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Pathologic responses to neoadjuvant chemoimmunotherapy in primary limited-stage small-cell lung cancer

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Abstract

Background: Immunotherapy has been proved to have a large effect on extensive-stage small cell lung cancer, but the role of immunotherapy in limited-stage small-cell lung cancer (LS-SCLC) is still unknown.

Methods: A retrospective study of six patients with LS-SCLC who were treated with neoadjuvant chemoimmunotherapy (durvalumab plus etoposide combined with cisplatin) was performed. Patients were evaluated by the safety, feasibility and pathologic responses of neoadjuvant chemoimmunotherapy.

Results: Neoadjuvant durvalumab combined chemotherapy was associated with few immediate adverse events and did not delay planned surgery. All patients achieved partial pathologic response (pPR) instead of major pathologic response, or pathologic complete response. No association was observed between programmed death-ligand 1 expression in tumor specimens and the pathologic response. However, tumors with high expression of immune cells such as CD4+ T cells, CD8+ T cells and FoxP3+ Tregs tended to have better pathologic responses than tumors with low expression of immune cells.

Conclusions: Neoadjuvant durvalumab combined chemotherapy could induce pPR with few side effects in resectable LS-SCLC. The immune cells in the tumor microenvironment might play an important role in neoadjuvant chemoimmunotherapy in resectable LS-SCLC.

KEYWORDS
limited-stage small-cell lung cancer (LS-SCLC), neoadjuvant chemoimmunotherapy, partial pathologic response, PD-L1, surgery

BACKGROUND

Small-cell lung cancer (SCLC) is a highly malignant tumor, accounts for 10–15% of all lung cancer pathologic types, and is divided into limited-stage small-cell lung cancer (LS-SCLC) and extensive-stage small-cell lung cancer (ES-SCLC).[1,2] Chemoradiotherapy was considered to be the main treatment for SCLC for a long time, but the risk of recurrence and metastasis remained high. However, recent retrospective studies have shown that the survival of early-stage SCLC with systemic chemotherapy after surgery is comparable to that of early-stage non-small-cell lung cancer (NSCLC).[3] Some data even show that the efficacy of surgery plus chemotherapy for stages II and IIIA SCLC is comparable to that of surgery for NSCLC of the corresponding stages. For the efficacy of surgery is far better than that of nonsurgical treatment,[4] the role of surgical treatment of LS-SCLC is underestimated in clinical practice. In addition to regular radiochemotherapy, immunotherapies that block the immune inhibition of programmed death 1 (PD-1) protein or programmed death-ligand 1 (PD-L1) have a huge effect in ES-SCLC,[5–7] and neoadjuvant chemoimmunotherapy induced a

Meng Lu and Ran Zhang contributed equally to this study.

major pathologic response (mPR) or even a pathologic complete response (PCR) in local advanced NSCLC in various clinical studies.[8–10] Therefore, based on the significant effect in ES-SCLC and local advanced NSCLC, neoadjuvant chemoimmunotherapy and radical surgery for LS-SCLC might have the advantage of improving prognosis.[5,11]

Durvalumab is a recombinant humanized anti-PD-L1 monoclonal antibody that blocks interactions between PD-1 and its ligands, and previous clinical trials have shown that durvalumab achieved a good effect in ES-SCLC with few side effects.[11,12] Durvalumab was therefore approved in China for ES-SCLC by the Chinese Center for Drug Evaluation in 2018, but its role in LS-SCLC is still unknown.[7,13] The safety and feasibility of neoadjuvant chemoimmunotherapy in local advanced NSCLC patients have also been proved in several studies,[9,14] but there have been no studies reported on neoadjuvant chemoimmunotherapy in LS-SCLC. Herein, we characterized the pathologic features of neoadjuvant chemoimmunotherapy in patients with LS-SCLC, report the clinical factors that might influence the pathologic response, and aim to provide the basis for improved treatment of LS-SCLC.

METHODS

Patient selection and data collection

We performed a retrospective study of six patients with LS-SCLC. All of these patients were in good physical

