

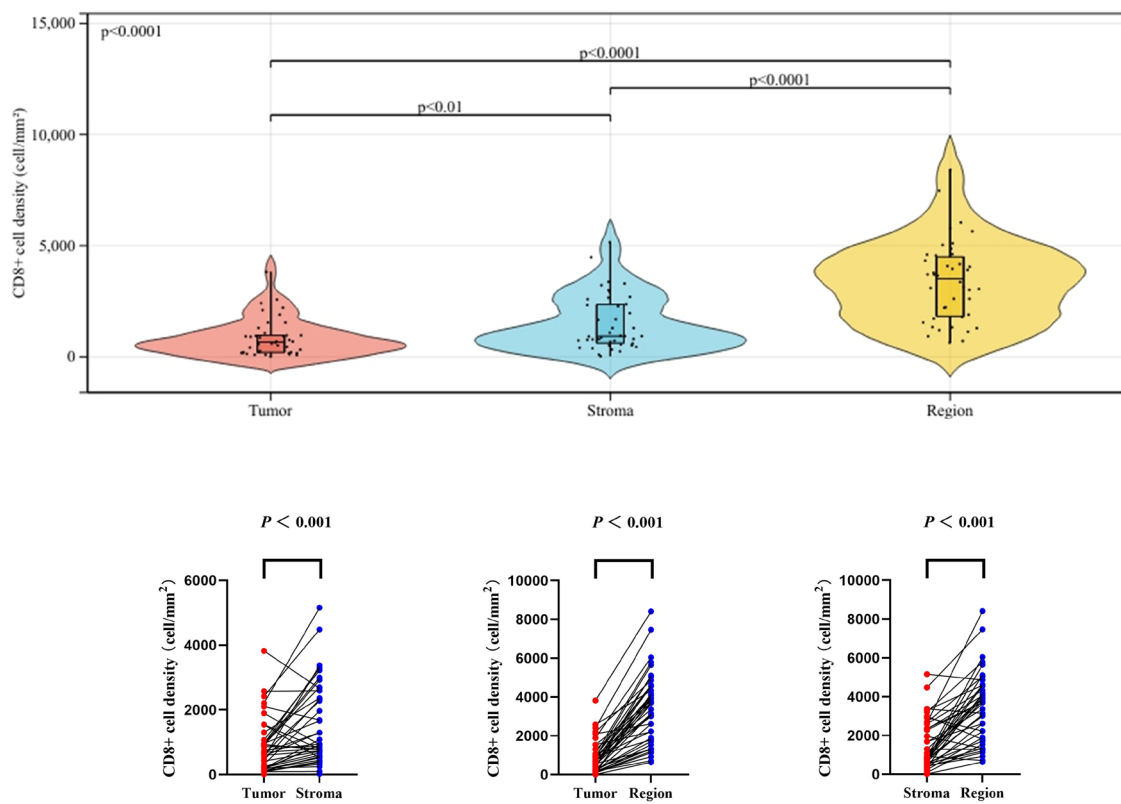


Figure S1 CD8⁺ T cell infiltration density and spatial distribution. Digital spatial analysis of CD8⁺ T cell distribution in the LCNEC tumor microenvironment showed compartmentalized infiltration patterns: maximal density at tumor-invasive margins ($3,388.0 \pm 1,810.0$ cells/mm²), intermediate stromal infiltration ($1,506.6 \pm 1,237.2$ cells/mm²), and minimal tumoral penetration (847.0 ± 826.3 cells/mm²).

