Efficacy of neoadjuvant therapy for lung squamous cell carcinoma and lung adenocarcinoma: A retrospective comparative study

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Abstract. Preoperative neoadjuvant therapy is widely used in cancer treatment; however, its efficacy in different subtypes of non-small cell lung cancer (NSCLC) is unknown. The present study compared the clinical efficacy of preoperative neoadjuvant therapy for two major NSCLC subtypes. Patients with NSCLC who underwent preoperative neoadjuvant therapy between January 2016 and August 2022 were reviewed. Patients were stratified according to histology and treatment strategy. Retrospective analysis was performed by comparing the basic clinical characteristics of the patients, clinicopathological characteristics of the tumors, imaging data and pathological responses to treatment. A total of 36 cases of lung squamous cell carcinoma (LUSC) and 31 cases of lung adenocarcinoma (LUAD) were included. After neoadjuvant chemotherapy combined with immunotherapy, the pathological response rates were higher for patients with LUSC than LUAD, but there was no statistically significant difference between the two subgroups (P=0.06). However, the pathological complete response rates after neoadjuvant chemotherapy combined with immunotherapy were significantly higher for LUSC than those after chemotherapy alone (P=0.01). These preliminary findings suggested that preoperative chemotherapy combined with immunotherapy could improve the pathological response of patients, particularly in those with LUSC. The present study provided new insights into the treatment of NSCLC.

Introduction

Lung cancer is the most common malignancy responsible for cancer-related death worldwide, accounts for 18% of all diagnosed cancers (1). Notably, 85% of patients with lung cancer are diagnosed with non-small cell lung cancer (NSCLC) (2). The 5-year survival rate for NSCLC varies; while patients with stage IA have a good prognosis (85%), only 6% of patients with stage IV cancer survive for 5 years (3). Surgery is currently the main treatment for early-stage NSCLC; however, for locally advanced NSCLC, preoperative platinum-based adjuvant chemotherapy improves the 5-year survival rate by only 5% compared to surgery alone (4). Immune checkpoint inhibitors (ICIs) improve survival in patients with advanced NSCLC compared with chemotherapy alone, and patients with NSCLC who received immunotherapy combined with chemotherapy were reported to have higher pathological complete response (pCR) rates and longer event-free survival (5,6). It has been reported that the rapid development of individualized treatment for lung cancer has brought hope to patients with lung cancer. To improve the prognosis of NSCLC, it is necessary to better understand the benefit of preoperative neoadjuvant therapy in specific patient populations.

NSCLC is primarily divided into lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). LUAD originates from cells that secrete surfactant components, and LUSC originates from cells lining the lung airways, the differentially expressed genes between LUAD and LUSC cause differences in the regulatory networks of DNA replication and repair and RNA splicing, and further cause differences in cell structure, which causes them to serve different roles in tumor cell proliferation and tissue invasion, so LUAD and LUSC are not only histologically distinct tumors, but also have unique biological characteristics and clinical features (7,8). Although often treated similarly, LUAD and LUSC have different prognoses and this is likely because the unique clinical characteristics and behavior of LUAD and LUSC remain largely unknown (9). There are currently no clear guidelines on the efficacy of neoadjuvant therapy for different subtypes of NSCLC (10).

The majority of previous clinical evaluations of post-neoadjuvant therapy have focused only on tumors, and there are few reports assessing pathological responses in the lymph node after neoadjuvant therapy (11). The CheckMate 816 trial was a rare exception to this practice, but it is clear that evidence for the efficacy of neoadjuvant immunotherapy in lymph nodes is insufficient (12). The main purpose of the present study was to review and analyze the clinical data from patients who had received neoadjuvant therapy for LUAD and LUSC, to preliminarily evaluate the efficacy of neoadjuvant

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Table I. Demographic and tumor characteristics of patients.

