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Comparison of Neoadjuvant Immunochemotherapy and Chemotherapy in Patients with Resectable Limited- Stage Small-Cell Lung Cancer: Outcomes, Adverse Events, Recurrence Profiles and Prognostic Markers

Song Wei
Beijing Chest Hospital
Fudong Xu
Beijing Chest Hospital
Yuting Wu
Beijing Chest Hospital
Yongmeng Li
Beijing Tuberculosis and Thoracic Tumor Research Institute
Ruixin Wu
Beijing Chest Hospital
Nanying Che
Beijing Chest Hospital
Gen Lin
lingen@bjxkyy.cn

Beijing Chest Hospital

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Abstract

Background

Limited-stage small-cell lung cancer (LS-SCLC) has a poor prognosis. While immune checkpoint inhibitors (ICIs) benefit extensive-stage disease, evidence on neoadjuvant ICI use in resectable LS-SCLC is scarce. This study compared neoadjuvant immunochemotherapy versus chemotherapy alone in this setting.

Methods

This retrospective study included 65 patients with resectable stage I–IIIB LS-SCLC. Twenty-one patients received neoadjuvant immunochemotherapy (nCI group: etoposide + platinum + ICI), and 44 received chemotherapy alone (nC group). Primary endpoints were pathological responses. Secondary endpoints included objective response rate (ORR), disease-free survival (DFS), overall survival (OS), safety, and surgical outcomes. Additionally, recurrence patterns and prognostic factors for DFS and OS were explored.

Results

The pathological complete response (pCR) rate was significantly higher in the nCI group (52.4% vs. 18.2%; P = 0.005). The major pathological response (MPR) rate was also higher (61.9% vs. 38.6%; P > 0.05). The nCI group showed favorable trends in ORR (90% vs. 68%), R0 resection (100% vs. 97.7%), median DFS (48.7 vs. 17.2 months; hazard ratio [HR] = 0.87, P = 0.69), and median OS (not reached vs. 41.6; HR = 0.43, P = 0.12). Grade 3–4 treatment-related adverse events (TrAEs) were comparable (38.1% vs. 31.8%). Recurrence patterns differed: nCI had more distant recurrence (72.7% vs. 25.8%), while nC had more local recurrence (18.2% vs. 51.6%). Non-pCR/non-MPR, postoperative pro-gastrin releasing peptide (Pro-GRP) positivity and Stage III were independent risk factors.

Conclusions

Neoadjuvant immunochemotherapy significantly improved pCR rates and showed promising survival trends in resectable LS-SCLC, with a manageable safety profile. It altered recurrence patterns and identified pathological response and Pro-GRP as key prognostic markers.

Introduction

Small cell lung cancer (SCLC) is a highly malignant neuroendocrine tumor characterized by strong invasiveness, early metastasis, and a high recurrence tendency, which poses a severe threat to patient survival and prognosis [1–3]. Limited-Stage Small Cell Lung Cancer (LS-SCLC) refers to tumors confined

to one hemithorax that can be safely encompassed within a single radiation field, corresponding to stages I–IIIB in the TNM staging system. Approximately one-third of patients with SCLC are diagnosed at this stage [4, 5]. Although the prognosis of patients with limited-stage disease is relatively better than that of those with extensive-stage disease, the 2-year Overall Survival (OS) rate remains below 50%, with a median OS of only 16–24 months. This current situation highlights the urgent need to optimize existing treatment strategies [6–10].

At present, concurrent chemoradiotherapy is the standard treatment regimen for LS-SCLC [11]. Based on the positive results of the ADRIATIC trial, patients with no disease progression after concurrent chemoradiotherapy can receive further consolidation therapy with durvalumab to achieve longer survival [12]. Real-world data indicate that the role of surgery in LS-SCLC remains controversial. Particularly for patients with N1-2 lymph node metastasis, the postoperative recurrence rate is as high as 60%, and there is a lack of high-level evidence supporting the advantage of surgery over concurrent chemoradiotherapy [13].

In recent years, breakthroughs in immune checkpoint inhibitors (ICIs)for advanced Non-Small Cell Lung Cancer (NSCLC) have brought a paradigm shift to lung cancer treatment. The CheckMate 816 phase Ⅲ trial showed that neoadjuvant therapy with nivolumab combined with chemotherapy could achieve a 60-month survival rate of 65% in patients with resectable NSCLC, significantly reducing the risk of death by 28% compared with chemotherapy alone [14]. The NCCN Guidelines have listed the neoadjuvant regimen of nivolumab combined with chemotherapy as a Category 1 recommendation for patients with stage II–IIIB NSCLC, formally establishing the role of immunotherapy in the neoadjuvant setting for lung cancer. This success has prompted the academic community to explore the expansion of neoadjuvant immunotherapy into the field of SCLC. In SCLC, the IMpower133 and CASPIAN trials demonstrated that in the extensive-stage setting, atezolizumab and durvalumab combined with chemotherapy yield longer progression-free survival (PFS) and OS than chemotherapy alone, laying an important foundation for the application of immunotherapy in LS-SCLC [15, 16].

Overall, guideline updates in the field of SCLC still lag behind clinical needs. Currently, the treatment mainly relies on the traditional model of concurrent chemoradiotherapy, and the application of neoadjuvant immunotherapy lacks support from large-scale phase Ⅲ studies. Although existing small-sample studies and retrospective analyses suggest that neoadjuvant chemotherapy combined with immunotherapy can improve pathological response rates and Disease-Free Survival (DFS) compared with neoadjuvant chemotherapy alone, these studies are still in the early stage, and relevant safety and long-term prognosis data remain limited. The specific advantages of neoadjuvant chemotherapy combined with immunotherapy over neoadjuvant chemotherapy alone have not been fully clarified.

In view of this, this study aims to systematically compare the differences in efficacy and safety between neoadjuvant chemotherapy combined with immunotherapy and neoadjuvant chemotherapy alone in patients with LS-SCLC, focusing on analyzing the differences in the depth of pathological response, clinical response rate, DFS, OS, and perioperative adverse event profiles between the two groups. It is

expected to provide evidence-based basis for the optimized selection of neoadjuvant therapy for LS-SCLC, promote the transition from empirical treatment to precise and individualized treatment, and ultimately provide references for improving SCLC treatment guidelines and enhancing patients' survival prognosis.