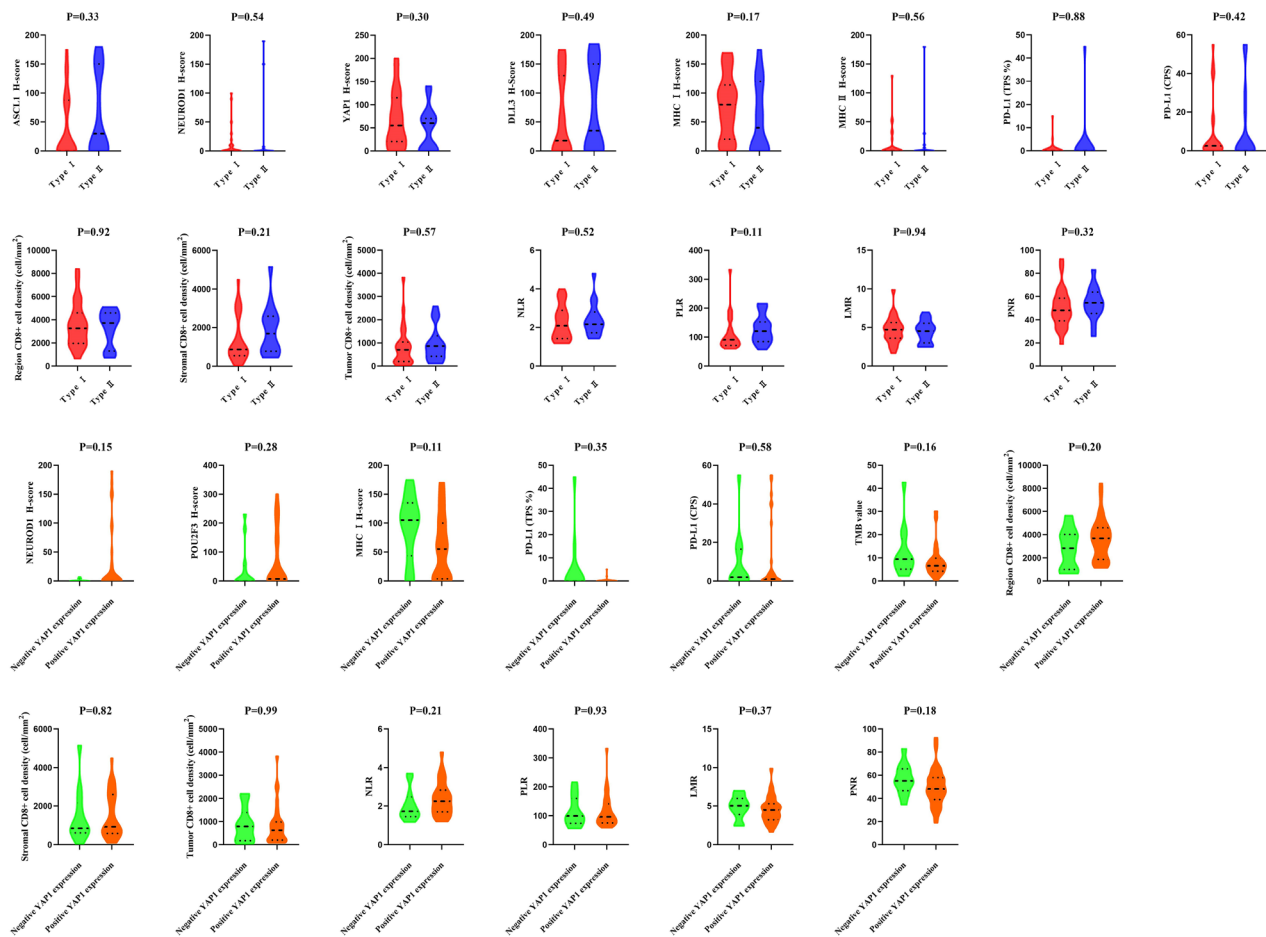


Figure S2 Comparative analysis of molecular subtype-stratified groups and YAP1 expression-defined cohorts demonstrated no statistically significant disparities in ancillary therapeutic biomarker profiles.

