# Distribution characteristics and prognosis of tumor-infiltrating lymphocytes in the brain metastases of small cell lung cancer: a retrospective cohort study

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**Background:** The efficacy of immunotherapy for brain metastases from small cell lung cancer (SCLC) is relatively low, and the tumor microenvironment of SCLC brain metastases is still unknown. Therefore, we investigated the distribution of tumor-infiltrating lymphocytes (TILs) and the expression of programmed cell death-ligand 1 (PD-L1) in patients with brain metastases from SCLC to explore the tumor microenvironment of SCLC brain metastases.

**Methods:** A retrospective analysis was performed on 12 surgical specimens of brain metastases from patients with SCLC treated in the Department of Neurosurgery of The First Affiliated Hospital of Anhui Medical University from June 2017 to June 2022. The inclusion criteria for this study were the following: (I) a pathologically confirmed diagnosis of SCLC brain metastases; (II) surgical resection of brain metastases; (III) age >18 years; (IV) and complete clinical data. Patient-related data were retrieved from the inpatient medical record system, telephone follow-up of patients date of death, and overall survival (OS). The immunofluorescence-based tissue microenvironment analysis panel (MAP) was utilized for the detection of TILs, including CD3, CD8, programmed cell death 1 (PD-1), and PD-L1, in formalin-fixed and paraffin-embedded archival specimens of brain metastases. The expression levels of PD-L1 in tumor cells were detected by immunohistochemistry. The correlation between the OS and the above-mentioned markers was analyzed in the 12 patients.

**Results:** Twelve patients were included in the study. The patients' ages ranged from 51–78 years with a median of 68 years, with 1 female and 11 males. Among 12 patients with SCLC brain metastases: positive rates of CD3$^+$ TILs in the tumor parenchyma *vs.* tumor stroma were 0.60%±0.94% *vs.* 1.76%±2.72% (P=0.01), respectively; positive rates of CD8$^+$ TILs in the tumor parenchyma *vs.* tumor stroma were 0.80%±0.78% *vs.* 2.46%±3.72% (P=0.02), respectively. There was no co-expression of CD8$^+$ and PD-1$^+$ TILs in the tumor parenchyma of 11 cases, and the infiltration density of coexpressed CD3$^+$ and PD-1$^+$ TILs was more than 10/mm$^2$ in only 1 case. There was no coexpression of CD3$^+$ and PD-1$^+$ TIL in the stroma of 10 cases, and the infiltration density of CD8$^+$ and PD-1$^+$ TILs was more than 10/mm$^2$ in 2 cases. Immunohistochemistry was used to detect the expression of PD-L1 in 12 cases of SCLC metastatic lesions, and 3 cases (25%) were positive. Survival analysis showed that patients with positive intraepithelial CD3$^+$ TILs had significantly longer OS [hazard ratio 3.383, 95% confidence interval (CI): 0.959–11.940; P=0.04].

**Conclusions:** Our study further demonstrated the immune microenvironment of SCLC brain metastases. The distribution of TILs in SCLC brain metastases is low and mainly distributed in the stroma, with the expression of PD-L1 in these tumor tissues being low. Further exploration of the immune microenvironment of SCLC brain metastases is of great significance for potential treatment.

**Keywords:** Small cell lung cancer (SCLC); brain metastases; tumor-infiltrating lymphocytes (TILs); microenvironment analysis panel (MAP); programmed cell death-ligand 1 (PD-L1)

## Introduction

Lung cancer remains a serious threat to human health, with small cell lung cancer (SCLC) accounting for 14% of all lung cancer cases (1). The brain is one of the most common metastatic sites of SCLC with about 10% of patients with SCLC presenting with brain metastases at the time of diagnosis, and this condition correlates with poor prognosis (2). Tumor-infiltrating lymphocytes (TILs) are highly heterogeneous lymphocytes in tumor tissues and play a key role in antigen-specific tumor immune response. In the physiological state, the inflow of lymphocytes into the central nervous system is strictly regulated, and lymphocytes are usually absent in the healthy brain parenchyma (3). In the pathological state, lymphocytes enter the cerebrospinal fluid through the dural sinus to form TILs. However, little is known on the immune microenvironment of SCLC brain metastases. Regarding the relationship between programmed cell death-ligand 1 (PD-L1) expression in brain metastases and patient survival, various degrees of correlation have been observed across studies. In this study, an immunofluorescence-based tissue microenvironment analysis panel (MAP) and immunohistochemistry were used to observe the expression of CD3, CD8, programmed cell death 1 (PD-1), and PD-L1 in 12 patients with SCLC brain metastases to provide a potential theoretical basis for clinical treatment with immune checkpoint inhibitors (ICIs). We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-552/rc).

