Original Article

Neoadjuvant immunochemotherapy demonstrated improved efficacy and comparable safety to neoadjuvant chemotherapy for limited-stage small-cell lung cancer: a cohort study

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Background: Small-cell lung cancer (SCLC) accounts for 10–15% of all lung cancers. Neoadjuvant therapy followed by surgery has been applied in treatment of limited-stage SCLC (LS-SCLC). The synergistic effect of neoadjuvant immunochemotherapy (NIC) has been validated in the treatment of non-small cell lung cancer (NSCLC). Therefore, we compared the safety and efficacy between NIC and neoadjuvant chemotherapy (NC) for treating LS-SCLC.

Methods: This retrospective study included 10 patients diagnosed with LS-SCLC (stage I–IIIB) from 2019 to 2021. Five patients received NIC, while the other five received NC. Patients received two cycles of etoposide and cisplatin chemotherapy (EP) regimen (75 mg/m^2 of cisplatin and 160 mg/m^2 of etoposide) with or without immunotherapy (durvalumab or pembrolizumab) every 3 weeks before surgery. Imaging evaluation was performed before neoadjuvant therapy and surgery. Imaging and pathological tumor response, neoadjuvant treatment-related adverse events, perioperative information, and complications were evaluated. The follow-up data were obtained from the regular reviews in hospital and by telephone. The follow-up was terminated at December 2023 or if the patient died or experienced recurrence.

Results: The objective response rate (ORR) was 80% (4/5) in the NIC group and 100% (5/5) in the NC group. No patients experienced progressive disease (PD). Patients in the NIC group achieved more improvement of pulmonary function than did those in the NC group. All NIC and NC patients had R0 resection. No significant difference in surgical information was found between the two groups. One of the five patients in the NIC group experienced alveolopleural fistula, while one of the five patients in the NC group experienced respiratory failure postoperatively and died thereafter. One patient in the two groups was diagnosed with hydrothorax after tube removal. Pathological downstaging occurred in 4 patients in the NIC group and 2 patients in the NC groups. The rate of pathological complete remission (pCR) and major pathological response (MPR) was 20% and 40% in the NIC group, respectively, while in the NC group, it was 20% and 20%, respectively. In one patient with NIC, adjuvant therapy was abandoned due to hepatic insufficiency. During the period of follow-up, one patient in the NIC group experienced brain metastasis 1 year after surgery, while one patient in the NC group was diagnosed with local lymph node metastasis and distant metastasis half a year later.

Conclusions: NIC might provide greater advantages in downstaging, pulmonary function improvement and pathological regression in patients with LS-SCLC than NC while providing similarly safety and surgical feasibility. These findings may help clinicians develop more individualized therapy. However, randomized controlled trials are required to further validate our findings.

Keywords: Small-cell lung cancer (SCLC); neoadjuvant immunochemotherapy (NIC); neoadjuvant chemotherapy (NC); surgery

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Introduction

Lung cancer is the most common malignancy worldwide and in China and has high morbidity and mortality (1). Small-cell lung cancer (SCLC) accounts for 10–15% of all lung cancers (2). According to the classification of the Veterans' Administration Lung Study Group, SCLC can be divided into limited-stage SCLC (LS-SCLC) [corresponding to stage I–IIIB of the tumor-node-metastasis (TNM) staging system] and extensive-stage SCLC (ES-SCLC; corresponding to stage IIIC–IV of the TNM staging system) (3).

Approximately one in three patients with SCLC present with LS-SCLC when diagnosed (4). It is widely accepted that surgery plus adjuvant chemotherapy is suitable for patients with $T_{1-2}N_0M_0$ LS-SCLC (5,6). Patients can gain longer overall survival (OS) than can those treated with concurrent chemoradiotherapy or surgery alone (7-9). Despite considerable effort had been made to develop a more applicable therapy for LS-SCLC, the survival is not satisfactory, with a 2-year OS rate of <50% (10). Thus, a more effective treatment modality is urgently needed.

Neoadjuvant therapy is widely applied in clinical practice due to its ability to shrink tumor size, downstage disease, provide greater opportunity for R0 resection, and obtain a longer OS. Recently, neoadjuvant chemotherapy (NC) followed by surgery has been applied in LS-SCLC due to its safety and feasibility. Some studies on NC have reported an objective response rate (ORR) of more than 80% (11) and a 5-year OS of 33–48% (12,13).

Immune checkpoint inhibitors (ICIs) have demonstrated noticeable efficacy in patients with SCLC. The CASPIAN (14) and IMPOWER-133 (15) trials indicated that immunotherapy plus chemotherapy in first-line therapy could yield longer progression-free survival (PFS) and OS than chemotherapy alone in patients with SCLC.

Several clinical trials (16) have also confirmed the synergistic effect of neoadjuvant immunochemotherapy (NIC) in treating non-small cell lung cancer (NSCLC), and some studies have also observed this effect for LS-SCLC (17,18). Other research (19,20) suggests that NIC confers greater advantage than NC in treating resectable patients with NSCLC. However, little is known regarding the administration of NIC in patients with LS-SCLC.