Methods

Study Design and Enrolled Population

This retrospective study analyzed data from patients with SCLC who were treated at Beijing Chest Hospital, Capital Medical University, between 2016 and 2024. The key inclusion criteria were: (I) aged 18–80 years; (II) pathological confirmation of SCLC via bronchoscopy or transthoracic needle aspiration; (III) pretreatment clinical stage I–IIIB SCLC [17]; (IV) received neoadjuvant chemotherapy combined with immunotherapy or neoadjuvant chemotherapy at our hospital; (V) underwent surgical resection at our hospital after neoadjuvant therapy. Patients with the following conditions were excluded: (I) lack of pretreatment or post-neoadjuvant therapy imaging evaluation at our hospital; (II) previous anticancer treatment (e.g., radiotherapy, interventional therapy, or drug therapy); (III) comorbid autoimmune disease or infectious disease; (IV) ongoing systemic immunosuppressive therapy; (V) comorbid other malignant tumors. A total of 65 patients were enrolled, including 21 patients in the neoadjuvant immunochemotherapy group (nCI group) and 44 patients in the neoadjuvant chemotherapy group (nC group). This study was approved by the hospital's Ethics Committee, conducted in accordance with the Declaration of Helsinki (revised 2013) and Good Clinical Practice guidelines, and all patients provided written informed consent (Ethics Approval No.: LW-2025-021).

Treatment

Patients received 1–4 cycles of etoposide plus a platinum-based agent (cisplatin or carboplatin), either in combination with or without an ICI. Each cycle lasted 3 weeks. After neoadjuvant therapy, the multidisciplinary oncology committee discussed the patients' individual risk factors and decided on surgical intervention. Surgical approaches included open radical surgery or video-assisted thoracoscopic surgery (VATS), with routine lymph node dissection. Postoperatively, the type of adjuvant therapy was determined by the attending physician, while respecting the wishes of patients and their families.

Endpoints and Assessments

The primary endpoint of this study was the pathological response in the two groups, and the secondary endpoints included objective response rate (ORR), DFS, OS, treatment-related adverse events (TrAEs), and surgical outcomes.

Pathological complete response (pCR) was defined as the absence of residual viable tumor cells (0%), and major pathological response (MPR) was defined as the presence of ≤ 10% residual viable tumor cells in the primary tumor bed following neoadjuvant therapy, irrespective of the status of lymph nodes [18]. Tumor response to neoadjuvant therapy was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [19]. Follow-up data were obtained from patients' regular examinations or treatments at our hospital; if unavailable, patients were contacted by telephone. The last follow-up date was May 31, 2025. DFS was defined as the time from surgery to tumor recurrence/progression or death from any cause, whichever occurred first. OS was defined as the time from the diagnosis of lung cancer to death from any cause or the date of the last follow-up. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [20].

Statistical Analysis

Categorical variables were presented as counts and percentages, and group comparisons were performed using the chi-square test or Fisher's exact test. After Normality Test, continuous variables were shown as the median and interquartile range (IQR), differences between groups were compared with the t-test, Wilcoxon test or analysis of variance (ANOVA). The median follow-up time was estimated using the reverse Kaplan-Meier method. Kaplan-Meier survival curves were used to visually represent changes in DFS and OS; the stratified log-rank test was used to compare differences in DFS and OS curves between the two groups, and the stratified Cox proportional hazards model was further used to quantify the intergroup hazard ratio. One-way repeated-measures ANOVA was used to compare changes in tumor marker levels at different time points. All analyses were performed using R software (version 4.1.2). A two-sided P-value < 0.05 was considered statistically significant.

Results

Patients and Treatments

From January 2016 to July 2024, a total of 65 patients were enrolled in this study. All patients received 1 to 4 cycles of neoadjuvant therapy, including 21 patients who received neoadjuvant immunochemotherapy (nCI group) and 44 patients who received neoadjuvant chemotherapy (nC group). All patients were treated with a chemotherapy regimen of etoposide combined with platinum-based drugs. The baseline characteristics of the patients were similar between the two treatment groups (Table 1). The demographic characteristics of the patients were representative of the broader population affected by lung cancer. However, the median age in the nCI group was slightly higher than that in the nC group, and the nCI group included more patients with stage III disease. Additionally, a higher proportion of patients in the nCI group received 3–4 cycles of neoadjuvant therapy.

Table 1
Clinical characteristics of included patients.

Characteristic	chemoimmunotherapy (N = 21)	chemotherapy (N = 44)	P-value
Age			0.123
Median (IQR), years	62 (52–69)	57.5 (52-63.5)	
Median (range), years	62 (43–74)	57.5 (37–73)	
Sex, number (%)			0.757
Female	4 (19.0)	11 (25.0)	
Male	17 (81.0)	33 (75.0)	
Clinical stage at diagnosis, number (%)			0.244
I-II	7 (33.3)	23 (52.3)	
III	14 (66.7)	21 (47.7)	
T stage, number (%)			0.396
1	5 (23.8)	10 (22.7)	
2	10 (47.6)	19 (43.2)	
3	2 (9.5)	11 (25.0)	
4	4 (19.0)	4 (9.1)	
N stage, number (%)			0.109
0	3 (14.3)	16 (36.4)	
1	7 (33.3)	7 (15.9)	
2	11 (42.4)	21 (47.7)	
Tumor Location Classification, number (%)			1
Central type	18 (85.7)	37 (84.1)	
Peripheral-type	3 (14.3)	7 (15.9)	
Smoking status, number (%)			1
Never	4 (19.0)	8 (18.2)	

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; T stage, Tumor stage; N stage, Node stage, NA, Not Applicable.