## Methods

### General information

A retrospective cohort analysis was conducted on 12 patients with SCLC who underwent resection of brain metastases at the Department of Neurosurgery of The First Affiliated Hospital of Anhui Medical University from June 2017 to June 2022; clinical data and molecular data from the surgical specimens were analyzed. The inclusion criteria for this study were the following: (I) a pathologically confirmed diagnosis of SCLC brain metastases; (II) surgical resection of brain metastases; (III) age >18 years; (IV) and complete clinical data (including age, sex, smoking history, treatment, and date of death). The exclusion criteria were the following: (I) no pathological specimen from SCLC brain metastases; (II) a history of other malignant tumors within the past 3 years (except cured local cancer or carcinoma in situ); (III) systemic disease (such as active infections, arrhythmias, or congestive heart failure) that

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**Highlight box**

**Key findings**
- Tumor-infiltrating lymphocytes (TILs) in small cell lung cancer (SCLC) brain metastases are predominantly distributed in the stroma, with overall low distribution.
- The expression of programmed cell death-ligand 1 in these tumor tissues is low.
- Positive intraepithelial CD3⁺ TILs correlated with significantly longer overall survival.

**What is known and what is new?**
- The efficacy of immunotherapy on brain metastases from SCLC is low, and there is still a lot of space for exploration of the tumor microenvironment of SCLC brain metastases.
- It provides potential biomarkers for future treatment studies of patients with brain metastases.

**What is the implication, and what should change now?**
- The findings highlight the importance of further exploring the immune microenvironment in SCLC brain metastases for potential therapeutic implications.

would prevent treatment; (IV) severe mental illness or an inability to comply with treatment; and (V) long-term use of hormones or immunosuppressants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (No. PJ2024-02-31). Individual consent for this retrospective analysis was waived.

### Experimental method

The data from 12 patients with SCLC brain metastases who met the above-described inclusion and exclusion criteria were collected, and the surgical specimens from these patients were subjected to immunofluorescence-based tissue MAP and immunohistochemistry. The patients' clinical diagnosis and treatment information were reviewed, and the date of death was noted.

### Analysis of TIL infiltration

TIL infiltration analysis based on immunofluorescence was performed in 12 cases of SCLC brain metastases. CD3, CD8, PD-1, PD-L1, and broad-spectrum pan-cytokeratin (pan-CK) were stained via immunofluorescence-based tissue MAP using a PANO7-plex IHC kit (catalog number 0004100100; Panovue, Beijing, China). Formalin-fixed, paraffin-embedded tissue sections were deparaffinized and rehydrated, and antigen retrieval was performed using citric acid solution (concentration 0.158%; GT100210; Gene Tech, Shanghai, China). After a blocking solution was used to quench the endogenous peroxidase activity, the sections were incubated at a constant temperature with their primary CD3 antibody (SP7; Abcam, Cambridge, England), CD8 antibody [C8/144B; Cell Signaling Technology (CST), Boston, USA], PD-1 antibody (EH33; CST, Boston, USA), and PD-L1 antibody (concentration 0.125%; E1L3N; CST, Boston, USA). They were then incubated with their respective secondary antibodies at a constant temperature, and the tablets were stained with hematoxylin, dehydrated with gradient alcohol, and sealed with transparent xylene and neutral gum. Pan-CK was used to distinguish tumor parenchyma and stroma: pan-CK positivity indicated tumor parenchyma, and pan-CK negativity indicated tumor stroma. The expression of CD3, CD8, PD-1, and PD-L1 in tumor parenchyma and stroma was observed and analyzed (a complete and clear brown or tan cell membrane was considered positive). It's worth noting that: positive rates

of CD3$^+$ TILs mean the ratio between CD3$^+$ TILs and total TILs.