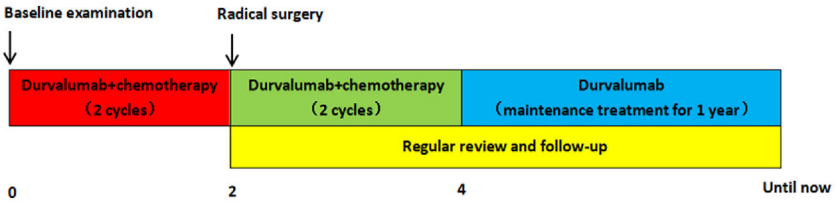

FIGURE 1 Timelines of patients

TABLE 1 Clinicopathological characteristics of all patients

Patient no.	1	2	3	4	5	6
Age/sex	58/M	45/F	60/M	56/M	40/F	54/M
Smoking index	300	–	400	600	–	800
Pre-neoadjuvant radiographic size (cm)	2.4	5.6	1.5	2.6	5.4	3.1
TNM classification	T2aN2M0	T3N2M0	T1bN2M0	T1cN2M0	T3N2M0	T2aN2M0
Clinical stage	IIIA	IIIB	IIIA	IIIA	IIIB	IIIA
Effect of neoadjuvant therapy	PR	PR	SD	PR	PR	SD
Gross pathologic size (cm)	1.5	1.0	2.0	1.0	1.8	3.0
Pathological stage	IIB	IIIA	IA2	IIIA	IIIA	IIIA
%RVT in primary tumor	25%	58%	72%	54%	30%	80%
Pathologic response	pPR	pPR	pPR	pPR	pPR	pPR
Cell density of CD4+ T cells (/mm^2)	1103	38	333	31	2148	129
Cell density of CD8+ T cells (/mm^2)	906	169	204	8	402	30
Cell density of FoxP3+ Tregs (/mm^2)	170	22	56	6	115	11
%PD-L1 in tumor cells	5	6	0	3	0	0
%PD-L1 in immune cells	42	40	25	20	20	3
Type of resection	Single lobectomy	Complex lobectomy	Single lobectomy	Single lobectomy	Complex lobectomy	Bilobectomy
Surgical approach	OPEN	VATS	OPEN	VATS	OPEN	OPEN
Time between neoadjuvant therapy and surgery (days)	35	33	44	31	30	38
Postoperative hospital stay (days)	4	4	5	3	6	5
Follow-up time (months)	7	23	22	19	17	17
Survival status	No	Yes	Yes	Yes	Yes	Yes
Relapse status	No	No	No	No	No	No

Abbreviations: OPEN, open thoracotomy; VATS, video-assisted thoracic surgery.

condition and were willing to have surgery at the initial diagnosis. In view of previous studies that suggested the value of surgery in LS-SCLC and the fact that immunotherapy has demonstrated great pathological benefits in locally advanced NSCLC and ES-SCLC, all of these patients were strongly in favor of neoadjuvant chemoimmunotherapy and surgical treatment after sufficient preoperative communication. All procedures performed in this study were in accordance with the Declaration of Helsinki and approved by the Tianjin Medical University Cancer Hospital Institutional Review Board.

All patients received two cycles of neoadjuvant chemoimmunotherapy (i.e. intravenous durvalumab plus chemotherapy [etoposide combined with cisplatin, EP] every 3 weeks) followed by R0 resections (4–6 weeks after the last dose of chemoimmunotherapy), then received two cycles of adjuvant chemoimmunotherapy after surgery. After four cycles of chemoimmunotherapy, all the patients received maintenance treatment of durvalumab alone for 1 year and had regular reviews including chest and abdominal CT, tumor markers, and brain MRI every 2–4 months (Figure 1). Safety was evaluated by the severity of adverse effects and feasibility was evaluated by the time of pre-operative preparation and post-operative recovery. The treatment effects of tumors were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) based on the Response Evaluation Criteria in Solid Tumors, version 1.1.[15,16]

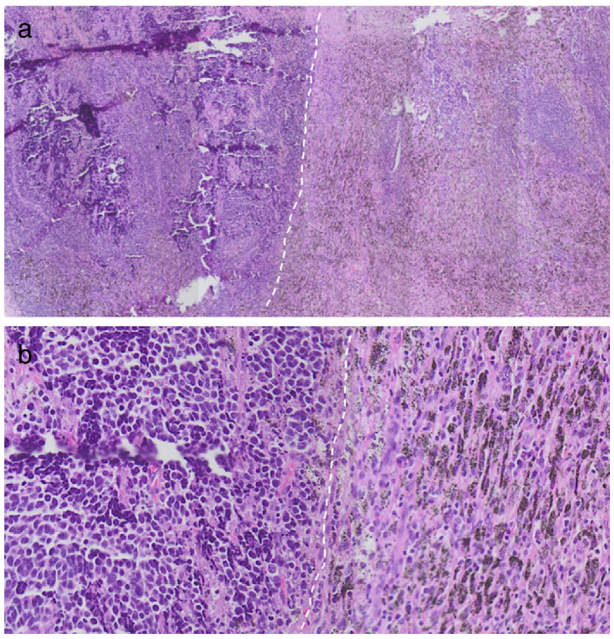

FIGURE 2 Representative pathologic responses to neoadjuvant durvalumab plus chemotherapy in primary tumor specimens of LS-SCLC (patient 5). (a) The characteristics of pathologic response at ×20 magnifications. (b) The characteristics of pathologic response at ×100 magnifications. The white dotted line separates the tumor cells from the degenerated tissues. The left side indicates the tumor cells, the right side indicates the degenerated tissues such as lymphocytes

Gross pathologic examination and histologic assessment

All tumor tissues were sectioned and each tumor slide was assessed. Two pathologists evaluated the average percentage of residual viable tumor cells (RVT), which was determined by the ratio of tumor area to tumor bed area in all slides. Hematoxylin and eosin (HE) stained slides from tumors were assessed histologically based on the immune-related pathologic response criteria (irPRC),[17] which defined the