Characteristic	chemoimmunotherapy (N = 21)	chemotherapy (N = 44)	P-value
Former or Current	17 (81.0)	36 (81.8)	
ECOG performance status (%)			0.655
0	19 (90.4)	41 (93.2)	
1	2 (9.6)	3 (6.8)	
Immunotherapy regimes, number (%)			NA
Durvalumab	7 (33.3)	0 (0)	
Tislelizumab	7 (33.3)	0 (0)	
Atezolizumab	5 (23.8)	0 (0)	
Serplulimab	1 (4.8)	0 (0)	
Sintilimab	1 (4.8)	0 (0)	
Neoadjuvant Therapy Cycle, number (%)			0.139
1	0 (0.0)	3 (6.8)	
2	13 (61.9)	33 (75.0)	
3	7 (33.3)	8 (18.2)	
4	1 (4.8)	0 (0.0)	
IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; T stage, Tumor stage; N stage, Node stage, NA, Not Applicable.			

Efficacy

Analysis of pathological response in the 65 patients who underwent surgery showed that the pCR rate was 52.4% in the nCI group and 18.2% in the nC group. The pCR rate in the nCI group was significantly higher than that in the nC group, with an odds ratio of 4.95 (95% confidence interval [CI]: 1.57–15.62, P = 0.005) between the two groups. The MPR rate was 61.9% in the nCI group compared with 38.6% in the nC group; this difference did not reach statistical significance (odds ratio: 2.58, 95% CI: 0.89 to 7.52, P > 0.05) (Fig. 1).

Results of radiological evaluation after neoadjuvant therapy showed that the ORR was 90.5% in the nCI group, which was better than the 68.2% ORR in the nC group, but the difference was not statistically significant (P > 0.05) (Table 2).

Table 2
Outcomes of Limited-Stage Small Cell Lung Cancer patients undergoing neoadjuvant therapy.

Characteristic	chemoimmunotherapy (N = 21)	chemotherapy (N = 44)	P-value
Postoperative pathology, number (%)			
pCR	11 (52.4)	8 (18.2)	0.005**
MPR	13 (61.9)	17 (38.6)	0.078
Efficacy Evaluation, number (%)			0.134
CR	3 (14.3)	6 (13.6)	
PR	16 (76.2)	24 (54.6)	
SD	2 (9.5)	14 (31.8)	
ORR (%)	90.5	68.2	0.067
Surgical margin, R0	21 (100.0)	43 (97.7)	1.000
Surgical Approach, number (%)			0.944
Open thoracotomy	11 (52.4)	25 (56.8)	
Video-assisted thoracoscopic surgery	10 (47.6)	19 (43.2)	

pCR, Pathological complete response; MPR, Major pathological response; CR, complete remission; PR, partial remission; SD, stable disease; R0, Residual Tumor 0.

R0 resection was achieved in all 21 patients (100%) in the nCI group and in 43 of 44 patients (97.7%) in the nC group (P > 0.05). A total of 10 patients (47.6%) in the nCI group underwent thoracoscopic surgery, and 19 patients (43.2%) in the nC group received thoracoscopic surgery. The proportion of patients undergoing minimally invasive surgery in the nCI group was slightly higher than that in the nC group, but the difference was not statistically significant (P > 0.05) (Table 2).

Survival

By the time of the last follow-up, tumor recurrence or metastasis occurred in 52.4% of patients (11/21) in the nCI group and 70.5% of patients (31/44) in the nC group. Death was reported in 19.0% of patients

(4/21) in the nCI group and 54.5% of patients (24/44) in the nC group. The median follow-up duration was 28 months (IQR: 18.0–44.8) in the nCI group and 33.7 months (IQR: 21.5–55.9) in the nC group.

The median DFS was 48.7 months (95% CI: 8.3–NA) in the nCI group and 17.2 months (95% CI: 9.0–70.9) in the nC group, with a hazard ratio (HR) for disease recurrence or progression of 0.87 (95% CI: 0.43–1.74, P = 0.69) between the two groups. At 2 years, the percentage of patients without disease progression or recurrence was 51.1% (95% CI: 33.2–78.5) in the nCI group and 38.5% (95% CI: 26.5–56.0) in the nC group; at 3 years, the corresponding percentages were 51.1% (95% CI: 33.2–78.5) and 33.2% (95% CI: 21.6–50.9), respectively (Fig. 2.A).

The median OS was not reached (95% CI: 44.8–NA) in the nCI group, while it was 41.6 months (95% CI: 33.9–NA) in the nC group, with an HR for death of 0.43 (95% CI: 0.15–1.25, P = 0.12) between the two groups. At 3 years, the percentage of surviving patients was 80.7% (95% CI: 65.3–99.6) in the nCI group and 54.5% (95% CI: 40.7–73.1) in the nC group; at 5 years, the corresponding percentages were 80.7% (95% CI: 65.3–99.6) and 45.1% (95% CI: 31.3–64.8), respectively (Fig. 2.B). In summary, the median DFS and OS in the nCI group were longer than those in the nC group, but no statistically significant differences were observed.

When analyzing DFS and OS among patients with different clinical stages, the median DFS of 30 patients with stage I–II disease was 33.9 months (95% CI: 12.9–NA), which was significantly better than the median DFS of 9.0 months (95% CI: 6.3–28.9) in 35 patients with stage III disease. The HR for disease recurrence or progression between the two groups was 0.52 (95% CI: 0.28–0.97, P = 0.038). The 2-year and 3-year percentages of patients without disease progression or recurrence were higher in the stage I–II group than in the stage III group. The median OS of patients with stage I–II disease was 73.9 months (95% CI: 42.4–NA), which was numerically better than the median OS of 34.2 months (95% CI: 33.4–NA) in patients with stage III disease, with an HR for death of 0.48 (95% CI: 0.22–1.04, P = 0.057). The 3-year and 5-year survival percentages were higher in the stage I–II group than in the stage III group (Figs. 2.C–D).