Characteristic	Total	LUSC	LUAD	P-value
n	67	36	31	
Mean age ± SD, years	59±10.21	62±8.54	55±10.71	0.01
Sex, n (%)				
Male	53 (79.10)	32 (88.89)	21 (67.74)	0.41
Female	14 (20.90)	4 (11.11)	10 (32.26)	
Smoking status, n (%)				0.89
Former or current	31 (46.27)	13 (36.11)	18 (58.06)	
Never	36 (53.73)	23 (63.89)	13 (41.94)	
cT, n (%)				0.23
1	9 (13.43)	4 (11.11)	5 (16.13)	
2	24 (35.82)	10 (27.78)	14 (45.14)	
3	21 (31.34)	15 (41.67)	6 (19.35)	
4	13 (19.41)	7 (19.44)	6 (19.35)	
cN, n (%)				0.08
1	24 (35.82)	16 (44.44)	8 (25.81)	
2	37 (55.22)	19 (52.78)	18 (58.06)	
3	6 (8.96)	1 (2.78)	5 (16.13)	
cStage, n (%)				0.09
2	12 (17.91)	9 (25.00)	3 (9.67)	
3	55 (82.19)	27 (75.00)	28 (90.33)	
Previous treatments, n (%)				>0.99
Chemotherapy	36 (53.73)	19 (52.78)	17 (54.83)	
Chemotherapy combined with immunotherapy	31 (46.27)	17 (47.22)	14 (45.17)	
Number of previous treatments, n (%)				0.63
≤2	34 (50.75)	17 (47.22)	17 (54.84)	
>2	33 (49.25)	19 (52.78)	14 (45.16)	

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; cT, clinical Tumor; cN, clinical Node; cStage, clinical Stage.

therapy in both tumors and lymph node remission of patients with two distinct pathological subtypes, and to provide clinical treatment guidelines.

Materials and methods

Patients and methods. The clinical data of patients who underwent surgery after neoadjuvant chemotherapy or chemotherapy combined with immunotherapy at The First Affiliated Hospital, Sun Yat-sen University (Guangzhou, China) between January 2016 and August 2022 were retrospectively analyzed. Patients who had received chemotherapy combined with immunotherapy were recruited from January 2020 to August 2022. The inclusion criteria were as follows: i) Aged ≥18 years; ii) all patients with biopsy-proven NSCLC with a defined histological subtype; iii) patients with lymph node metastasis, no distant metastasis, potentially operable but not suitable for immediate resection (based on imaging information), classified according to the tumor-lymph node-metastasis (TNM) staging system of the 8th edition of the American Joint Committee on Cancer (13); iv) received chemotherapy or chemotherapy combined with immunotherapy before surgery; v) unspecified driver gene mutations, including anaplastic lymphoma kinase and epidermal growth factor receptor; vi) no history of other malignancies prior to treatment and no prior antitumor therapy; and vii) Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 or 1 (14). The general information and treatment data of the patients, such as age, sex, smoking history, histopathological type, clinical TNM stage, chemotherapy regimen and frequency, imaging changes before and after treatment, and final pathological TNM stage, were recorded in detail.

Treatment. All patients received platinum-based chemotherapy or ICIs combined with chemotherapy, and were evaluated using the same procedures before and after neoadjuvant therapy. Tumor changes were assessed based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) (15). Pathological response to treatment was graded; pCR was defined as the complete absence of residual tumor cells. and

Table II. Comparison of radiological and pathological responses in patients after neoadjuvant therapy.

Characteristic	Total (%)	LUSC (%)	LUAD (%)	P-value
n	67 (100.00)	36 (53.73)	31 (46.27)	
Radiological response				
CR	9 (13.43)	7 (19.44)	2 (6.45)	0.16
PR	38 (56.72)	19 (52.78)	19 (61.29)	0.62
SD	18 (26.87)	9 (25.00)	9 (29.03)	0.79
PD	2 (2.98)	1 (2.78)	1 (3.23)	1.00
Pathological response				
pCR	19 (28.36)	14 (38.89)	5 (16.13)	0.06
MPR	6 (8.96)	3 (8.33)	3 (9.68)	>0.99
Downstaging of T stage	51 (76.12)	27 (75.00)	24 (77.42)	>0.99
Downstaging of N stage	55 (82.09)	31 (86.11)	24 (77.42)	0.50

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; pCR, pathological complete response; MPR, major pathological response.

major pathological response (MPR) was defined as the presence of residual viable tumor cells ≤10%. Pathological stable disease (SD) is defined as the presence of >50% viable tumor cells in the resected cancer specimen; incomplete pathological response is defined as the presence of >50% viable tumor cells in the resected cancer specimen >10% viable tumor cells present (16).