Therefore, in this study, we compared the data of patients with LS-SCLC receiving NIC or NC to better inform the treatment of this disease. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1256/rc).

Highlight box

Key findings

- Neoadjuvant immunochemotherapy (NIC), compared to neoadjuvant chemotherapy (NC), demonstrated improved efficacy and comparable safety among patients with limited-stage small-cell lung cancer (LS-SCLC).

What is known and what is new?

- Neoadjuvant therapy has been widely applied by clinicians for the treatment of LS-SCLC. However, the relative advantages of NIC over NC have not been examined.
- Our study examined the efficacy of the additional immune checkpoint inhibitors in neoadjuvant therapy for LS-SCLC, providing more improvement of pulmonary function, greater opportunity for clinical downstaging and pathological regression. Furthermore, no significant difference was found in safety and surgical feasibility between these regimens.

What is the implication, and what should change now?

- Our findings indicate that NIC is more suitable for treating patients with LS-SCLC than NC and can improve treatment outcomes. However, larger sample sizes in randomized controlled trials are needed to confirm these results.

Methods

Patient selection

This study retrospectively analyzed patients diagnosed with LS-SCLC (stage I–IIIB) from 2019 to 2021. All patients were in good physical health and received neoadjuvant therapy and surgery in Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Clinical Research Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (2024 No. 1102). Informed consent was taken from all individual participants. Patients' perioperative data were obtained from the Clinical Information System of Sir Run Run Shaw Hospital while the follow-up data were acquired from regular in-hospital visits and telephone inquiries. The follow-up was terminated in December 2023 or when the patient died or experienced recurrence.

Neoadjuvant and adjuvant therapy

Patients received two cycles of the etoposide and cisplatin chemotherapy (EP) regimen (75 mg/m^2 of cisplatin and 160 mg/m^2 of etoposide) with or without immunotherapy (durvalumab or pembrolizumab) every 3 weeks before surgery. The adjuvant therapy was followed dependent on the patients' physical condition and pathological response.

The safety was evaluated by the severity of adverse events (AEs). AEs were diagnosed on the basis of regular examinations, including weekly blood routine and biochemical examinations, in addition to thyroid function, myocardial enzyme spectrum, coagulation function, and electrocardiography findings. Skin reactions and gastrointestinal reactions were confirmed in accordance to patients' complaints and medical records.

Tumor response evaluation

Patients' data, including computed tomography (CT), bronchoscopy, abdominal ultrasound, brain magnetic resonance imaging, and positron emission tomography findings, were obtained before neoadjuvant therapy and operation. The eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging was used to assess the degree of cTNM, ycTNM, and ypTNM. Meanwhile, the evaluation of tumor response was performed according to the Response Evaluation Criteria in Solid Tumor version 1.1 (RECST 1.1). In this system, tumor response was classified as complete response (CR; disappearance of targeted lesions), partial response (PR; decline in targeted lesions of more than 30%), progressive disease (PD; enlargement of targeted lesions of more than 20%), and stable disease (SD; absence of CR, PR, or PD).

Surgical treatment

Lobectomy with lymph node dissection (more than two fields) was performed for all patients. The perioperative information was recorded in detail, such as length from second neoadjuvant therapy to surgery, duration of operation, amount of blood loss, postoperative complications, length of tube removal, and the length of in-hospital stay after surgery.

Pathological examination

Pathological reports, including depth of invasion, lymph node metastasis, and tumor regression proportion (TRP) were evaluated by two independent investigators. According to the College of American Pathologists and the National Comprehensive Cancer Network guidelines, TRP was defined as proportion of the remaining residual lesion. Pathological complete remission (pCR) was considered to be no remaining residual lesion. Major pathological response (MPR) was considered to be a TRP of ≤10%.

Statistical analysis

Continuous variables with a nonnormal distribution are expressed as the median value (range the lowest value to the highest one). Categorical variables are presented as the frequency and percentage. The sample size of this study was too small to draw conclusions regarding statistically significant differences. Therefore, all data are described in detail to clarify the difference between two groups.

Results

Basic characteristics of patients

This retrospective study included 10 patients (5 in the NIC groups and 5 in the NC group) diagnosed as LS-SCLC (stage I–IIIB) from 2019 to 2021 (*Figure 1*). The characteristics of all patients are displayed in *Table 1*. The mean age of patients in the NIC group was 61 years (range,

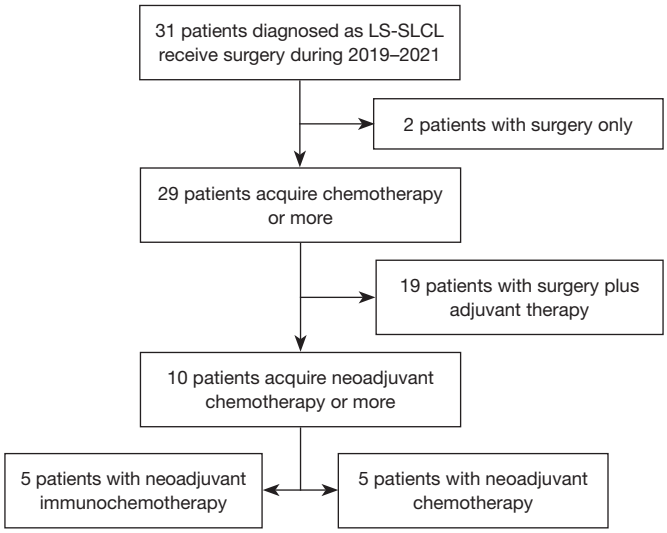

Figure 1 Selection of patients. LS-SCLC, limited-stage small-cell lung cancer.