When analyzing prognostic survival differences among patients with different pathological response statuses, stratification was performed based on pCR and MPR, respectively. The median DFS of 19 patients with pCR was not reached (95% CI: 17.0–NA), which was significantly higher than the median DFS of 10.0 months (95% CI: 6.6–21.2) in 46 patients without pCR (Non-pCR). The HR for disease recurrence or progression between the two groups was 0.30 (95% CI: 0.13–0.72, P = 0.006). The 2-year and 3-year percentages of patients without disease progression or recurrence were higher in the pCR group than in the Non-pCR group. The median OS was not reached in patients with pCR, which was significantly longer than the median OS of 41.6 months (95% CI: 33.4–NA) in the Non-pCR group.The HR for death between the two groups was 0.22 (95% CI: 0.07–0.74, P = 0.014). The 3-year and 5-year survival percentages were higher in the pCR group than in the Non-pCR group (Figs. 2.E–F).

The median DFS of 30 patients with MPR was 90.6 months (95% CI: 19.0–NA), which was significantly higher than the median DFS of 9.7 months (95% CI: 5.7–21.2) in 35 patients without MPR (Non-MPR).

The HR for disease recurrence or progression between the two groups was 0.42 (95% CI: 0.22–0.79, P = 0.007). The 2-year and 3-year percentages of patients without disease progression or recurrence were higher in the MPR group than in the Non-MPR group. The median OS of patients with MPR was not reached (95% CI: 89.3–NA), which was significantly higher than the median OS of 34.2 months (95% CI: 27.6–73.9) in patients with Non-MPR. The HR for death between the two groups was 0.29 (95% CI: 0.12–0.68, P = 0.004). The 3-year and 5-year survival percentages were higher in the MPR group than in the Non-MPR group (Figs. 2.G–H).

Multivariate Cox proportional hazards regression analysis showed that among the included factors (treatment modality, clinical stage, pCR, and MPR), only clinical stage I–II and achievement of pCR after treatment were independent protective factors for reducing the risk of disease recurrence. Additionally, clinical stage I–II and achievement of MPR after treatment were independent protective factors for reducing the risk of death (Figs. 2.I–J).

Kaplan-Meier estimates of the duration of (C) Disease-Free Survival and (D) Overall Survival between the Stage I-II and Stage III. Kaplan-Meier estimates of the duration of (E) Disease-Free Survival and (F) Overall Survival between the Pathological complete response and the non-Pathological complete response. Kaplan-Meier estimates of the duration of (G) Disease-Free Survival and (H) Overall Survival between the Major pathological response and the non-Major pathological response. Multivariate Cox proportional hazards model analysis of (I) Disease-Free Survival and (J) Overall Survival across subgroups including treatment modality, clinical stage, Pathological complete response and Major pathological response. pCR, Pathological complete response; MPR, Major pathological response; mo, month.

Tumor Markers

We continuously monitored the levels of pro-gastrin-releasing peptide (Pro-GRP) and neuron-specific enolase (NSE) before neoadjuvant therapy, after neoadjuvant therapy, and postoperatively. Complete data were available for 42 patients (18 in the nCI group and 24 in the nC group). Overall, with the progression of the disease and treatment, Pro-GRP levels showed a closer correlation with treatment efficacy than NSE levels. After neoadjuvant therapy, the levels of Pro-GRP and NSE in both groups decreased significantly compared with those before treatment. A slight further decrease in both markers was noted postoperatively when compared to levels after the completion of neoadjuvant therapy (Figs. 3.A–B).

Pro-GRP and NSE were categorized and defined as positive according to the following criteria: Pro-GRP > 80 pg/mL; NSE > 40 ng/mL. Among 56 patients with postoperative tumor marker data (20 in the nCI group and 36 in the nC group), 8 patients had postoperative Pro-GRP levels that did not return to negative (2 in the nCI group and 6 in the nC group). Most of these patients with persistently positive postoperative Pro-GRP levels were Non-MPR patients (Fig. 3.C). Survival prognosis analysis showed that patients with positive postoperative Pro-GRP had significantly worse DFS and OS than those with negative

postoperative Pro-GRP (Figs. 3.D–E). The median DFS was 48.7 months (95% CI: 17.0–NA) in patients with negative postoperative Pro-GRP, compared with 5.4 months (95% CI: 4.2–6.6) in patients with positive postoperative Pro-GRP, with an HR for recurrence of 0.29 (95% CI: 0.13–0.65, P = 0.002). The median OS was not reached (95% CI: 42.4–NA) in patients with negative postoperative Pro-GRP, compared with 27.6 months (95% CI: 6.3–48.9) in patients with positive postoperative Pro-GRP, with an HR for death of 0.23 (95% CI: 0.09–0.59, P = 0.002). Multivariate Cox proportional hazards regression analysis showed that after adjusting for treatment modality, clinical stage, and pathological response status, postoperative Pro-GRP positivity was an adverse prognostic factor for patients' DFS and OS (Supplementary Table 1). No correlation was found between Pro-GRP levels before or after neoadjuvant therapy, NSE levels at any time point, and DFS or OS (P > 0.05).

Recurrence Patterns

The postoperative disease recurrence rate was 52.4% (11/21) in the nCI group and 70.5% (31/44) in the nC group. Among these, the intrathoracic locoregional recurrence rate was 18.2% in the nCI group and 51.6% in the nC group. The incidence of distant metastasis was 72.7% and 45.2% in the nCI group and nC group, respectively. The rates of concurrent intrathoracic locoregional recurrence and distant metastasis were 9.1% and 3.2% in the nCI group and nC group, respectively (Fig. 4). Detailed information on patients with recurrence or metastasis is provided in Supplementary Table 2.

Subsequent Treatment

At the final analysis of OS, 95.2% of patients in the nCI group received any type of subsequent cancer therapy. One patient (4.8%) in the nCI group did not receive subsequent therapy, and this patient was a Non-MPR patient. In the nC group, 93.2% of patients received any type of subsequent cancer therapy. The 3 patients who did not receive subsequent therapy included 1 patient with pCR, 1 patient with MPR, and 1 patient with Non-MPR. Among patients with disease recurrence (11 in the nCI group and 31 in the nC group), the proportions receiving subsequent systemic therapy were 90.9% and 93.5%, respectively. Detailed information on subsequent treatment modalities is summarized in Supplementary Table 3.