### IHC characteristics of tumor tissue

Using the 22C3 pharmDx test kit (Agilent Technologies, Carpinteria, CA, USA), the PD-L1 tumor proportion score (TPS) and combined positive score (CPS) were determined in the 12 cases of brain metastases. TPS is defined as the percentage of tumor cells among the total number of tumor cells stained with any intensity of the PD-L1 membrane. CPS is defined as the percentage of PD-L1-positive cells among the total number of tumor cells. The paraffin sections were deparaffinized, washed, repaired with antigen, sealed with serum, incubated with first and second antibodies, and stained with hematoxylin for microscopic examination. The expression rate was evaluated with the CPS and TPS scoring methods, with a TPS score >1% indicating PD-L1 positivity.

### Clinical data collection

Patient-related data were retrieved from the inpatient medical record system and included age, sex, smoking history, treatment, telephone follow-up of patients date of death, and overall survival (OS).

### Statistical methods

SPSS 26.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and the Wilcoxon rank-sum test was used to analyze the differences in the TILs expressing positivity for CD3, CD8 PD-1, and PD-L1 between the tumor parenchyma and stroma. $P<0.05$ was considered to indicate a statistically significant difference. OS was defined as the time from the resection of brain metastases to death due to any cause. The Kaplan-Meier survival curve and the log-rank test were used to compare the differences in survival between the different expression groups described above.

## Results

### General condition of the patients

The patients' ages ranged from 51–78 years with a median of 68 years, with 1 female and 11 males. Half (50%) of the patients had a history of heavy smoking. In addition to surgery, three patients received chemotherapy (chemo), two patients were treated with ICIs, and seven patients did not

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**Table 1** Basic data and clinical treatment information of patients with small cell lung cancer brain metastasis

| Characteristics | Value | Median survival time (month) |
|---|---|---|
| Patient number | 12 | 5 |
| Age at first diagnosis, median [range], years | 68 [51–78] | – |
| Sex, n (%) | | |
| Female | 1 (8.33) | 2 |
| Male | 11 (91.67) | 8 |
| Smoking, n (%) | | |
| Smoking | 6 (50.0) | 11 |
| Non-smoking | 6 (50.0) | 3 |
| Postoperative treatment modality, n (%) | | |
| Chemotherapy | 3 (25.0) | 16 |
| Immunotherapy | 2 (16.67) | 9.5 |
| Untreated | 7 (58.33) | 4.5 |
| Pathological stage, n (%) | | |
| Stage IV | 12 (100.0) | 5 |
| Extensive stage | 12 (100.0) | 5 |

receive any treatment after the operation (*Table 1*).

### *Immunofluorescence microenvironment analysis*

**Distribution of TILs in brain metastases**

All 12 tumor tissue specimens showed different degrees of TIL infiltration, but the degree of TIL invasion was generally low. The positive rates of CD3+ TILs and CD8+ TILs in the tumor parenchyma of SCLC brain metastases were 0.60%±0.94% and 0.80%±0.78%, respectively, while the positive rates of CD3+ TILs and CD8+ TILs in the tumor stroma were 1.76%±2.72% and 2.46%±3.72%, respectively (*Figure 1*). There was no difference in the positive rate of CD3+ TILs or CD8+ TILs either in the tumor parenchyma or stroma. Among the 12 samples of brain metastases, no CD8+ and PD-1+ co-expressing TILs were found in the parenchyma of 11 cases, and the infiltration density of coexpressed CD3+ and PD-1+ TILs was more than 10/mm$^2$ in only one case. There was no coexpression of CD3+ and PD-1+ TILs in the tumor stroma of 10 cases, and the infiltration density of CD8+ and PD-1+ TILs in two samples was more than 10/mm$^2$. The

correlation analysis of different TIL markers showed that the positive rate of CD3+ TILs in the stroma was positively correlated with that of CD8+ TILs (P=0.03). The positive expression of CD8+ TILs in the stroma was positively correlated with the that of PD-1 in the stroma (P=0.01).