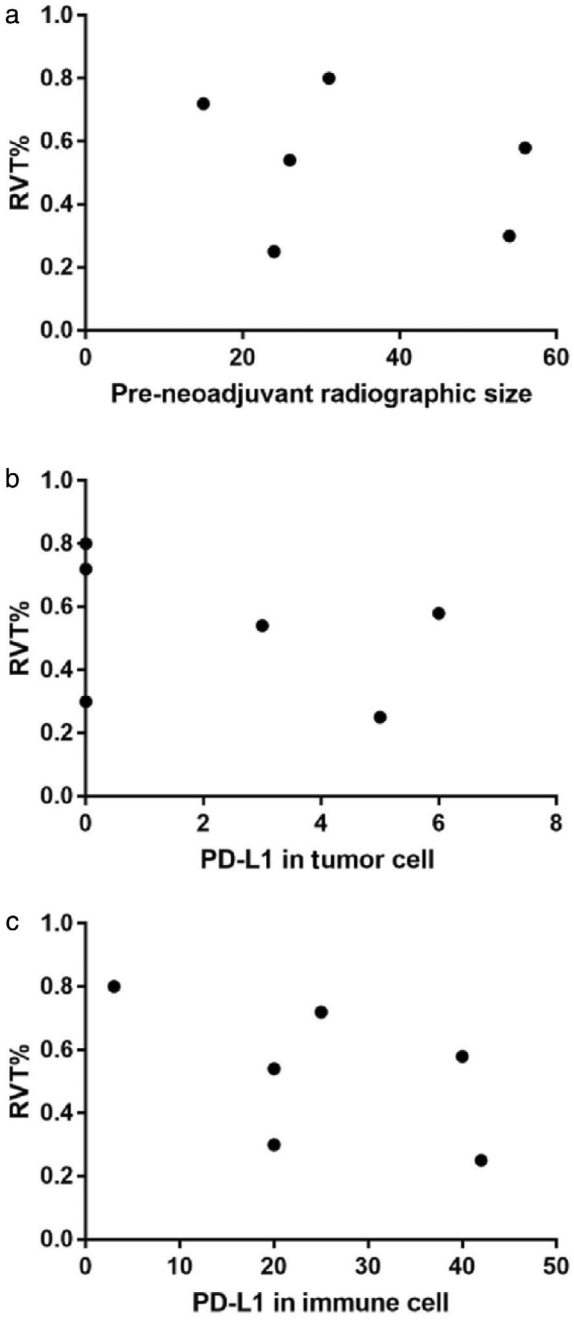

FIGURE 3 Correlation of pathologic response with pre-neoadjuvant radiographic tumor size (A) and the PD-L1 expressions of the primary tumor (B, C). Each dot indicates one patient

tumor regression bed as a major feature of pathologic response, specifically accompanied by fibrosis with neovascularization and immune cell proliferation. In this system, the tumor bed is defined as the regression bed, the RVT, and the necrosis. Tumors were grouped as having a PCR (absence of any viable invasive tumor cells), mPR (% RVT ≤ 10%), partial pathologic response (pPR, 10% < % RVT < 90%) and no pathologic response (nPR, % RVT ≥ 90%) according to the %RVT.

Immunohistochemistry

The primary tumors were made into consecutive slides of 5 μm thickness, and all tissue sections were deparaffinized, rehydrated, and pretreated for antigen retrieval. PD-L1 was analyzed by immunohistochemistry using the Monoclonal Rabbit Anti-Human PD-L1 clone SP263 (Ventana, Roche). Furthermore, fluorescence staining was conducted on immune cells with primary antibodies (CD4 [Clone EPR6588, ab133616; Abcam], CD8 [Clone EPR22483-288, ab245118; Abcam], and FoxP3[Clone 236A/E7, ab20034; Abcam]). The cell densities of these immune cells in resected tumors were calculated.

Statistical analysis

All data were analyzed using SPSS 23.0 (IBM Corporation). The correlation between clinicopathological factors and