Safety and Surgery-Related Complications

TrAEs occurred in 90.5% of patients in the nCI group and 52.3% of patients in the nC group. Grade 3 or 4 TrAEs occurred in 38.1% of patients in the nCI group and 31.8% in the nC group. The most common TrAEs of any grade were myelosuppression (66.7% in the nCI group vs. 52.3% in the nC group) and nausea (47.6% in the nCI group vs. 20.5% in the nC group). The most common grade 3 or 4 TrAEs were myelosuppression (33.3% in the nCI group vs. 27.3% in the nC group) and nausea (4.8% in the nCI group vs. 4.5% in the nC group). All severe adverse events in both groups were alleviated after symptomatic treatment, and no deaths were caused by adverse events. Postoperative complications occurred in 9.5% of patients in the nCI group, including 1 case of poor postoperative wound healing and 1 case of chylothorax. No postoperative complications were observed in the nC group (P > 0.05). The median

estimated blood loss was the same between the two groups. No perioperative deaths occurred (Supplementary Table 4).

Discussion

This retrospective study compared the efficacy and safety of neoadjuvant immunochemotherapy and neoadjuvant chemotherapy alone in patients with resectable LS-SCLC. The core findings of the study showed that neoadjuvant immunochemotherapy significantly increased the rate of pCR, and the MPR rate also showed a trend of increase. Other key outcomes, including ORR, DFS, and OS also numerically favored the ICI-containing regimen. Compared with chemotherapy alone, ICI-combined chemotherapy did not increase the incidence of grade 3–4 TrAEs. The addition of ICIs to neoadjuvant chemotherapy neither increased the risk of surgery-related adverse events nor expanded the scope of surgical resection. Meanwhile, pathological response (pCR/MPR), clinical stages and postoperative Pro-GRP levels were identified as reliable prognostic markers. This study provides real-world evidence for neoadjuvant therapy of LS-SCLC, aiming to support clinical decision-making.

In recent years, breakthroughs have been made in the use of ICI-combined chemotherapy for the treatment of extensive-stage small-cell lung cancer (ES-SCLC). The IMpower133 study demonstrated that atezolizumab combined with chemotherapy extended median OS by 2 months compared with chemotherapy alone (12.3 months vs. 10.3 months) [15]. In the CASPIAN study, the durvalumab-combined chemotherapy group also extended patients' median OS compared with the chemotherapy-alone group (12.9 months vs. 10.5 months) [16]. In addition, a meta-analysis involving 15 cohorts showed that surgical treatment improved survival outcomes in patients with LS-SCLC compared with non-surgical treatment [21–23]. These findings have therefore prompted researchers to explore the application of ICIs in neoadjuvant therapy for LS-SCLC [24]. Whether neoadjuvant immunochemotherapy can improve patients' pathological response rate and survival outcomes has become the focus of current clinical research.

In this study, a higher proportion of patients in the nCI group achieved pCR and MPR compared with the nC group (pCR: 52.4% vs. 18.2%; MPR: 61.9% vs. 38.6%). This conclusion is consistent with the findings of Zhu et al. and Liu et al. in LS-SCLC [25, 26]. In the CheckMate 816 study, for patients with resectable NSCLC, neoadjuvant nivolumab combined with chemotherapy resulted in a higher proportion of patients achieving pCR compared with chemotherapy alone (24.0% vs. 2.2%). From the perspective of pathological response, this indicates that adding immunotherapy to neoadjuvant therapy can significantly enhance antitumor efficacy, possibly due to a synergistic effect where "chemotherapy sensitizes immunity, and immunity enhances chemotherapy efficacy" [14]. In the analysis of radiological efficacy assessment, the ORR of the nCI group was better than that of the nC group; the proportion of patients with complete response (CR) was similar between the two groups, but the proportion of patients with partial response (PR) in the nCI group was higher than that in the nC group. This trend is

consistent with the results of the KEYNOTE-604 study and the CASPIAN study, where the addition of ICIs significantly improved patients' ORR compared with chemotherapy alone [27, 16].

In the ADRIATIC study, the durvalumab group achieved significant improvements in both OS and PFS compared with the placebo group; the durvalumab group had a median PFS of 16.6 months, a median OS of 55.9 months, and a 3-year OS rate of 56.5% [12]. In our study, the median DFS of the nCI group was 48.7 months, which was higher than the 17.2 months of the nC group. The median OS of the nCI group was not reached (95% CI: 44.8–NA), with 3-year and 5-year OS rates both at 80.7%. The nC group had a median OS of 41.6 months, with 3-year and 5-year OS rates of 54.5% and 45.1%, respectively. Although PFS in the ADRIATIC study was defined as the time from randomization to disease progression or death from any cause, the median DFS and OS of the nCI group were significantly better than the PFS and OS reported in the ADRIATIC study. However, OS data still require further follow-up to mature. Integrating the above pathological response, radiological efficacy assessment, and survival data, for resectable stage I–IIIB LS-SCLC, neoadjuvant immunochemotherapy followed by surgery may bring more benefits to patients compared with the current standard treatment of concurrent chemoradiotherapy.