### Spatial distribution difference of TILs

In the MAP analysis of brain metastases, the spatial distribution of TIL infiltration was significantly different between the tumor parenchyma and tumor stroma. The positive rate of CD3+ TILs in the tumor parenchyma was significantly lower than that in tumor stroma (0.60% *vs.* 1.76%; P=0.01); similarly, the positive rate of CD8+ TILs was significantly greater in the tumor stroma than in the tumor parenchyma (2.46% *vs.* 0.80%; P=0.02) (*Figure 2*).

### *Expression of PD-L1 in SCLC brain metastases*

IHC was used to determine the expression of PD-L1 in brain metastases. The TPS and CPS indicated that 3 of the 12 (25%) brain metastasis specimens were positive for PD-L1. Moreover, three specimens were PD-L1 positive, which was consistent with the PD-L1 expression in the tumor parenchyma by MAP method (*Figure 3*).

### *Other markers of SCLC brain metastases*

Pathological IHC detection of the synaptophysin (Syn), chromogranin A (CgA), S-100, and Ki-67 markers in 12 patients was retrospectively collected and analyzed. Syn was expressed positively in 10 of 11 (90.9%) patients, CgA in 4 of 10 (40%) patients, and S-100 in 1 of 9 (11.1%) patients. The Ki-67 proliferative index of the whole cohort had a mean value of 70.5% and a median value of 77.5%. Correlation analysis of the Ki-67 proliferation index and SCLC brain metastasis immune microenvironment markers revealed a positive correlation between Ki-67 and parenchymal CD8+ TILs (P=0.02). Ki-67 was positively correlated with total CD8+ TILs (P=0.048).