Table 1 Baseline characteristics of patients

Characteristics	NIC (patient No.)					NC (patient No.)				
	1	2	3	4	5	1	2	3	4	5
Age (years)	68	56	66	70	45	71	72	65	57	62
Sex	M	M	M	M	M	M	M	M	M	F
Smoking index (pack-years)	None	None	40	50	25	50	50	40	45	None
Comorbidities										
Pulmonary disease	–	–	Y	–	–	–	Y	–	–	–
Cardiac disease	Y	–	–	–	–	–	–	–	–	–
Diabetes mellitus	–	–	–	–	–	–	–	–	–	–
Hypertension	Y	–	–	Y	–	–	–	–	–	–
Location	RUL	RLL	LUL	LUL	LUL	LUL	RUL	RLL	LUL	LLL
Histopathological confirmation method	Bron.	Bron.	Aspi.	Aspi.	Aspi.	Aspi.	Bron.	Bron.	Aspi.	Bron.
Neoadjuvant therapy	EP; Dur.	EP; Dur.	EP; Dur.	EP; Dur.	EP; Pem.	EP	EP	EP	EP	EP

Aspi., aspiration; Bron., bronchoscopy biopsy; Dur., durvalumab; EP, etoposide and cisplatin chemotherapy; F, female; LLL, left lower lobe; LUL, left upper lobe; M, male; NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; Pem., pembrolizumab; RLL, right lower lobe; RUL, right upper lobe; Y, with the corresponding comorbidity.

45–70 years), while that in the NC group was 65 years (range, 57–72 years). Only one patient in the NC group was female, while the remaining patients were male. The majority of patients were smokers (NIC: 3/5; NC: 4/5). None of the smoking index scores were lower than 25 pack-years. Bronchoscopy biopsy and aspiration were two methods adopted in the study to confirm the histopathological results. Durvalumab was selected as the ICI for 80% (4/5) of the patients in the NIC group, while the other ICI being pembrolizumab.

Radiographic response to neoadjuvant therapy

The radiographic response to the therapy is summarized

Table 2 Response to neoadjuvant therapy

Staging data	NIC (patient No.)					NC (patient No.)				
	1	2	3	4	5	1	2	3	4	5
Diameter (mm)										
Pretreatment	21	38	46	41	34	17	16	27	34	19
Presurgery	17	12	22	21	17	10	5	16	23	10
T staging										
Pretreatment	1	3	2	2	2	1	1	1	2	1
Presurgery	1	1	1	1	1	1	1	1	1	1
N staging										
Pretreatment	1	2	0	2	2	0	2	0	2	0
Presurgery	1	2	0	0	2	0	0	0	2	0
Clinical stage										
Pretreatment	IIA	IIIB	IIA	IIIA	IIIA	IA	IIIA	IA	IIIA	IA
Presurgery	IIA	IIB	IA	IA	IIB	IA	IA	IA	IIB	IA
Clinical response	SD	PR	PR	PR	PR	PR	PR	PR	PR	PR

NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; PR, partial remission; SD, stable disease.

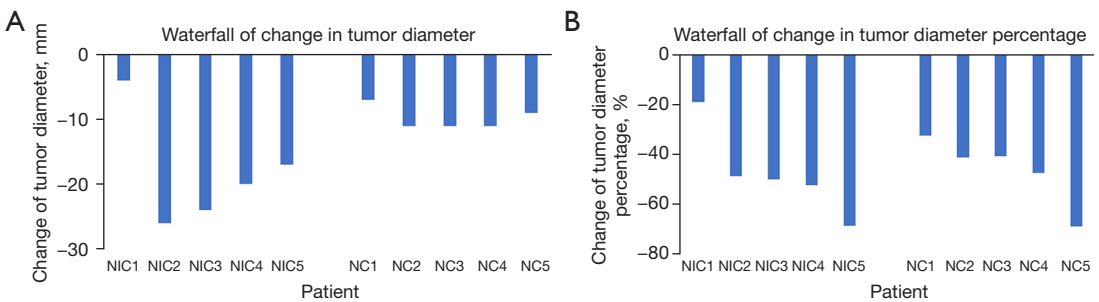

Figure 2 Change of maximum tumor diameter compared to baseline. (A) Change in transverse tumor diameter; (B) percentage change in transverse tumor diameter. NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy.

in *Table 2*. The tumor's diameter compared to the baseline values decreased in both the NIC and NC groups. Although the values of diameter shrinkage in the NIC group were larger than those in the NC group (*Figure 2A*), the percentage of the diameter shrinkage was similar (*Figure 2B*). Furthermore, downstaging of T staging was achieved in four patients in the NIC group and one patient in the NC group, respectively (*Figure 3A*,*3B*). One patient in each group had a lower N staging after neoadjuvant therapy (*Figure 3C*,*3D*). The number of patients in clinical stage IA before surgery is more than those before the neoadjuvant therapy. Response to the therapy was evaluated according RECIST 1.1. Four patients in the NIC group and all patients in the NC group experienced PR. Only one patient in the NIC group experienced SD.