In various cancers, including NSCLC, pathological response has been shown to be associated with patient-level survival [28–31]. However, no prospective studies have robustly established an association between pathological complete response and survival in patients with SCLC, possibly due to the low incidence of pCR induced by neoadjuvant chemotherapy and heterogeneous methods for assessing pathological response [14]. In this trial, in addition to the higher pCR and MPR rates in the nCI group, we also observed a close association between pCR and DFS, as well as between MPR and OS. This association may be one of the reasons for the survival benefits of this regimen. This strong correlation between pathological response and clinical benefit is particularly noteworthy, suggesting that pathological response is a promising early indicator for evaluating therapeutic efficacy in resectable LS-SCLC. In addition, we also found for the first time that patients with postoperative Pro-GRP levels not returning to negative had significantly poor prognosis, which updates the current understanding of prognostic markers for LS-SCLC. Most patients with postoperative Pro-GRP levels not returning to negative were non-MPR patients, and they had the worst prognosis among non-MPR patients. This suggests that some LS-SCLC patients, especially those with stage III LS-SCLC, may have developed tumor hematogenous metastasis. Combining the recommendation in the NCCN Guidelines for dynamic monitoring of tumor markers in LS-SCLC patients and the advantage of good accessibility of tumor marker detection, we propose that postoperative Pro-GRP levels (with a cutoff value of > 80 pg/mL) can be used as a core indicator for clinical follow-up. Postoperative follow-up should be intensified for postoperative non-MPR patients, especially those with positive Pro-GRP, and subsequent treatment should be strengthened to improve prognosis. In addition, the combined assessment of Pro-GRP and pathological response may further improve the accuracy of prognostic prediction, and future studies with larger sample sizes are needed to verify the value of this combined model.

The patterns of disease recurrence differed between the two treatment groups. Patients in the nCI group mainly had distant organ recurrence and metastasis, while those in the nC group mainly had

intrathoracic local recurrence. This suggests that chemotherapy alone may provide suboptimal local tumor control. Based on this, moving immunotherapy to the neoadjuvant phase may intervene in the tumor microenvironment earlier than consolidation therapy, reducing the source of recurrence. At the same time, different recurrence patterns also guide the focus of postoperative follow-up for patients.

This study shows that the safety of neoadjuvant immunotherapy combination in LS-SCLC patients is acceptable. Compared with chemotherapy alone, the combination of ICIs and chemotherapy did not lead to a significant increase in the incidence of grade 3–4 TrAEs. With reference to the IMpower133 study, KEYNOTE-604 study, CASPIAN study, CAPSTONE-1 study, and ASTRUM-005 study, no new adverse events were observed in this study [15, 16, 27, 32, 33]. Meanwhile, combined immunotherapy did not increase surgical difficulty, and 100% R0 resection was achieved. Although 2 patients in the nCI group developed postoperative complications, they all had a good outcome after treatment, with no perioperative deaths. The proportion of minimally invasive surgery was slightly higher in the nCI group; existing studies have shown that minimally invasive surgery helps improve patients' physical function recovery [34]. The deeper pathological regression and higher ORR observed in the nCI group may explain their relatively better surgical outcomes, although the underlying mechanism requires further clarification. Therefore, it is necessary to emphasize the potential value of neoadjuvant immunochemotherapy and subsequent surgical treatment for LS-SCLC patients, especially those with locally advanced disease, and promote the treatment of LS-SCLC into the "neoadjuvant immunotherapy era".

This study has the following limitations: it failed to include patients who could not undergo surgery due to disease progression after neoadjuvant therapy, which may lead to higher overall pCR and MPR rates compared with other studies and may also result in prolonged DFS and OS. Second, due to the relatively small number of included patients and the single-center retrospective design, there may be bias in the overall characteristics of the involved patients. In addition, the follow-up time was insufficient to observe complete survival data. These factors may affect the validity of the results of this study. Future multicenter studies with larger sample sizes are still needed to verify the current findings.

In conclusion, for LS-SCLC patients, neoadjuvant immunochemotherapy has better efficacy and survival benefits compared with neoadjuvant chemotherapy alone, with controllable safety. Therefore, neoadjuvant chemotherapy combined with immunotherapy represents a highly feasible and promising treatment strategy worthy of further validation in larger, prospective studies to confirm its role in clinical practice.

Declarations

Ethical Statement

This study was approved by the Clinical Research Ethics Committee of Beijing Chest Hospital, Capital Medical University (LW-2025-021). All participants provided written informed consent for the cohort study. This study was performed in accordance with the Declaration of Helsinki.

Competing interests

The authors declare no conflict of interest.

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Author Contribution

Gen Lin (Conceptualization, Writing - Review & Editing, Supervision, Project administration). Song Wei (Writing - Original Draft, Methodology, Software, Validation, Formal analysis, Data Curation, Visualization, Funding acquisition). Nanying Che (Conceptualization, Resources, Writing - Review & Editing, Supervision, Project administration). Fudong Xu (Investigation, Resources, Validation, Data Curation). Yuting Wu (Investigation). Yongmeng Li (Investigation). Ruixin Wu (Visualization).

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Data availability

Gen Lin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures), are available from the corresponding author on reasonable request.

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Figures

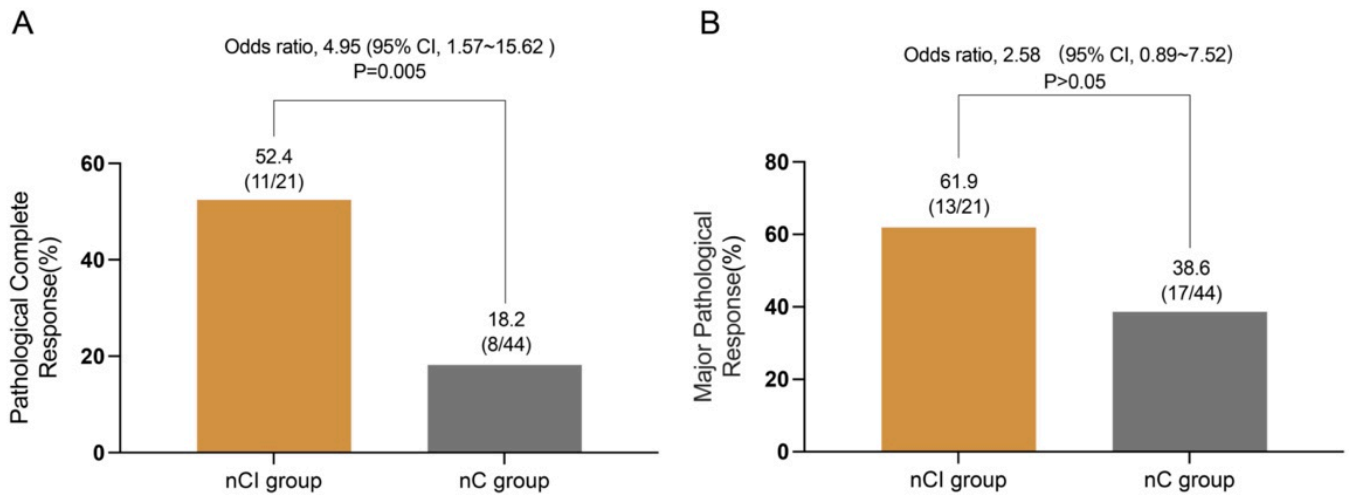


Figure 1

The distribution condition of pathological response. (A) Pathological complete response and (B) Major pathological response between the immunochemotherapy group and chemotherapy group. nCI group= immunochemotherapy group, nC group= chemotherapy group. Pathological complete response was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes. Major pathological response was defined as ≤10% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes.