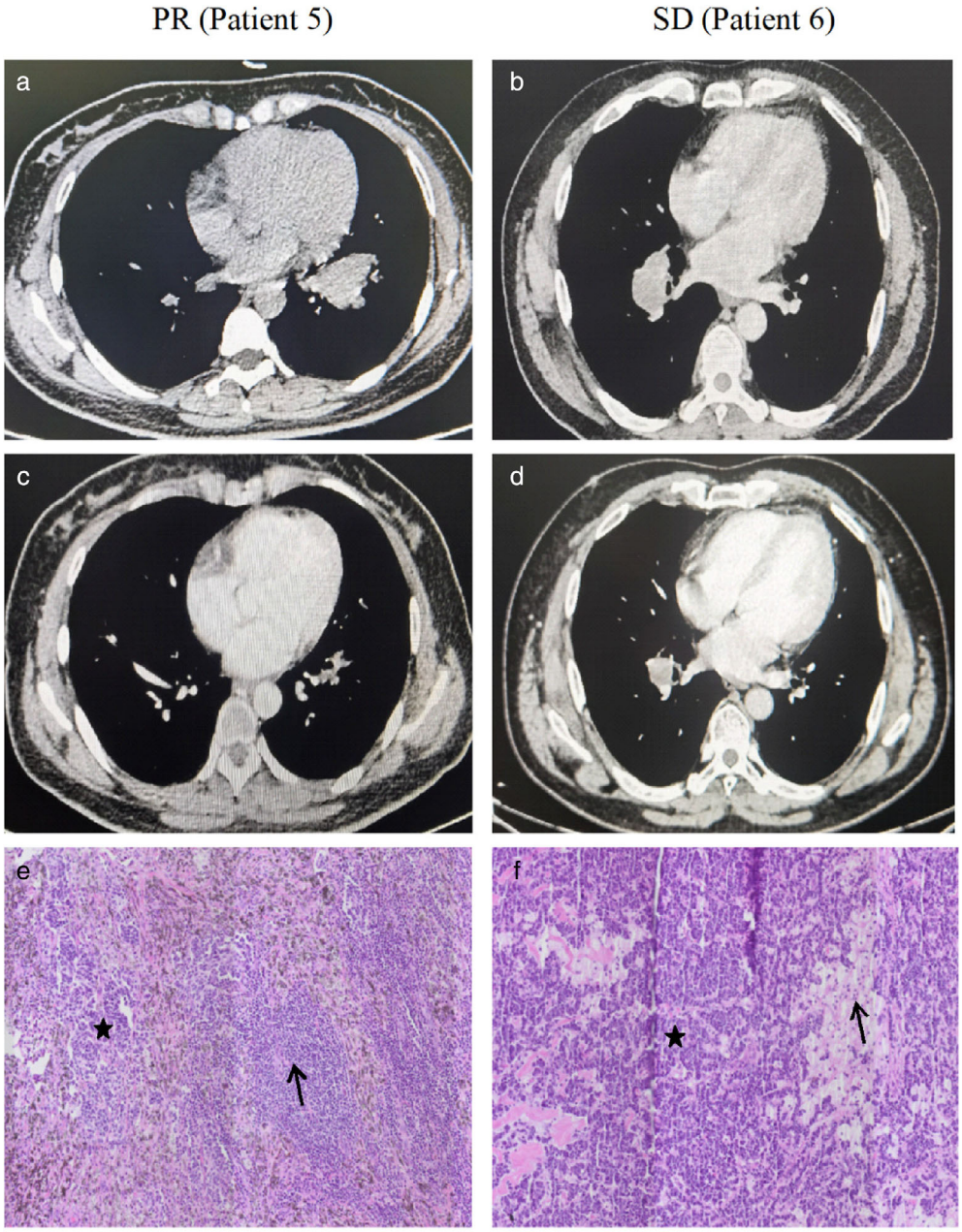

FIGURE 4 Patterns of radiologic and pathologic response to neoadjuvant chemoimmunotherapy. Left column: patient 5 (PR), 30% of RVT in the resected specimen; right column, patient 6 (SD), 80% of RVT in the resected specimen. (A, C) Chest CT imaging of patient 5 before and after the administration of neoadjuvant chemoimmunotherapy. (E) Representative sections of tumor specimens after HE staining in patient 5. (B, D) Chest CT imaging of patient 6 before and after the administration of neoadjuvant chemoimmunotherapy. (F) Representative sections of tumor specimens after HE staining in patient 6. The black star indicates the RVT and the black arrow indicates the lymphocytes. Magnifications×20

pathologic response was conducted by the Pearson's correlation coefficient test, all p values were based on a two-sided hypothesis, and $p < 0.05$ was considered statistically significant.

RESULTS

Safety and feasibility

Six patients who were diagnosed with resectable LS-SCLC received neoadjuvant chemoimmunotherapy and R0 resections in our department from July 2020 to July 2021. All patients underwent baseline tumor staging and were clinically staging IIIA–IIIB (resectable IIIB, T3 or T4) preoperatively. The clinicopathological characteristics of all patients are listed in Table 1. The median age of the patients was 52.17 ± 7.91 (40–60) years, and 66.7% (4/6) were male and long-term smokers. Neoadjuvant durvalumab combined EP did not induce any severe toxic effects in patients, and all patients were discharged from hospital within 1 week after surgery without severe surgical complications. The median time between the last administration of chemoimmunotherapy and radical resection was 35.2 (range 30–44) days, and no surgical delays occurred. Until September 2022, after a median of 18 (range 7–23) months of postoperative follow-up, 83.3% (5/6) of patients were alive. One patient died 7 months after surgery because of severe pneumonia induced by bacterial infection (patient 1). No patients were diagnosed with any tumor relapses during the follow-up time.