### *Percentage of TILs in SCLC brain metastases was correlated with OS*

To further assess the prognostic value of TIL expression, a survival analysis was performed of the 12 patients. The median OS of patients with a CD3+ TIL positive rate >1% in the tumor stroma of brain metastases was 21.5 months, while that of patients negative for stromal CD3+ TILs was
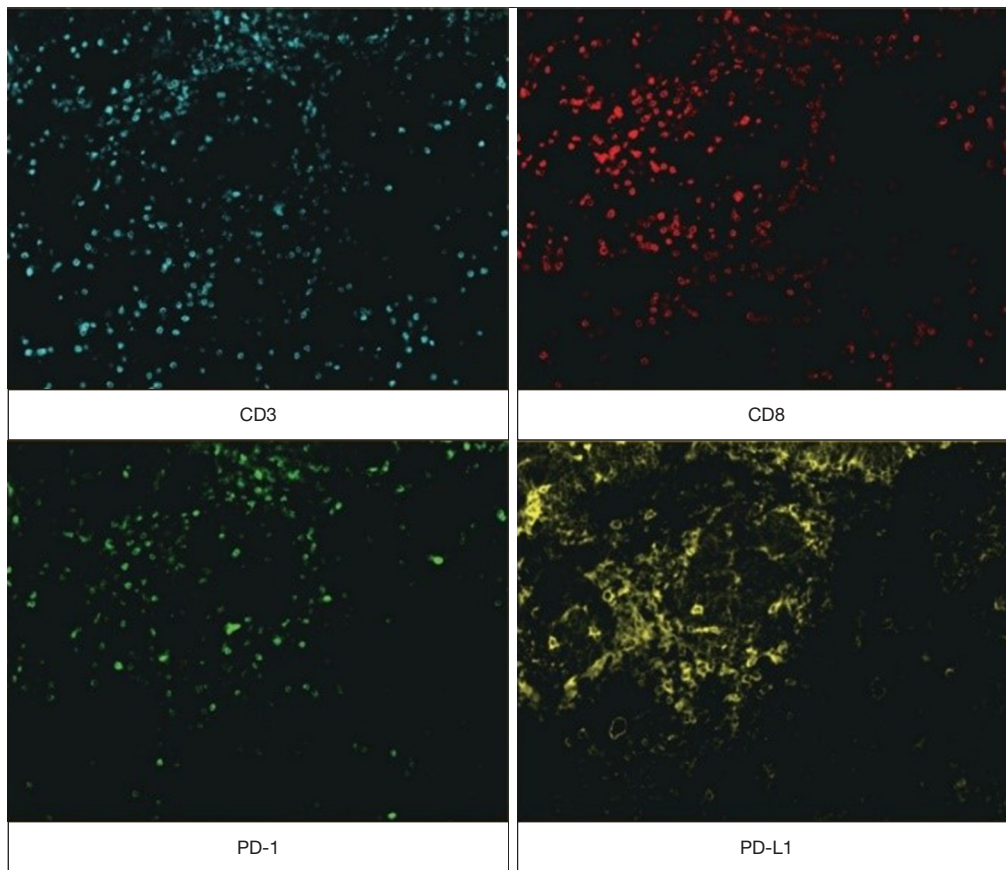
**Figure 1** MAP results of tumor tissue for CD3 (indigo upper left), CD8 (red upper right), PD-1 (green bottom left), and PD-L1 (yellow bottom right) in the brain metastases of small cell lung cancer. Magnification: ×100. PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; MAP, microenvironment analysis panel.
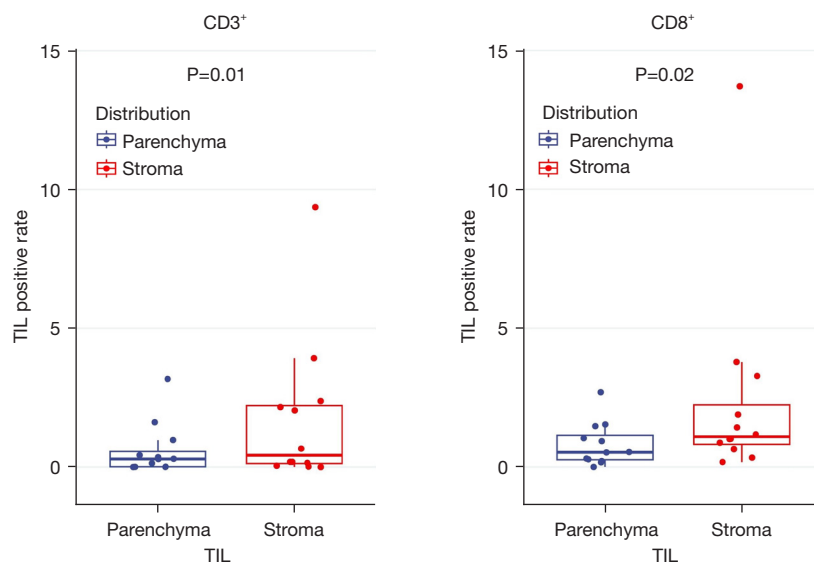