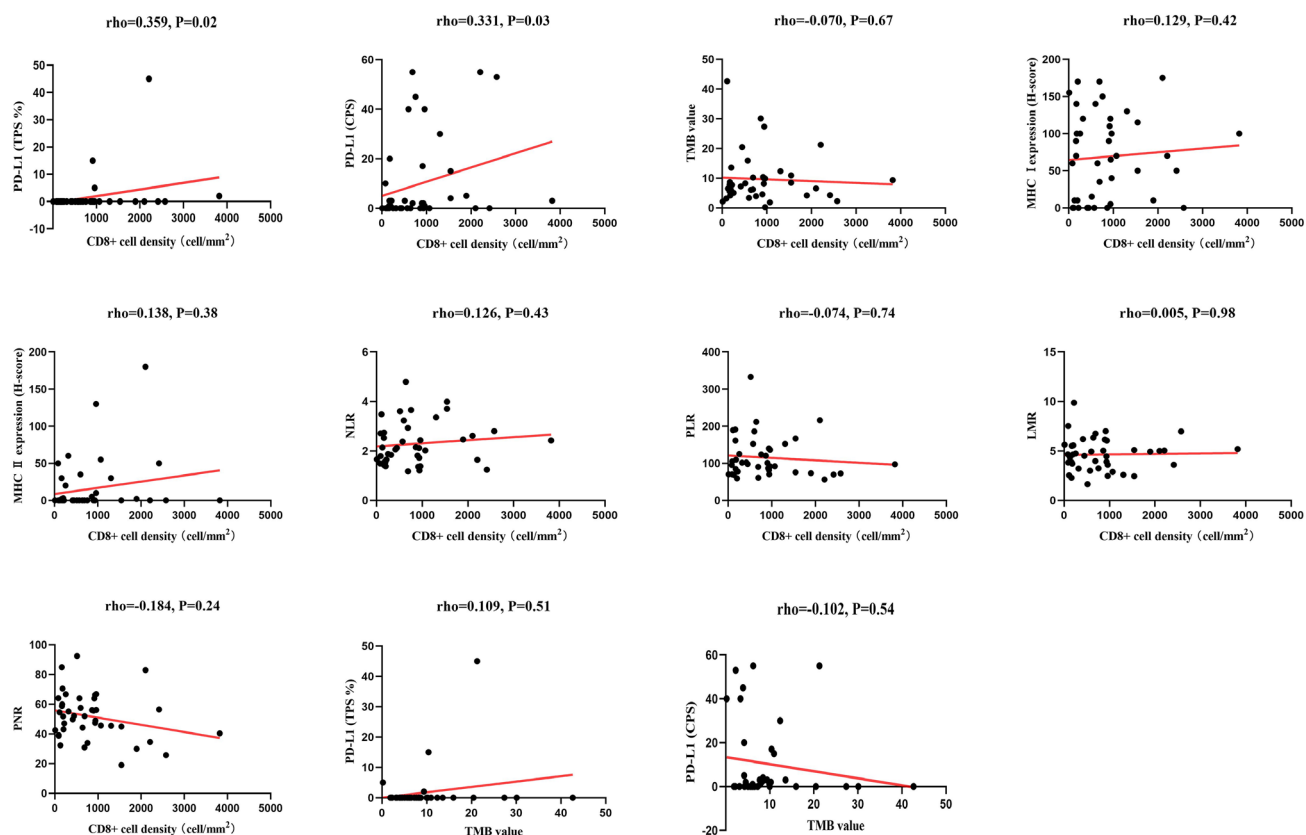


Figure S3 Spearman's rank correlation analysis revealed no significant associations among other groups of PD-L1 expression (assessed by TPS/CPS), tumor mutational burden (TMB), and CD8⁺ tumor-infiltrating lymphocyte density.

Table S1 Antibodies used for immunohistochemistry

Marker	Clone	Catalog number	Company	Dilution	Positive reactivity location
ASCL1	24B72D11.1	#556604	BD Biosciences, San José, CA, USA	1:50	Nucleus
NEUROD1	EPR17084	#ab205300	Abcam, Cambridge, U.K.	1:200	Nucleus
POU2F3	E5N2D	#36135	Cell Signaling Technology, Leiden, The Netherlands	1:300	Nucleus
YAP1	EP1674Y	#ab52771	Abcam, Cambridge, U.K.	1:300	Nucleus, cytoplasm
DLL3	EPR22592-18	#ab229902	Abcam, Cambridge, UK	1:200	Cell membrane
MHC I	EMR8-5	#ab70328	Abcam, Cambridge, U.K.	1:500	Cell membrane
MHC II	LGII-612.14	# 68258S	Cell Signaling Technology, Leiden, The Netherlands	1:400	Cell membrane
PD-L1	22C3	M3653	Agilent DaKo, Denmark	1:50	Partial or complete membrane
p53	DO-7	GM7001	Gene Tech, Shanghai, China	Working solution	Nucleus
Rb	EPR17512	#ab181616	Abcam, Cambridge, U.K.	1:1000	Nucleus
CD8	SP16	ZA-0508	ZSGB-BIO	Working solution	Cell membrane

Table S2 Demographics of the included patients and samples

Parameter	Value
Age (years), median (range)	63 (52–80)
Sex, n (%)	
Male	37 (88.1)
Female	5 (11.9)
Smoking history, n (%)	
Yes	39 (92.9)
No	3 (7.1)
Tumor laterality, n (%)	
Left lung	20 (47.6)
Right lung	22 (52.4)
Tumor location, n (%)	
Central	18 (42.9)
Peripheral	24 (57.1)
Histology, n (%)	
Pure	36 (85.7)
Combined	6 (14.3)
TNM stage, n (%)	
I	22 (52.4)
II	13 (30.9)
III	7 (16.7)
Neoadjuvant therapy, n (%)	
Yes	4 (9.5)
No	38 (90.5)
Postoperative chemotherapy, n (%)	
Yes	21 (50.0)
No	14 (33.3)
Unknown	7 (16.7)
Postoperative radiotherapy, n (%)	
Yes	9 (21.4)
No	26 (61.9)
Unknown	7 (16.7)
Postoperative immunotherapy, n (%)	
Yes	3 (7.1)
No	32 (76.2)
Unknown	7 (16.7)