Features of pathologic response in primary tumors

The RVT differed in various cases. The %RVT incresed from 25% (patient 1) to 80% (patient 6), with a median percentage of 53 ± 22%. Although there was no PCR or mPR in primary tumors, all achieved pPR in postoperative tumor specimens with no nPR, and infiltrating lymphocytes were widely distributed in tumor microenvironments (Figure 2). As Figure 3 shows, the radiographic tumor sizes before neoadjuvant chemoimmunotherapy had no relationship with %RVT in resected tumors, and no associations between PD-L1 expression and %RVT were found, while both PD-L1-positive and PD-L1-negative tumors achieved pPR. However, tumors with radiographic PR had a better pathologic response (%RVT 42 ± 17%) than tumors with SD (%RVT 76 ± 6%) ($p = 0.006$) (Figure 4).

Fluorescence staining of immune cells

Fluorescence staining was performed to explore the variations of immune cells (CD4+ T cells, CD8+ T cells, and FoxP3+ Tregs) after neoadjuvant chemoimmunotherapy, and the cell densities of these immune cells in the tumor microenvironments were analyzed. The scatter diagram in Figure 5 indicates that the inflamed tumor microenvironment after neoadjuvant chemoimmunotherapy showed pathological benefit, and the immunofluorescence staining showed that tumors with abundant CD4+, CD8+, and FoxP3+ Tregs tended to have a lower %RVT after neoadjuvant chemoimmunotherapy (Figures 6–8).

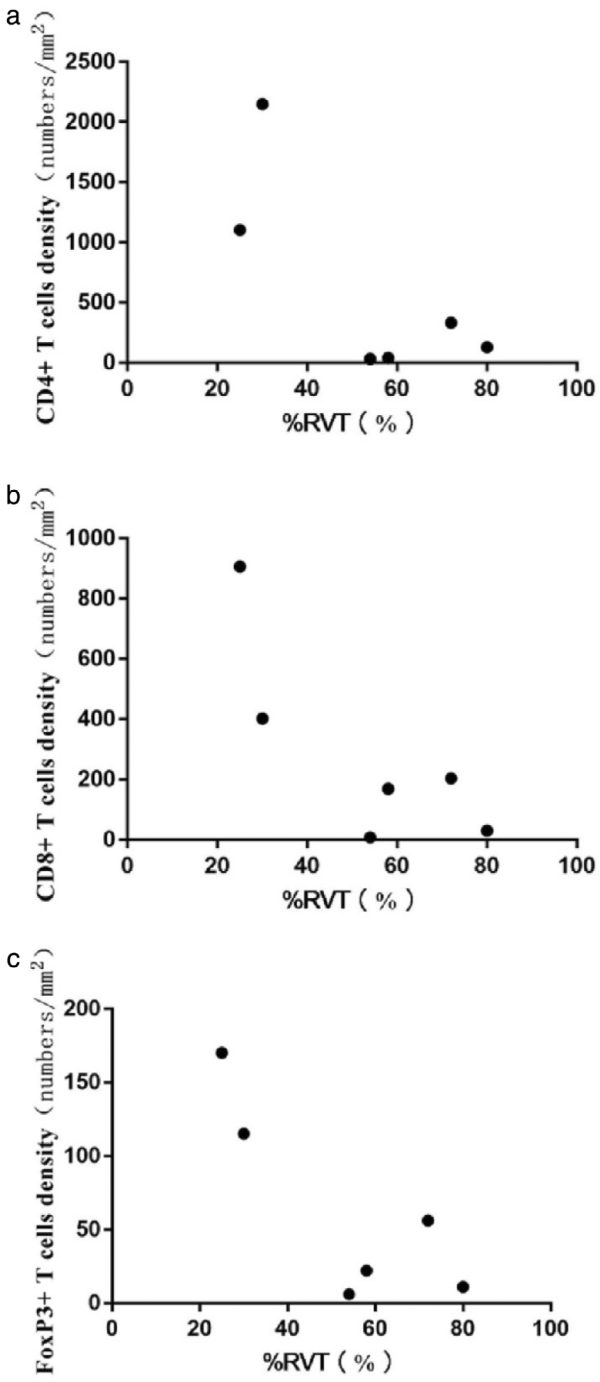

FIGURE 5 Scatter diagram of the correlation of immune cells with % RVT. (a) Correlation of CD4+ T cells with %RVT. (b) Correlation of CD8+ T cells with %RVT. (c) Correlation of FoxP3+ Tregs with %RVT