**Figure 2** Spatial differences in the distribution of CD3^{+} TILs and CD8^{+} TILs. TIL, tumor-infiltrating lymphocyte.
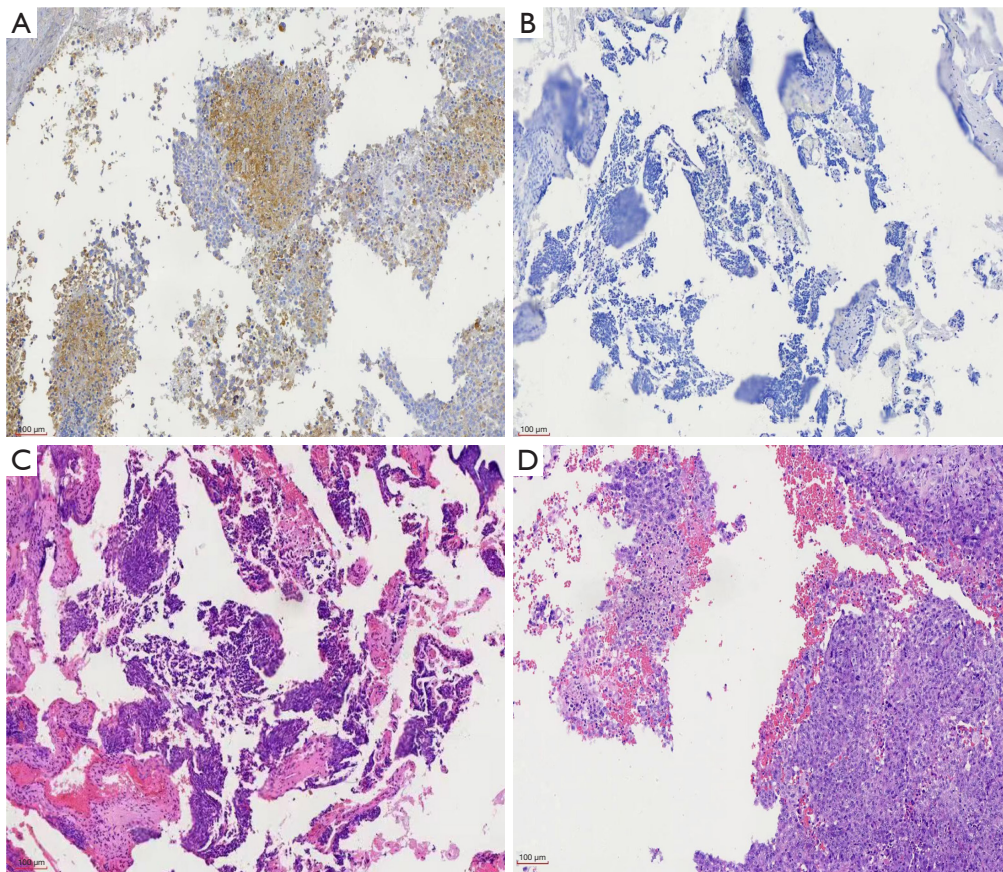
**Figure 3** Immunohistochemical characteristics of the tumor tissue. (A) Positive PD-L1 expression after immunohistochemical staining. (B) Negative PD-L1 expression after immunohistochemical staining. (C) Positive PD-L1 expression before immunohistochemical staining. (D) Negative PD-L1 expression before immunohistochemical staining. PD-L1, programmed cell death-ligand 1.
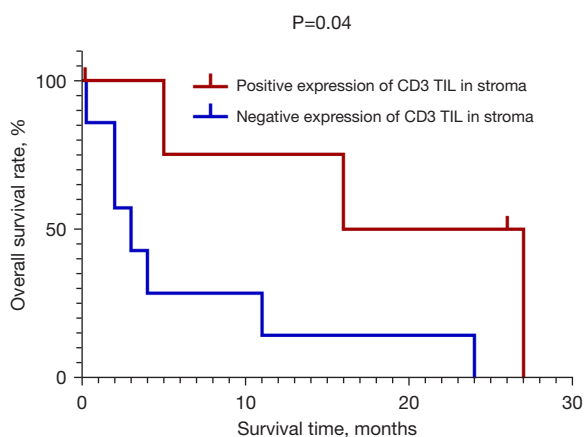


**Figure 4** Kaplan-Meier curve of stratification according to CD3+ TIL expression in stroma. TIL, tumor-infiltrating lymphocyte.

3 months [hazard ratio 3.383, 95% confidence interval (CI): 0.959–11.940; P=0.04; *Figure 4*]. Also patients with >1% positivity for CD8+ TILs in the stroma of brain metastases had longer OS compared to those with <1% positivity (16 *vs.* 3.5 months), although this difference was not statistically significant (P=0.47).

## Discussion

The central nervous system is one of the most common metastatic sites of SCLC. TILs are the main components of the tumor immune microenvironment and the key cell subtypes involved in immune response. PD-1 is mainly expressed in immune cells, while its ligand PD-L1 is expressed both in tumor cells and immune cells. The

binding of PD-1 to PD-L1 inactivates the cytotoxic T cells that recognize tumor cells, resulting in immune escape [4]. The blockade of PD-1/PD-L1 pathway through anti-PD-1 or anti-PD-L1 monoclonal antibodies restore anti-tumoral immune response. The administration of anti-PD-L1 antibodies combined with platinum-based chemo has become standard first-line treatment for extensive stage SCLC [5-8]. In fact, a meta-analysis showed an OS benefit for patients treated with ICI + chemo *vs.* chemo alone, but patients with brain metastases were few and no definitive conclusions may be drawn [9].