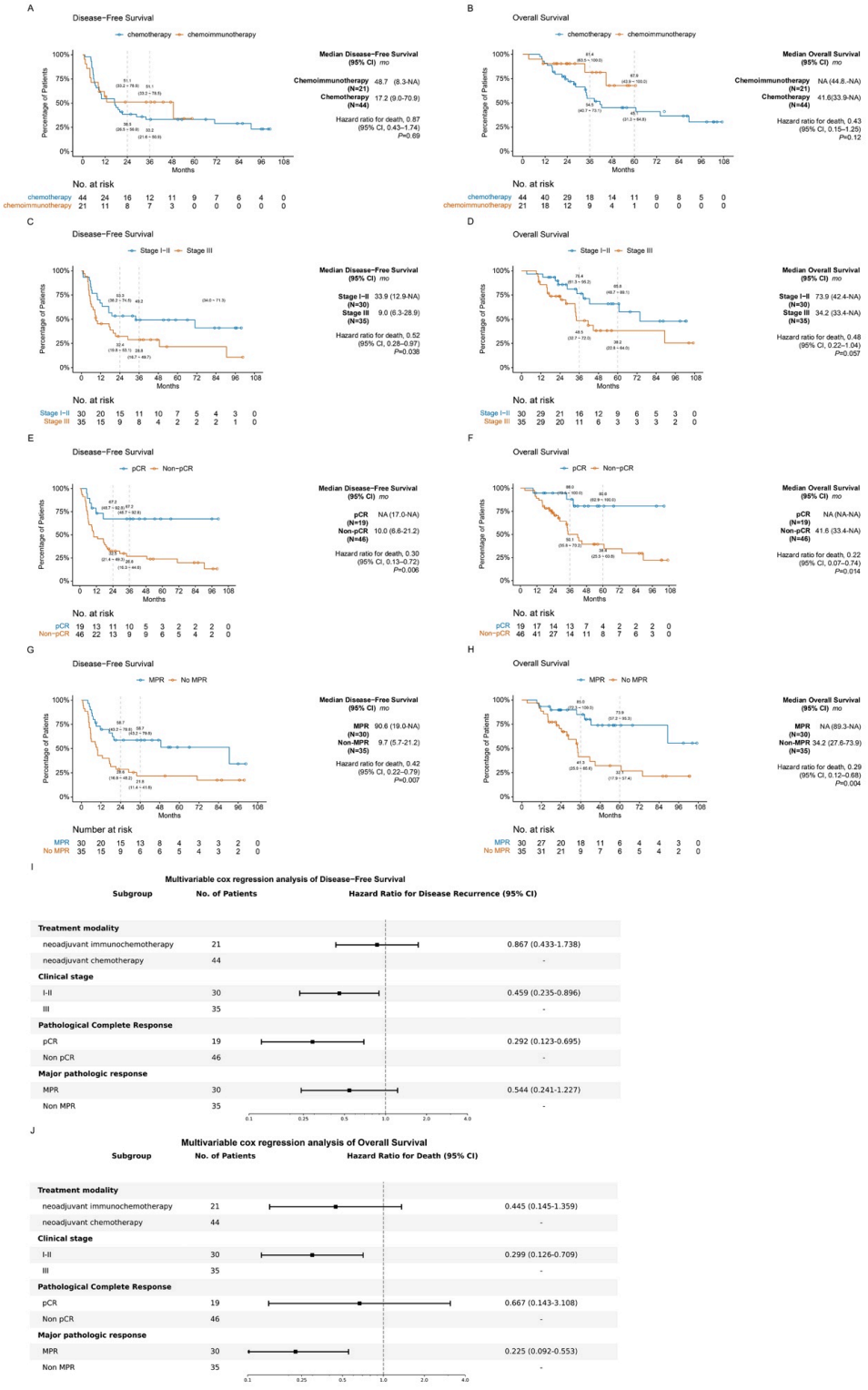


Figure 2

Disease-Free Survival and Overall Survival. Kaplan-Meier estimates of the duration of (A) Disease-Free Survival and (B) Overall Survival between the immunochemotherapy group and chemotherapy group.

Kaplan-Meier estimates of the duration of (C) Disease-Free Survival and (D) Overall Survival between the Stage I-II and Stage III. Kaplan-Meier estimates of the duration of (E) Disease-Free Survival and (F)

Overall Survival between the Pathological complete response and the non-Pathological complete response. Kaplan-Meier estimates of the duration of (G) Disease-Free Survival and (H) Overall Survival between the Major pathological response and the non-Major pathological response. Multivariate Cox proportional hazards model analysis of (I) Disease-Free Survival and (J) Overall Survival across subgroups including treatment modality, clinical stage, Pathological complete response and Major pathological response. pCR, Pathological complete response; MPR, Major pathological response; mo, month.