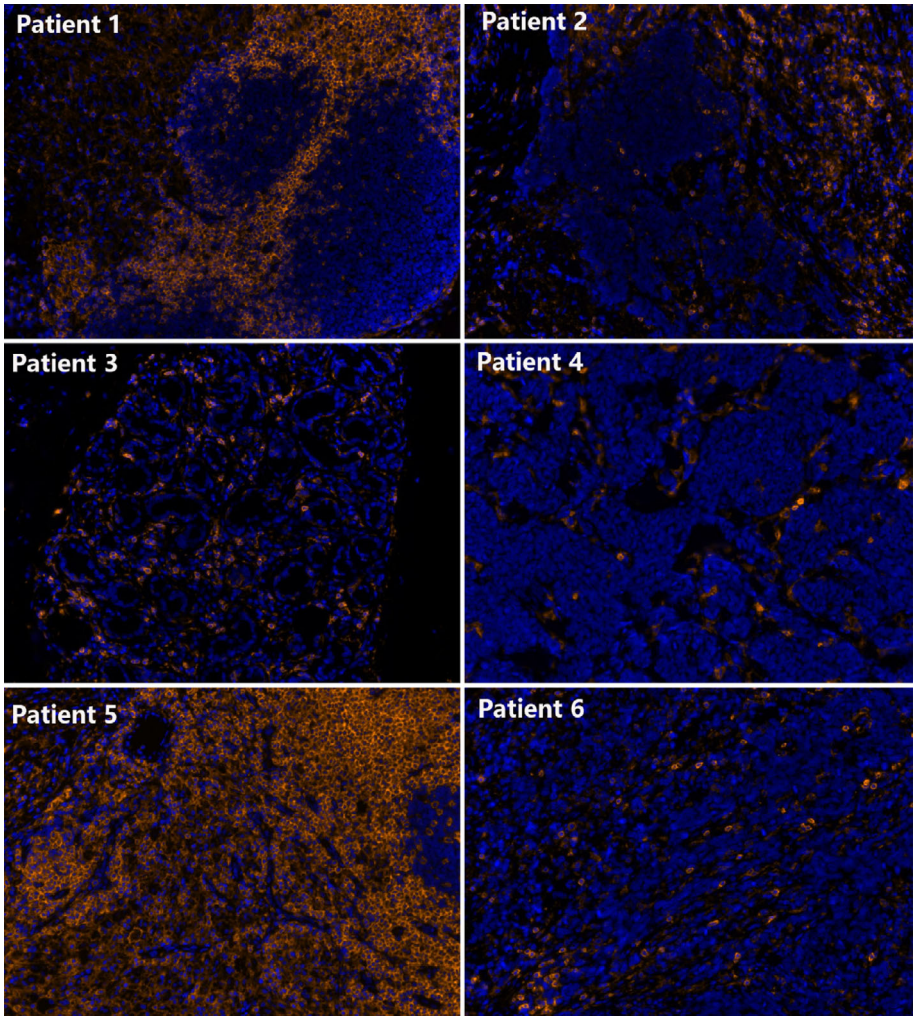

FIGURE 6 Immunofluorescent staining of immune cells to neoadjuvant chemoimmunotherapy in resected primary tumors. The orange fluorescence indicates the CD4+ T cells

DISCUSSION

SCLC is an extremely malignant type of lung cancer and is not sensitive to conventional treatment such as chemoradiotherapy.[18,19] Chemotherapy alone had low effectiveness in ES-SCLC, whereas the combination with immunotherapy significantly improved the survival rate in ES-SCLC.[18,20–22] Radical surgery plus adjuvant chemotherapy is the routine treatment for limited T1-2N0 LS-SCLC, but the long-term prognosis is still unsatisfactory.[20,23,24] Nowadays immunotherapy combined with chemotherapy provides the synergistic effect in local-advanced NSCLC,[8] and thus provides a basis for the application of immunotherapy in LS-SCLC.

As reported before, neoadjuvant chemotherapy promoted earlier elimination of micrometastatic diseases, reduced the surgery risks, and improved tolerability to treatment in patients with NSCLC.[10,25] In this study, the neoadjuvant durvalumab plus chemotherapy (EP) in patients with staging IIIA–IIIB LS-SCLC resulted in few adverse events and did not delay the anticipated surgery. Only one patient encountered severe pneumonia induced by the bacteria infection 7 months after surgery, which had no direct relationship with the chemoimmunotherapy. The evaluation of the pathologic response ratio after neoadjuvant therapy allowed the early estimation of curative efficacy, and potentially predicts disease-free (DFS) and overall survival (OS).[26] Clinical trials reported that neoadjuvant chemoimmunotherapy achieved a mPR in 46–83% and a PCR in 38–56% of patients with NSCLC,[8,14] but chemoimmunotherapy hardly achieved mPR in LS-SCLC, as shown in our study. However, Li *et al.*[27] reported PCR after receiving neoadjuvant durvalumab combined chemotherapy in one LS-SCLC patient, and Yan *et al.*[28] reported that neoadjuvant atezolizumab combined with chemotherapy significantly improved PCR in LS-SCLC without unknown adverse events and no surgical delays. These two studies also provide hope for neoadjuvant chemoimmunotherapy in LS-SCLC. All patients in this study had less than 90% RVT in tumor beds and achieved pPR, consistent with the phenomena of immunologic activation and tumor necrosis. No tumor relapses occurred during the follow-up period. The prognosis statistics and the efficacy of neoadjuvant chemoimmunotherapy for LS-SCLC needs to be further assessed in the future.

