	1	−0.021	0.215
adjuvant chemotherapy	−0.173	0.111	−0.059	0.067	0.028	−0.074	0.134	−0.024	0.037	−0.034	0.048	−0.021	1	0.043
N stage	−0.143	−0.181	0.027	−0.05	0.036	0.203	0.036	−0.026	0.002	0.777	0.909	0.215	0.043	1

All variates classification rules base on Table S1

*PDL1 showing PDL1 expression in tumor cells (using 50% as the cutoff value)

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Table 3.

Multivariate analysis of the correlation between clinical and pathological variables and OS.

Factor	Hazard	95%CI	*p* value
Complete Resection			
R0/complete	1.000		
R1/2/incomplete	2.354	1.289-4.297	0.005
Smoking index			
<400	1.000		
≥400	2.524	1.323-4.814	0.005
CD3 percentage			
≤6%	1.000		
>6%	0.505	0.288-0.884	0.017
PD-L1 expression in TILs			
<8%	1.000		
≥8%	2.182	1.061-4.486	0.034
PD-L1 expression in tumor cells			
<50%	1.000		
≥50%	5.296	1.454-19.28	0.011
LNR			0.004
LNR=0	1.000		
LNR>0,≤0.214	4.920	1.636-14.793	0.005
LNR>0.214	6.005	1.880-19.178	0.002

LNR= Ratio of metastatic lymph nodes.