Statistical analysis. Statistical analysis was performed using SPSS 23.0 (IBM Corp.). Continuous variables are presented as mean ± standard deviation. Student's t-test was used to compare independent samples of normally distributed continuous variables, and the Mann-Whitney U test was used to compare non-normally distributed continuous variables. Categorical data are presented as frequencies (percentages). Comparisons of categorical variables between groups were made using Fisher's exact test or Pearson's χ^2 test. Univariate logistic regressive analysis was used to evaluate the influence of certain clinical variables on pathological remission. $P<0.05$ was considered to indicate a statistically significant difference.

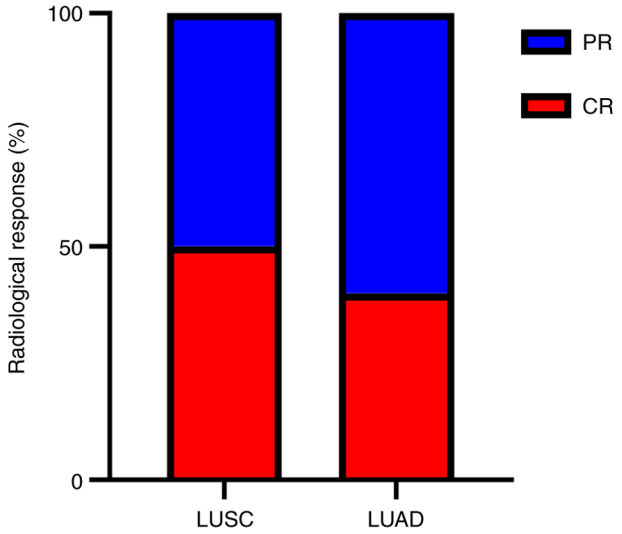

Figure 1. Radiological response in patients with pCR. LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; CR, complete remission; PR, partial remission.

Results

Patient characteristics. In the present study, a total of 67 cases were identified, including 36 patients with LUSC and 31 patients with LUAD. The basic information and clinical characteristics of the patients are shown in Table I. All patients underwent surgery after neoadjuvant therapy. Patients were predominantly male (79.10%), and most patients were diagnosed with stage III NSCLC (82.19%) and ipsilateral mediastinal and/or subcarinal lymph node metastasis (N2) (55.22%). No significant differences were demonstrated in patient characteristics between LUSC and LUAD except for age. However, age was not a risk factor for clinical efficacy when data were analyzed using univariate logistic regression.

Efficacy. According to RECIST 1.1 criteria, 9 (13.43%) patients achieved CR, 38 (56.72%) patients achieved PR, 18 (26.87%) patients achieved SD and 2 (2.98%) patients achieved PD. There was no significant difference in radiological response after neoadjuvant therapy between patients with LUAD or LUSC (Table II).

Next, the pathological response of the two NSCLC subtypes were compared, 38.89% of patients with LUSC achieved pCR after surgery compared with 16.13% of patients with LUAD (Table II). Lymph node regression rates were comparable between the two groups (86.11% vs. 77.42%; Table II). LUSC appeared to be more responsive to neoadjuvant therapy, but there were no statistically significant differences in tumor regression and lymph node downstaging after neoadjuvant therapy between the LUSC and LUAD groups.

Radiological response in patients with pCR. Analysis of the concordance between two different subtypes of radiological responses and pCR was performed. The results demonstrated

Table III. Univariate logistic regressive analysis for pathological response.