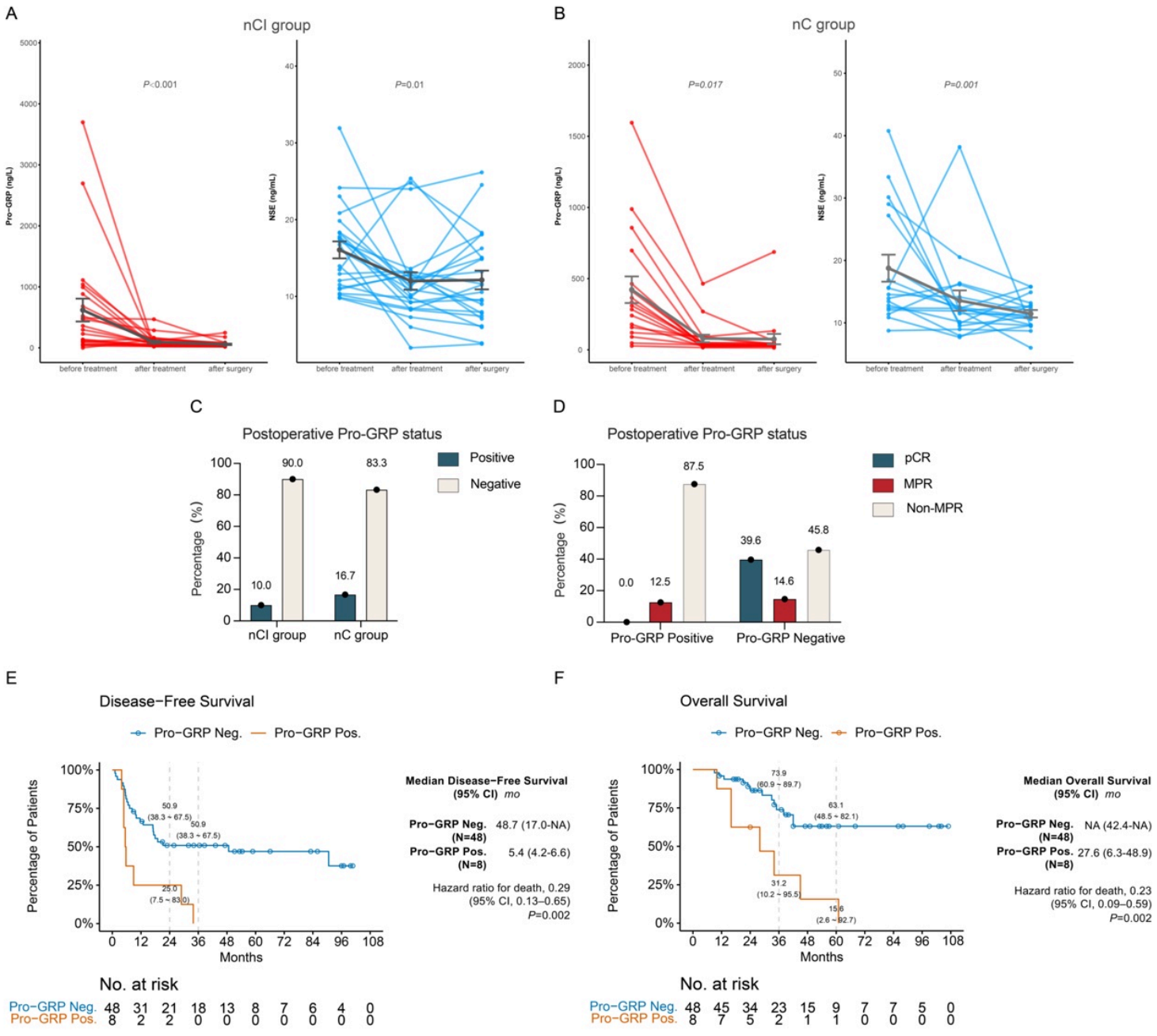


Figure 3

Tumor markers in both groups. Progastrin-releasing peptide and Neuron specific enolase levels decreased significantly in (A) immunochemotherapy group and (B) chemotherapy group after treatment.

(C) The postoperative positive rate of progastrin-releasing peptide in immunochemotherapy group and the chemotherapy group. (D) Different pathological response statuses corresponding to postoperative patients with progastrin-releasing peptide positive or negative status. Kaplan-Meier estimates of the duration of (E) Disease-Free Survival and (F) Overall Survival between postoperative patients with progastrin-releasing peptide positive and negative status. Pro-GRP, Progastrin-releasing peptide; NSE, Neuron specific enolase; Neg., negative; Pos., positive; mo, month.

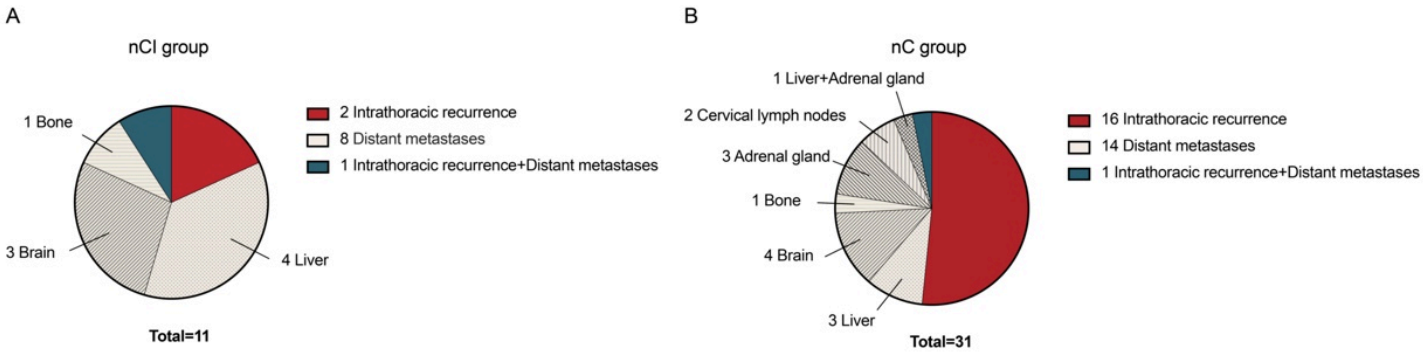


Figure 4

Recurrence pattern. Distribution of recurrence patterns in immunochemotherapy group (A) and chemotherapy group (B).

Supplementary Files

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- SupplementaryMaterial.docx