Pulmonary function

Four patients in the NIC group and three in the NC group underwent pulmonary function tests before neoadjuvant therapy and surgery. The other three patients only received the test before the surgery. Two patients with NIC improved their pulmonary function, while two patients with NC experienced deterioration in pulmonary function (*Table 3*).

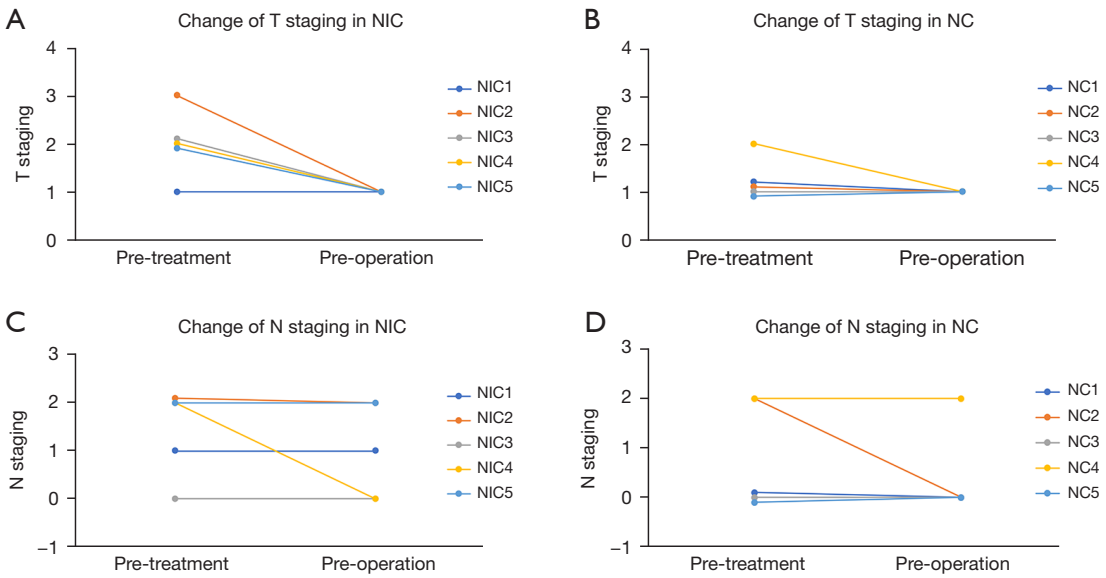

Figure 3 Change in T and N staging after neoadjuvant therapy. (A) T staging of NIC; (B) T staging of NC; (C) N staging of NIC; (D) N staging of NC. NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy.

Table 3 Pulmonary function response to neoadjuvant therapy

Diagnosis from PFT	NIC (patient No.)					NC (patient No.)				
	1	2	3	4	5	1	2	3	4	5
Pretreatment	Normal	Mild	Severe	Normal	–	Normal	Moderate to severe	Normal	–	–
Presurgery	Normal	Normal	Mild	Normal	Normal	Normal	Severe	Normal	Mild	Normal

NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; PFT, pulmonary function test.

The details of pulmonary change were presented in *Figure 4*.

Surgical outcome

The surgical outcomes are summarized in *Table 4*. The median time from the last administration of neoadjuvant therapy to radical surgery was 25 days (range, 22–34 days) in the NIC group and 29 days (range, 21–31 days) in the NC group. One patient in each group experienced AEs, with one patient experiencing hepatic insufficiency in the NIC group and one patient experiencing agranulosis in the NC group. No patients underwent a delay in surgery due to complications. All patients in the NIC group initially underwent video-assisted thoracoscopy surgery (VATS). Among the patients in the NC group, one underwent conversion to open surgery due to hemorrhage of the pulmonary artery. In terms of resection type, lobectomy was adopted in all patients of the NIC and NC groups except for one patient in the NIC group who received bilobectomy. In addition, 100% of patients in both groups had R0 resection. The median operation time in the NIC group was 160 minutes (range, 80–255 minutes), while that in patients in the NC group was 110 minutes (range, 80–220 minutes). During surgery, the median blood loss was 50 mL (range, 20–200 mL) in the NIC group and 50 mL (range, 20–500 mL) in the NC group. The median length of tube removal was 3 days (range, 3–9 days) in the NIC group. One patient experienced alveolopleural fistula postoperatively. In the NC group, 3 days (range, 2–13 days) were required for chest tube removal. One patient suffered respiratory failure postoperatively and died then. One patient among both groups was diagnosed with hydrothorax after tube removal and received additional chest tube intubation. Delayed tube removal and postoperative complications contributed to the long length of discharge after surgery. No rehospitalization after discharge was recorded in the two groups.