Characteristic	pCR/MPR (%)	Non-pCR/MPR (%)	OR (95% CI)	P-value
n	25 (100.00)	42 (100.00)		
Sex			0.38 (0.09-1.54)	0.18
Male	22 (88.00)	31 (73.81)		
Female	3 (12.00)	11 (26.19)		
Mean age ± SD, years	57±10.39	62±9.87	1.03 (0.98-1.09)	0.17
Smoking status				
Never	11 (44.00)	20 (47.62)	1.16 (0.43-3.13)	0.77
Former or current	14 (56.00)	22 (52.38)		
Histological type				
LUSC	17 (68.00)	19 (45.24)	0.39 (0.14-1.09)	0.07
LUAD	8 (32.00)	23 (54.76)		
cT				
1	5 (20.00)	3 (7.14)	0.65 (0.38-1.14)	0.14
2	9 (36.00)	16 (38.10)		
3	8 (32.00)	13 (30.95)		
4	3 (12.00)	10 (23.81)		
cN				
1	11 (44.00)	13 (30.96)	0.80 (0.36-1.81)	0.59
2	11 (44.00)	26 (61.90)		
3	3 (12.00)	3 (7.14)		
cStage			0.52 (0.15-1.86)	0.32
2	6 (24.00)	6 (14.29)		
3	19 (76.00)	36 (85.71)		
Previous treatment			5.74 (1.93-17.01)	0.002
Chemotherapy	7 (28.00)	29 (69.05)		
Chemotherapy combined with immunotherapy	18 (72.00)	13 (30.95)		
Number of previous treatments			2.00 (0.73-5.47)	0.18
≤2	10 (40.00)	24 (57.14)		
>2	15 (60.00)	18 (42.86)		

LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; pCR, pathological complete response; MPR, major pathological response; OR, odds ratio; cT, clinical Tumor; cN, clinical Node; cStage, clinical Stage.

Table IV. Comparison of pathological remission of neoadjuvant chemotherapy and neoadjuvant immunotherapy in LUSC.

Characteristic	Chemotherapy (%)	Chemotherapy combined with immunotherapy (%)	P-value
n	19 (100.00)	17 (100.00)	
pCR	4 (21.05)	10 (58.82)	0.01
MPR	5 (26.31)	12 (70.59)	0.59
Downstaging of T stage	11 (57.89)	16 (94.12)	0.02
Downstaging of N stage	13 (68.42)	8 (47.06)	0.31

LUSC, lung squamous cell carcinoma; pCR, pathological complete response; MPR, major pathological response.

that among all patients who achieved pCR, 50% of patients with LUSC had radiographic CR (7/14) compared with 40% of patients with LUAD (2/5) (Fig. 1).

Regression analysis of risk factors for postoperative pathological response. Univariate logistic regression models were used to assess whether sex, age, pathological subtype, clinical stage,

neoadjuvant therapy modality and number of previous neoadjuvant therapies could be risk factors for pCR and MPR events. The results demonstrated that chemotherapy combined with immunotherapy was a risk factor affecting pCR and MPR. (odds ratio 5.74; 95% confidence interval 1.93-17.01; P<0.002; Table III).

To further clarify the role of ICIs in NSCLC, the effects of neoadjuvant chemotherapy and neoadjuvant chemotherapy combined with immunotherapy on NSCLC subtypes were compared. Compared with chemotherapy alone, chemotherapy combined with immunotherapy improved the pCR and MPR rates; specifically, the pCR rate of LUAD increased from 11.76 to 21.43% (Table SIII) and that of LUSC increased from 21.05 to 58.82% (Table IV). Although LUSC had a higher pCR rate than LUAD after chemotherapy or chemotherapy combined with immunotherapy, no statistically significant difference was demonstrated between the two subtypes (chemotherapy combined with immunotherapy, pCR P=0.07; chemotherapy, pCR P=0.66; Tables SI and SII). Moreover, in LUSC, neoadjuvant chemotherapy combined with immunotherapy significantly improved the pCR rate (P=0.01; Table IV), whereas there was no significant difference in LUAD (P=0.64; Table SIII).