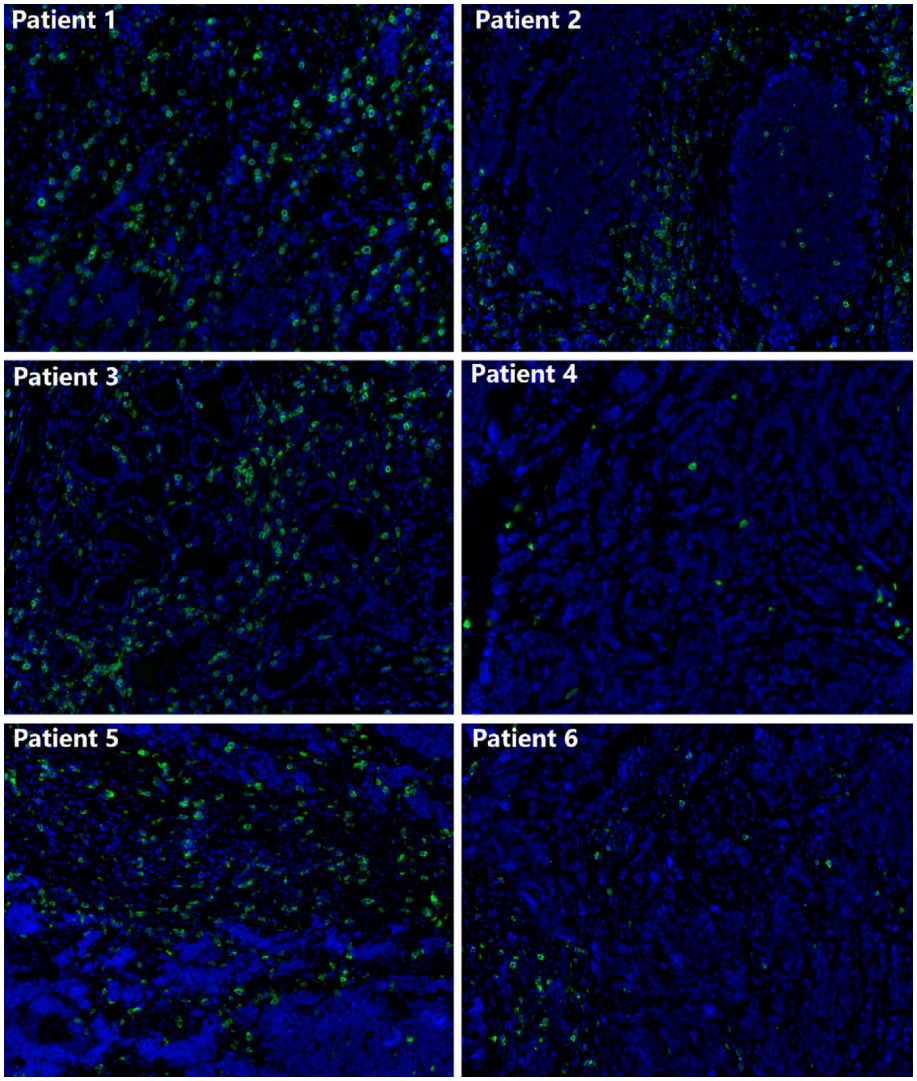

FIGURE 7 Immunofluorescent staining of immune cells to neoadjuvant chemoimmunotherapy in resected primary tumors. The green fluorescence indicates the CD8+ T cells

We also studied the dynamic changes in response to neoadjuvant chemoimmunotherapy, such as the changes in tumor size. Of these six patients, four achieved radiographic PR and two achieved radiographic SD. The tumors with PR had a better pathologic response than tumors with SD ($p = 0.006$), which indicates that the pathologic regression after chemoimmunotherapy was consistent with the radiographic changes. The PD-L1 expression levels in tumor cells were extremely low in all patients, and the PD-L1 expression had no significant relationship with the pathologic response (%RVT), indicating that PD-L1 expression might not be a good predictor for pathologic response in LS-SCLC.

As reported in previous research, the therapeutic effect of immunotherapy was closely related to the tumor's immune microenvironment. If the immune cells in tumor's microenvironment were in the state of extreme deficiency, the immune checkpoint inhibitors could hardly come into play.[29,30] Our study revealed that the immune cells, including CD4+ T cells, CD8+ T cells, and FoxP3+ Tregs, could influence the pathologic response. Tumors with higher expression of immune cells presented a lower %RVT, indicating that the inflamed tumor environment increased the pathologic response and played a key role in immunotherapy in LS-SCLC.