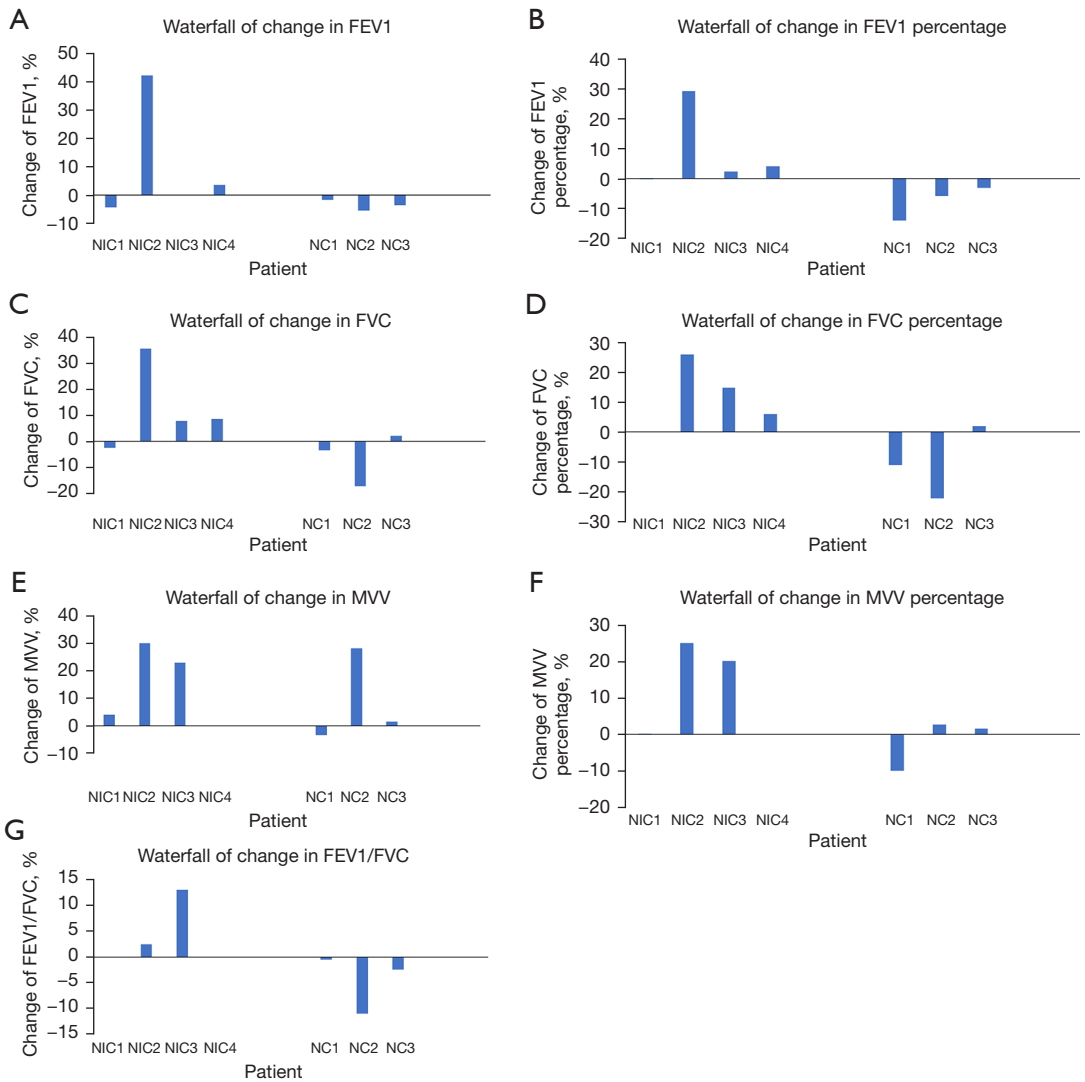

Figure 4 Change in pulmonary function after neoadjuvant therapy. (A) Change in FEV1; (B) FEV1 percentage; (C) FVC; (D) FVC percentage; (E) MVV; (F) MVV percentage; (G) FEV1/FVC. MVV, maximum voluntary ventilation; NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Pathological response to neoadjuvant therapy

The pathological results are displayed in *Table 5*. All patients in NIC group were staged as IIA–IIIB clinically before the treatment. Four of them achieved pathological downstaging after surgery, which means three patients staged as IA postoperatively and one patient staged from IIIB to IIB. Only two patients in NC group achieved downstaging. Tumor regression had been observed in all patients in both two groups. In NIC group, two patients achieved MPR and one achieved pCR. Meanwhile, one MPR (also pCR) was achieved in the NC group.