Table S3 Expression of therapeutic biomarkers

Case number	ASCL1 expression	NEUROD1 expression	POU2F3 expression	DLL3 expression	Stromal PD-L1 expression	Tumor PD-L1 expression	MHC I expression	MHC II expression
1	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive
2	Negative	Positive	Negative	Negative	Positive	Negative	Negative	Negative
3	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative
4	Positive	Negative	Negative	Positive	Positive	Positive	Positive	Negative
5	Negative	Negative	Positive	Negative	Positive	Negative	Negative	Negative
6	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative
7	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Negative
8	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Positive
9	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative
10	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative
11	Negative	Positive	Negative	Negative	Positive	Negative	Positive	Negative
12	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative
13	Negative	Negative	Negative	Negative	Positive	Positive	Positive	Negative
14	Positive	Negative	Positive	Positive	Positive	Negative	Positive	Negative
15	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative
16	Positive	Negative	Positive	Positive	Positive	Negative	Positive	Negative
17	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive
18	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative
19	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative
20	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Negative
21	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Negative
22	Negative	Negative	Positive	Negative	Positive	Negative	Positive	Negative
23	Negative	Negative	Positive	Negative	Positive	Positive	Positive	Negative
24	Negative	Positive	Positive	Positive	Negative	Negative	Positive	Positive
25	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative
26	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Positive
27	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Negative
28	Negative	Positive	Negative	Positive	Negative	Negative	Negative	Negative
29	Negative	Negative	Negative	Negative	Positive	Negative	Negative	Negative
30	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive
31	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Negative
32	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative
33	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative
34	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive
35	Negative	Positive	Positive	Negative	Positive	Negative	Positive	Positive
36	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative
37	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative
38	Positive	Positive	Negative	Positive	Positive	Negative	Positive	Negative
39	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative
40	Negative	Positive	Positive	Negative	Positive	Negative	Positive	Positive
41	Negative	Negative	Negative	Negative	Positive	Negative	Positive	Negative
42	Positive	Positive	Negative	Positive	Positive	Positive	Positive	Positive

Table S4 Univariate analyses for prognostic significance of clinicopathologic parameters in surgically resected pulmonary large cell neuroendocrine carcinoma patients