In this study, we collected specimens of brain metastases from 12 patients with SCLC. We found that, consistently with the other study [10], $CD3^+$ and $CD8^+$ TILs infiltrated more prominently in the tumor stroma, indicating that the TILs density in the stroma of brain metastases was higher than that in the parenchyma of brain metastases. Previous research has also suggested that $CD3^+$ and $CD8^+$ TILs are also more prominent in the stroma than the parenchyma of the primary SCLC tissues [11]. There are two pathways for the upregulation of PD-L1 expression: endogenous induction and exogenous induction [12]. We did not observe a correlation between PD-L1 expression and TIL infiltration, and the colocalized expression of PD-L1 and TILs was low, which may suggest that the expression of PD-L1 in brain metastases of SCLC is mainly caused by an internal tumor mechanism (i.e., endogenous induction) rather than adaptive immune response [13]. The study has the following limitations: This study was a retrospective design, the majority of patients (7/12) lacked postoperative systemic or local treatment, and the sample size was small, which may have also affected the lack of statistical significance of the association between $CD8^+$ TILs in the stroma and the OS.

Previous study has compared the differences in the immune microenvironment between primary lung cancer (including lung adenocarcinoma and SCLC, among others) and matched brain metastases, and found that brain metastases lose the PD-L1 expression and TILs present in the primary lesions [14]. The positivity of PD-L1 expression in SCLC primary specimens has been inconsistently reported across different studies, ranging from 0 to 82%. We observed PD-L1 expression in 25% of SCLC brain metastases, which is close to the average estimated PD-L1 positive rate of 26% reported in the literature [15]. In non-small cell lung cancer (NSCLC) brain metastases, spatial differences in the distribution of TILs in brain metastases have also been reported; that is, the density of TILs in the stroma of brain metastases was higher than that in the parenchyma [16]. Regarding the relationship between PD-L1 expression in brain metastases and patient survival, various degrees of correlation have been observed across studies. This inconsistency may be related to differences in PD-L1 antibodies, the definition of the critical value, sample size, and sampling location [17].

PD-L1 expression has been proposed as a predictive marker of ICI efficacy in NSCLC [18]. In contrast, there are no predictive molecular markers for SCLC, and data on SCLC brain metastases regarding PD-L1 expression and characterization of TILs are scarce. PD-L1 expression appears to be lower in patients with metastatic SCLC than in those with NSCLC, and its predictive role has not been demonstrated [19]. When we compared the OS among different subgroups, we found that patients with a positive rate of $CD3^+$ TIL stromal infiltration had a significantly longer median OS. These findings suggest that stromal $CD3^+$ TIL infiltration may serve as a prognostic marker for SCLC brain metastasis and provide possible directions for the design of future prospective clinical studies.

## Conclusions

In summary, we investigated the tumor microenvironment of SCLC brain metastasis using an immunofluorescence-based tissue MAP. Our findings suggest that TILs are poorly distributed in SCLC brain metastases and are most prominent in the stroma. Moreover, we found that PD-L1 positivity rate was low in this type of tumor tissue and that TILs correlated with OS. These findings could provide a rationale for studying PD-L1 expression and TIL infiltration in the brain. Furthermore, our results suggest potential biomarkers for future immunotherapy studies incorporating patients with brain metastases. As this study included a retrospective design with a small sample size of patients including only two treated with ICI, future research with a larger sample is needed to explore the efficacy and biomarkers of ICIs in the treatment of patients with SCLC and brain metastases.

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## Footnote

*Reporting Checklist:* The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-552/rc

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*Peer Review File:* Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-552/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-552/coif). M.T.M. receives royalties from Wolters Kluwer (UpToDate), outside this study. The other 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). The study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (No. PJ2024-02-31). Individual consent for this retrospective analysis was waived.

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