Postoperative therapy and prognosis

The postoperative data are presented in *Table 5*. All patients were planned to receive 4 cycles of adjuvant therapy. However, several patients deviate from the plan. Two patients in NIC group only received 2 cycles considering the unexpected complications after the surgery (show in *Table 4)*. One suffered hydrothorax and the other alveolopleural fistula. Both of their recovery was suboptimal and they agree to receive only two cycles postoperatively. One NIC patient discontinued adjuvant therapy on the basis that he complicated hepatic insufficiency with neoadjuvant therapy

Table 4 Surgical outcomes

Peri-operative data	NIC (patient No.)					NC (patient No.)				
	1	2	3	4	5	1	2	3	4	5
Days from last neoadjuvant therapy to surgery	22	25	25	26	34	21	30	31	29	26
Adverse effects of neoadjuvant therapy	–	–	–	Hepatic insufficiency	–	–	–	Agranulosis	–	–
Operation type	VATS	VATS	VATS	VATS	VATS	VATS	Open	VATS	VATS	VATS
Resected type	L	B-L	L	L	L	L	L	L	L	L
Curability	R0	R0	R0	R0	R0	R0	R0	R0	R0	R0
Operation (time/min)	160	144	255	215	80	90	220	145	80	110
Blood (loss/mL)	50	20	50	200	50	20	500	20	50	50
Time to tube removal (days)	3	3	4	3	9	2	13	4	3	5
Time to discharge after surgery (days)	5	11	5	5	10	12	18	5	4	7
Postoperative complications	–	Hydrothorax	–	–	Alveolopleural fistula	Hydrothorax	Respiratory failure	–	–	–
Rehospitalization after discharge	N	N	N	N	N	N	N	N	N	N

NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; VATS, video-assisted thoracoscopy surgery; L, lobectomy; B-L, bilobectomy; N, no rehospitalization.

(shown in *Table 4*) while pCR was evident by pathological report. In NC group, only one patient withdrew the treatment plan because he died due to respiratory failure 18 days after the surgery.

During the period of follow-up, one patient in the NIC group experienced brain metastasis 1 year after the surgery. His CT scan reported possible pulmonary artery invasion before neoadjuvant therapy and increased the possibility of metastasis. One patient in the NC group was diagnosed with local lymph node metastasis and distant metastasis half a year after surgery although no high-risk factor was figured out in the whole process.

Discussion

SCLC involves rapid growth, aggressiveness, early metastasis and poor prognosis (21). Although substantial efforts have been exerted toward its treatment, there remains a lack of satisfactory means to improving the radical treatment and prognosis of patients with LS-SCLC. Surgery is considered to be a necessary treatment in LS-SCLC (22,23), and neoadjuvant therapy has also been widely utilized by clinicians in practical treatment of SCLC. Studies have demonstrated the priority of NC (11) and NIC (17,18) in LS-SCLC. However, whether the addition of ICI can provide additional benefit has not been sufficiently examined.

Our exploratory study mainly focused on the perioperative effect of neoadjuvant therapy in LS-SCLC patients. ORR is one of the most commonly used indices for evaluating the effect. Lad *et al.* (24) reported that ORR of patients with LS-SCLC treated with NC was 66%. In this study, every patient presented with shrinkage of tumor mass and ORR reached 80% in NIC group and 100% in NC group. This discrepancy might result from the benefit conferred by the EP regimen. Lad *et al.* (24) chose cyclophosphamide, vincristine and doxorubicin for chemotherapy. Fujimori *et al.* (11) showed a high ORR (95.5%) with platinum-based chemotherapy. The similar ORR (84.2%) also presented by Liu *et al.* (18) who adopted NIC containing cisplatin and etoposide. Meanwhile, Liu found more preoperative therapy cycles brought more tumor size decreasing. Unfortunately, we could not provide evidence for this suggestion for only 2 cycles adopted. Besides, our study found downstaging of clinical stage in two groups after neoadjuvant therapy and more clinical

Table 5 Pathological results, postoperative treatment, and prognosis

Post-discharge data	NIC (patient No.)					NC (patient No.)				
	1	2	3	4	5	1	2	3	4	5
Clinical stage (cTNM)	IIA	IIIB	IIA	IIIA	IIIA	IA	IIIA	IA	IIIA	IA
Pathological stage (ypTNM)	IIA	IIB	IA	IA	IA	IA	IA	IA	IIB	IA
Tumor regression proportion (%)	70	60	0	10	70	50	0	80	70	70
Pathological response	–	–	pCR	MPR	–	–	pCR	–	–	–
Invasion										
STAS	–	–	–	–	–	–	–	–	–	–
Lymphovascular	–	Y	–	–	–	–	–	–	–	–
Neural	Y	–	–	–	–	–	–	–	–	–
No. of dissected lymph nodes	19	19	26	19	30	22	0	18	22	24
Adjuvant chemotherapy	EP	EP	EP	None	EP	EP	None	EP	EP	EP
Times of adjuvant chemotherapy	4	2	4	–	2	4	–	4	4	4
Adjuvant immunotherapy	Dur.	Dur.	Dur.	None	Pem.	–	–	–	–	–
Times of adjuvant immunotherapy	4	2	12	–	2	–	–	–	–	–
Length of relapse (days)	–	–	363	–	–	–	–	212	–	–
Location of relapse	–	–	Brain	–	–	–	–	Local lymph	–	–
Disease-free survival (days)	679	Missed	363	764	1,190	980	18	212	1,218	1,416
Overall survival (days)	679	Missed	Missed	764	1,190	980	18	Missed	1,218	1,416

Dur., durvalumab; EP, etoposide and cisplatin chemotherapy; MPR, major pathological response; NC, neoadjuvant chemotherapy; NIC, neoadjuvant immunochemotherapy; Pem., pembrolizumab; pCR, pathological complete remission; STAS, spread through air space; TNM, tumor-node-metastasis; Y, with the corresponding pathological invasion.

stage IA could lead to an increased possibility of radical resection.