Clinicopathologic parameters	OS		DFS	
	P value	HR (95% CI)	P value	HR (95% CI)
Age, ≤65 vs. > 65 years	0.93	1.040 (0.442–2.443)	0.95	1.023 (0.473–2.215)
Sex, male vs. female	0.49	0.650 (0.190–2.222)	0.42	0.604 (0.177–2.058)
Smoking story, no vs. yes	0.51	0.509 (0.068–3.796)	0.40	0.422 (0.057–3.122)
TNM stage, I–II vs. III	0.007*	0.263 (0.099–0.699)	0.02*	0.321 (0.121–0.852)
Tumor location, central vs. peripheral	0.42	0.689 (0.280–1.692)	0.28	0.636 (0.278–1.455)
Tumor laterality, left vs. right	0.54	0.762 (0.322–1.803)	0.31	0.662 (0.300–1.461)
Tumor histology, pure vs. combined	0.14	0.470 (0.170–1.293)	0.31	0.624 (0.249–1.564)
NLR, low vs. high	0.98	0.988 (0.426–2.290)	0.34	0.692 (0.323–1.481)
PLR, low vs. high	0.28	0.630 (0.272–1.462)	0.67	0.846 (0.397–1.804)
LMR, low vs. high	0.26	1.637 (0.701–3.823)	0.09	1.958 (0.902–4.251)
PNR, low vs. high	0.88	0.938 (0.406–2.164)	0.49	1.303 (0.611–2.779)
Preoperative neoadjuvant chemotherapy, no vs. yes	0.52	1.942 (0.259–14.560)	0.77	1.238 (0.290–5.287)
Postoperative chemotherapy, no vs. yes	0.32	0.563 (0.183–1.737)	0.048*	0.321 (0.104–0.988)
Postoperative radiotherapy, no vs. yes	0.31	0.605 (0.230–1.595)	0.14	0.527 (0.224–1.240)
Postoperative immunotherapy, no vs. yes	0.41	0.591 (0.169–2.063)	0.50	0.658 (0.193–2.240)
Adjuvant chemotherapy regimen, NSCLC vs. SCLC	0.47	1.527 (0.484–4.817)	0.66	0.787 (0.275–2.253)
ASCL1 expression, Neg vs. Pos	0.15	1.927 (0.784–4.741)	0.02*	2.653 (1.149–6.126)
NEUROD1 expression, Neg vs. Pos	0.95	1.036 (0.381–2.817)	0.89	0.944 (0.412–2.164)
POU2F3 expression, Neg vs. Pos	0.29	0.637 (0.276–1.474)	0.76	1.126 (0.521–2.436)
YAP1 expression, Neg vs. Pos	0.47	1.382 (0.579–3.297)	0.85	0.924 (0.404–2.117)
DLL3 expression, Neg vs. Pos	0.23	1.679 (0.723–3.897)	0.08	1.997 (0.929–4.292)
Tumor PD-L1 expression, Neg vs. Pos	0.27	24.645 (0.081–7456.335)	0.17	4.108 (0.555–30.436)
Stromal PD-L1 expression, Neg vs. Pos	0.56	1.282 (0.551–2.987)	0.99	1.003 (0.462–2.177)
MHC I expression, Neg vs. Pos	0.92	0.952 (0.372–2.437)	0.92	0.954 (0.402–2.264)
MHC II expression, Neg vs. Pos	0.13	0.498 (0.201–1.237)	0.78	0.885 (0.372–2.109)
Rb expression, Neg vs. Pos	0.49	1.384 (0.555–3.452)	0.67	0.839 (0.375–1.874)
P53 gene, normal vs. abnormal	0.94	1.052 (0.304–3.643)	0.86	0.896 (0.265–3.028)
RB gene, normal vs. abnormal	0.49	0.723 (0.290–1.803)	0.67	1.192 (0.534–2.664)
Molecular subtype, I vs. II	0.73	0.852 (0.346–2.099)	0.47	1.347 (0.596–3.044)
TTF-1 expression, Neg vs. Pos	0.80	0.888 (0.360–2.190)	0.40	0.699 (0.302–1.618)
Visceral pleural invasion, no vs. yes	0.97	0.984 (0.411–2.357)	0.75	0.881 (0.402–1.934)
Trachea invasion, no vs. yes	0.90	1.074 (0.362–3.181)	0.96	1.027 (0.388–2.719)
Vascular invasion, no vs. yes	0.02*	0.369 (0.155–0.875)	0.04*	0.444 (0.203–0.970)
Nerve invasion, no vs. yes	0.48	2.066 (0.276–15.448)	0.71	0.758 (0.178–3.223)
STAS, no vs. yes	0.001*	0.211 (0.084–0.527)	0.02*	0.359 (0.153–0.843)
Necrosis, ≤30% vs. >30%	0.03*	2.67 (1.102–6.467)	0.10	1.938 (0.889–4.227)
Fibrosis, ≤10% vs. >10%	0.63	0.782 (0.288–2.125)	0.89	1.061 (0.447–2.517)
Nucleolus, mixed vs. obvious	0.52	1.331 (0.563–3.143)	0.89	1.059 (0.488–2.297)
Positive NE marker, ≤1 vs. >1	0.79	0.889 (0.373–2.121)	0.56	0.788 (0.353–1.759)
Region CD8 ⁺ cell density, low vs. high	0.94	0.969 (0.419–2.244)	0.84	1.084 (0.504–2.331)
Stroma CD8 ⁺ cell density, low vs. high	0.22	0.589 (0.252–1.375)	0.09	0.507 (0.233–1.105)
Tumor CD8 ⁺ cell density, low vs. high	0.78	1.124 (0.486–2.603)	0.88	1.058 (0.496–2.258)
TLS, absent vs. present	0.14	1.942 (0.807–4.672)	0.35	1.468 (0.653–3.300)

*, statistically significant difference.

Table S5 *P53/RB* gene and protein expression based on *DLL3* expression in lung large cell neuroendocrine carcinoma

Parameter	DLL3 expression		P value
	Negative	Positive	
p53 expression			0.67
Negative	2	4	
Positive	16	17	
<i>P53</i> gene			0.70
Wild-type	3	5	
Mutated type	15	16	
Rb expression			>0.99
Negative	8	10	
Positive	10	11	
<i>RB</i> gene			>0.99
Wild-type	10	11	
Mutated type	8	10	