Discussion

Patients with locally advanced NSCLC can benefit from neoadjuvant chemotherapy, and programmed cell death 1 inhibitor combined with chemotherapy has been reported to enhance the immune response further against tumor cells (17,18). However, NSCLC is a diverse and complex disease with distinct differences in clinical, histopathological and molecular characteristics between the LUAD and LUSC subtypes (19,20). In the present study, a comprehensive analysis was performed to evaluate the clinical efficacy of neoadjuvant therapy in these two distinct NSCLC pathological types.

In clinical trials, MPR and pCR are currently the most common modalities for assessing pathological responses to neoadjuvant immunotherapy and are also used for assessing survival (21). Several previous studies have reported an association between pCR status and survival in NSCLC (22,23). Neoadjuvant immunotherapy can reduce the primary tumor volume and enable radical resection (24). It exerts its antitumor effects by inducing antigens that trigger a durable and powerful T-cell immune response (25,26). In the CheckMate 816 study, squamous and non-squamous NSCLC were reported to have similar pCR rates to immunotherapy combined with chemotherapy with 25.3% for squamous and 22.8% for non-squamous NSCLC (11). In the present study, although there was no significant difference in the pCR rate between LUAD and LUSC after neoadjuvant chemotherapy combined with immunotherapy, the pCR rate of LUSC was higher than that of LUAD.

The pCR and MPR rates in response to neoadjuvant chemotherapy and neoadjuvant immune-combined chemotherapy in different pathological subtypes were compared. It was demonstrated that, compared with chemotherapy alone, the pCR and MPR of both pathological subtypes were increased and the pCR of LUSC was significantly improved after combined immunotherapy. Furthermore, the radiological CR in LUSC was closer to pathological pCR. A previous study reported that a higher primary pathological response was observed after neoadjuvant chemotherapy in patients with squamous cell carcinoma (26%) compared with that in patients with adenocarcinoma (12%), possibly because of greater necrosis of the initial tumor tissue in squamous cell carcinoma (27). Moreover, compared with adenocarcinoma, programmed cell death 1 ligand 1 expression is more extensive in squamous cell carcinoma and the infiltration of immune cells such as macrophages is more obvious, thus the response to tumors is more thorough, which may be responsible for the difference in the responses of squamous cell carcinoma and adenocarcinoma to immunotherapy (28).

At present, pCR and MPR only assess primary tumors and exclude lymph nodes (29). Although lymph node involvement is often one of the key prognostic factors in lung cancer, there are few studies which have evaluated lymph nodes after neoadjuvant therapy. In recent years, researchers have emphasized the significance of lymph node changes following adjuvant therapy (30). The aim of the present study was to evaluate the effect of neoadjuvant therapy on lymph nodes. However, no significant changes in lymph nodes were identified regardless of subtype or treatment regimen.

There are certain limitations to the present study. First, as it is a retrospective study, estimation of diagnostic efficacy, as well as differences in scanner and image acquisition parameters, could potentially lead to bias. Consequently, each sample was re-evaluated for pathology and radiological response, as part of the present study, to minimize bias. Secondly, the study was limited by the relatively small sample size and there may be unavoidable confounding factors; therefore, future studies with larger sample sizes are needed to confirm these findings. Third, the observation period was relatively short and the long-term overall survival rate was not analyzed, as although the data collected in this retrospective study are from January 2016 to August 2022, the data for chemotherapy combined with immunotherapy are from January 2021 to August 2022. Thus, the observation period was relatively short and complete survival data were not collected; therefore, subsequent long-term follow-up and more mature data are necessary. Despite these limitations, the findings of the present study demonstrated the difference in sensitivity to neoadjuvant therapy between pathological subtypes of NSCLC.

In conclusion, it was found that of the two major subtypes of NSCLC, LUSC was more sensitive to immunotherapy and had better clinical outcomes compared with LUAD.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YG and HSZ were responsible for study conception and design; HSZ provided administrative support; YG, HSZ, ZHL, XJY, ZWT and BZ contributed to the collection of patient data; ZHL,

XJY and ZWT collected and assembled the data; and YG and BZ performed data analysis and interpretation. All authors read and approved the final manuscript. YG and HSZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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