In this study, no patient experienced a delay in scheduled surgery due to AEs from neoadjuvant therapy. VATS tended to be adopted by surgeons on the basis of lesion shrinkage. This was similar to the studies which compared the efficacy of NIC versus that of NC in patients with NSCLC (19,20). Some studies (25,26) assert that neoadjuvant therapy can increase the complexity of surgery based on the increased vascular fragility and local tissue adhesion. In our study, no difference was found in the operation time, blood loss, or time to tube removal and discharge between the two groups. Moreover, R0 resection was achieved in all patients. Therefore, our findings suggest that additional ICI does not cause excessive surgical complications. The safety and feasible of NIC was also supported by Fujimori (11) and other researchers (17,18). However, we could not draw the conclusion statistically based on the small sample size.

Pulmonary function has seldom been compared in studies of neoadjuvant therapy. We found that improvement of pulmonary function, as reflected by forced expiratory volume in 1 second (FEV1), FEV1%, and forced vital capacity (FVC), was achieved in the NIC group. This finding was consistent with the study of Zhu *et al.* (27) in NSCLC. We suggested that the combination of immunotherapy and chemotherapy could increase the surgical tolerability for patients with a history of poor pulmonary function. Unfortunately, our study only paid attention to the ventilation function and neglected the function of gas exchange.

Pathological response is considered capable of predicting disease-free survival and OS to some degree (28). Duan *et al.* (29) reported improved pCR in patients with LS-SCLC and NIC. Li *et al.* (30) also described a case in which pCR was achieved in a patient with LS-SCLC receiving neoadjuvant durvalumab plus chemotherapy. Mei *et al.* (31) found that

patients receiving neoadjuvant serplulimab combined with chemotherapy could achieve pCR. In this study, pCR (20%) was found in both NIC and NC groups, but MPR (40%) was more common in the NIC group (versus 20% in NC). The data of NIC resembled those reported by Liu *et al.* (18) (pCR 30%, MPR 40%), but were lower than those reported by Duan *et al.* (29) (pCR 61.5%, MPR 92.3%). This might partly result from the cycles of neoadjuvant therapy (3 for Duan *et al.* while 2 for others). According to the value of TRP, the NIC group achieved greater tumor remission from neoadjuvant therapy. Above all, we suggested the possible advantage of NIC over NC.

Chemotherapy has been widely administered in patients with LS-SCLC (6,32). The predominant regimen is platinum (cisplatin or carboplatin) with etoposide applied for four to six cycles. In this study, all participants in both groups received standard therapy except one NIC patient with pCR complained hepatic insufficiency and one NC patient died postoperatively. Among the survival, one patient in NIC experienced brain metastasis while one in NC group presented local lymph recurrence and distant metastasis. these might come from the limitation of our therapy as radiotherapy was abandoned by all participants. Radiotherapy had been verified its preponderance of local and distant relapse in LS-SCLC (33). It is recommended that the more suitable modality for LS-SCLC should be optimized.

This study involved certain limitations which should be discussed. First, the sample size was too small to conduct a meaningful statistical analysis. Second, as this was a retrospective study, the feasibility and safety of multimodality therapy for LS-SCLC could not be confirmed, and a randomized controlled trial would be more persuasive. Third, the neoadjuvant therapy in the NIC group was not executed in uniform fashion, as one patient selected pembrolizumab while the others used durvalumab. Finally, the collection of patient data was suspended when they relapsed or metastasis occurred. More information would contribute to clarifying the long-term effect of neoadjuvant therapy.

Conclusions

Compared with NC, NIC may confer greater advantages in clinical downstaging, improvement of pulmonary function and pathological regression in patients with LS-SCLC while providing similar feasibility and safety. These findings can help clinicians develop more individualized therapy. However, randomized controlled trials are required to further confirm our findings.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1256/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1256/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1256/coif). 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) and was approved by the Clinical Research Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (2024 No. 1102). Informed consent was taken from all individual participants.