The study had some drawbacks. First, the sample size was small, which might influence the statistical data. Second, only a short postoperative follow-up period was included due to time limitations, thus the prognosis of all patients needs to be evaluated in the future. However, the study preliminarily confirmed the safety and feasibility of radical surgery after neoadjuvant durvalumab plus chemotherapy (EP) in IIIA–IIIB LS-SCLC for the first time, and also confirmed that tumors with radiographic PR presented a better pathologic response to neoadjuvant chemoimmunotherapy, which will be of great value in screening out patients who are not suitable for surgery in the future. It is necessary to continue long-term studies to evaluate whether or not the pPR could translate into prolonged DFS or OS, and the relationship between %RVT and prognosis.

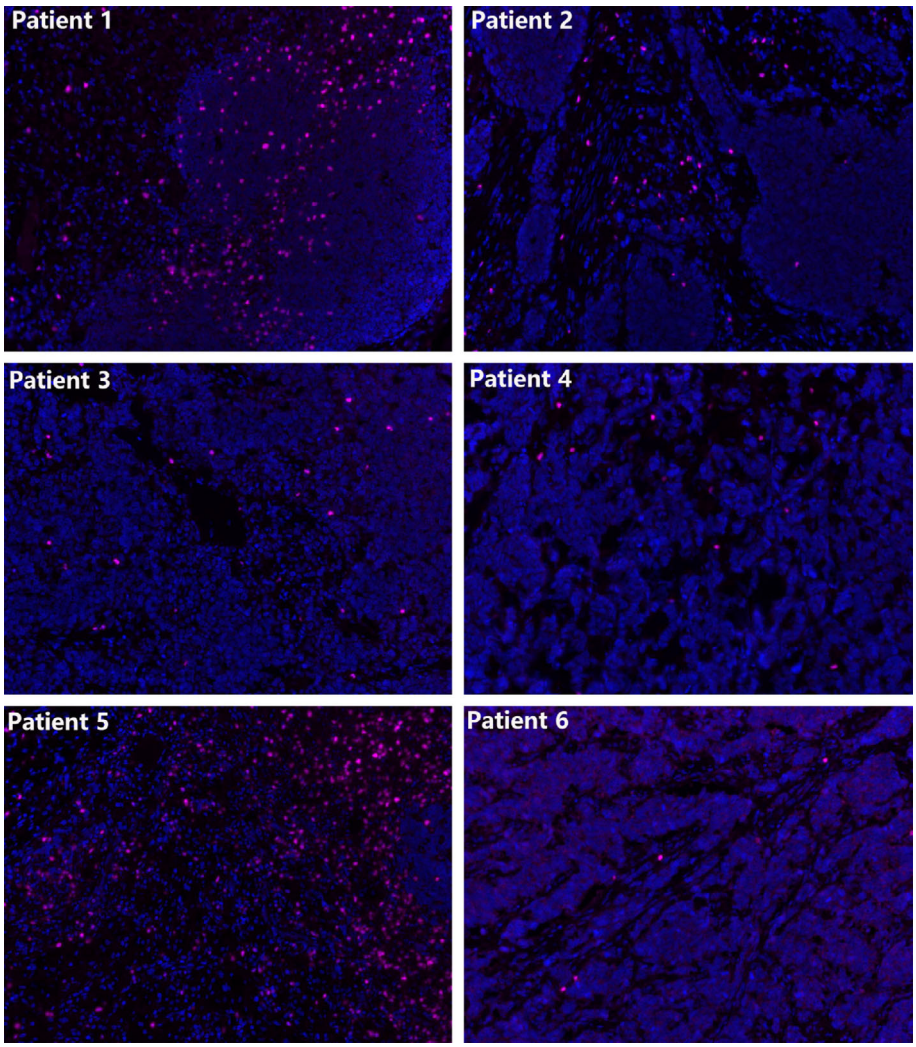

FIGURE 8 Immunofluorescent staining of immune cells to neoadjuvant chemoimmunotherapy in resected primary tumors. The pink fluorescence indicates the FoxP3+ Tregs

CONCLUSION

In summary, this study found that neoadjuvant durvalumab plus chemotherapy achieved pPR with few side effects in resectable LS-SCLC. More significantly, we confirmed that the inflamed tumor microenvironment was associated with a lower %RVT in primary tumors, indicating that the immune cells might play an important role in chemoimmunotherapy in LS-SCLC. These findings will help surgeons to recognize patients who are sensitive to neoadjuvant chemoimmunotherapy and therefore develop a personalized treatment plan for resectable LS-SCLC.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization: Meng Lu and Jian You. Methodology: Li-sha Qi and Ya-lei Wang. Investigation: Meng Lu and Li-sha Qi. Formal analysis: Ran Zhang and Xiao-xuan Sun. Resources: Ran Zhang and Jian You. Writing – original draft: Meng Lu and Ran Zhang. Writing – reviewing and editing: Meng Lu, Xiao-xuan Sun, and Jian You. Visualization: Li-sha Qi. Supervision: Xiao-xuan Sun. Funding acquisition: Jian You.

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Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

FUNDING STATEMENT

Not applicable.

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