References

1. Rudin CM, Ismaila N, Hann CL, et al. Treatment of small-cell lung cancer: American society of clinical oncology endorsement of the American college of chest physicians guideline. J Clin Oncol 2015;33:4106-11.
2. Abdelhamid K, Kakourou A, Degrauwe N, et al. Small-cell lung cancer: management and novelties. Rev Med Suisse 2020;16:1079-85.
3. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging 2012;11:253-8.
4. Wang S, Zimmermann S, Parikh K, et al. Current diagnosis and management of small-cell lung cancer. Mayo Clin Proc 2019;94:1599-622.
5. Guo X, Wang B, Sun J, et al. Role of surgery in potentially resectable small-cell lung cancer based on the eighth edition of the TNM classification: a population study of the us seer database. Clin Respir J 2024;18:e70024.
6. Huang JQ, Liang HW, Liu Y, et al. Treatment patterns and survival outcomes in patients with stage T1-2N0M0 small cell lung cancer undergoing surgery: a retrospective cohort study. World J Oncol 2024;15:126-35.
7. Yang CF, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-64.
8. Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. Ann Surg 2018;268:1105-12.
9. Chen F, Wang Z, Gu X, et al. Different treatment modalities on the prognosis of patients with stage I-IIIa small cell lung cancer: a population based study. J Thorac Dis 2024;16:2822-34.
10. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116-25.
11. Fujimori K, Yokoyama A, Kurita Y, et al. A pilot phase 2 study of surgical treatment after induction chemotherapy for resectable stage I to IIIA small cell lung cancer. Chest 1997;111:1089-93.
12. Brock MV, Hooker CM, Syphard JE, et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. J Thorac Cardiovasc Surg 2005;129:64-72.
13. Tsuchiya R, Suzuki K, Ichinose Y, et al. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: the Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101). J Thorac Cardiovasc Surg 2005;129:977-83.
14. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.
15. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-9.
16. Luchtenborg M, Riaz SP, Lim E, et al. Survival of patients with small cell lung cancer undergoing lung resection in England, 1998-2009. Thorax 2014;69:269-73.
17. Lu M, Zhang R, Qi LS, et al. Pathologic responses to neoadjuvant chemoimmunotherapy in primary limited-stage small-cell lung cancer. Thorac Cancer 2022;13:3208-16.
18. Liu J, Wang L, Shu W, et al. Safety and effectiveness of neoadjuvant immunotherapy combined with chemotherapy followed by surgical resection in patients with stage I-IIIA small-cell lung cancer: a retrospective single-arm clinical trial. J Thorac Dis 2022;14:4405-15.
19. Dai F, Wu X, Wang X, et al. Neoadjuvant immunotherapy combined with chemotherapy significantly improved patients' overall survival when compared with neoadjuvant chemotherapy in non-small cell lung cancer: A cohort study. Front Oncol 2022;12:1022123.
20. Zhao J, Hao S, Li Y, et al. Comparative efficacy and safety of neoadjuvant immunotherapy with chemotherapy versus chemotherapy alone in non-small cell lung cancer: a propensity score and inverse probability treatment weighting analysis. Immunotargets Ther 2023;12:113-33.
21. Raso MG, Bota-Rabassedas N, Wistuba, II. Pathology and classification of SCLC. Cancers (Basel) 2021;13.
22. Jia J, Trassl L, Kong F, et al. Improved survival of patients with stage III small-cell lung cancer with primary resection: A SEER-based analysis. Transl Oncol 2024;49:102070.
23. Li H, Song L, Zhou Y, et al. The effects of surgical resection in the treatment of limited-stage small cell lung cancer: a multicenter retrospective study. Updates Surg 2024;76:1483-92.
24. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest

1994;106:320S-323S.
25. Edelman MJ, Suntharalingam M, Burrows W, et al. Phase I/II trial of hyperfractionated radiation and chemotherapy followed by surgery in stage III lung cancer. Ann Thorac Surg 2008;86:903-10.
26. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
27. Zhu Y, Li JQ, Chang Q, et al. Impact of neoadjuvant immunotherapy on pulmonary function and perioperative outcomes in patients with resectable non-small cell lung cancer. Zhonghua Yi Xue Za Zhi 2022;102:393-8.
28. Weissferdt A, Pataer A, Vaporciyan AA, et al. Agreement on major pathological response in NSCLC patients receiving neoadjuvant chemotherapy. Clin Lung Cancer 2020;21:341-8.
29. Duan H, Shi L, Shao C, et al. A multicenter, single-arm, open study of neoadjuvant or conversion atezolizumab in combination with chemotherapy in resectable small cell lung cancer (Cohort Study). Int J Surg 2023;109:2641-9.
30. Li Z, Zhang B, Yang F, et al. Pathological complete response to radical surgery after receiving durvalumab plus neoadjuvant chemotherapy for 1 limited-stage small cell lung cancer patient: a case report. Transl Cancer Res 2022;11:973-9.
31. Mei T, Wang T, Lei C, et al. Pathological complete response to neoadjuvant therapy with serplulimab and chemotherapy in stage IIIB small cell lung cancer: a case report and literature review. Front Immunol 2023;14:1272450.
32. Park SY, Park S, Lee GD, et al. The role of adjuvant therapy following surgical resection of small cell lung cancer: a multi-center study. Cancer Res Treat 2023;55:94-102.
33. Bogart JA, Waqar SN, Mix MD. Radiation and systemic therapy for limited-stage small-cell lung cancer. J Clin Oncol 2022;40:661-70.

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