Original Article

The efficacy of neoadjuvant immunotherapy combined with chemotherapy in resectable stage II–IV non-small cell lung cancer: a preliminary study

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Background: Lung cancer is currently the world's leading malignancy in terms of morbidity and mortality. Neoadjuvant therapy is widely used in clinic to improve R0 resection rates and long-term survival after surgery, and patients with locally resectable non-small cell lung cancer (NSCLC) may benefit from neoadjuvant therapy.

Methods: Data from 78 patients with stage II to IV NSCLC who had received neoadjuvant immunotherapy combined with chemotherapy from January 2019 to May 2022 were collected. The patients were categorized into groups based on their eligibility for posttreatment surgery, the level of pathological remission, and receipt of adjuvant therapy. The progression-free survival (PFS) and survival rates of patients in each group were compared. Efforts were made to identify the factors that influence patients' prognoses.

Results: The incidence of adverse events in patients who received neoadjuvant immunotherapy combined with chemotherapy was 19%. The proportion of patients receiving neoadjuvant immunotherapy and chemotherapy undergoing surgery was 83.33%, and the rate of R0 resection was 64.10%. The pathological complete response (pCR) and major pathological response (MPR) rates were 26.25% and 21.87%, respectively. Patients who received adjuvant therapy were less likely to experience recurrent metastases than were those who did not receive adjuvant therapy (χ^2=7.183; P=0.007<0.05).

Conclusions: Neoadjuvant immunotherapy combined with chemotherapy has a low incidence of adverse events in resectable stage II–IV NSCLC, does not significantly increase the difficulty of surgery, and provides greater benefit in terms of PFS for patients who receive operation and adjuvant therapy.

Keywords: Lung cancer; neoadjuvant immunotherapy combined with chemotherapy; surgery

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Introduction

Background

Lung cancer is currently the most common malignancy in the world in terms of morbidity and mortality, and several clinical trials of neoadjuvant immunochemotherapy in patients with locally advanced non-small cell lung cancer (NSCLC) are underway to improve R0 resection rates and long-term postoperative survival. Tumor cells impede the immune system's killing of other tumor cells by binding programmed cell death 1 ligand 1 (PD-L1) on their surface to programmed death-1 (PD-1) on the surface of T cells. Immunotherapy enables the immune cells to effectively identify and eliminate tumor cells. A recent investigation (1) revealed that neoadjuvant immunotherapy when combined with chemotherapy induces B cells to release antibodies and collaborate with T cells to destroy tumors. In the NADIM (neoadjuvant chemotherapy and nivolumab in resectable NSCLC) trial, three cycles of neoadjuvant immunotherapy in combination with chemotherapy improved 3-year survival in patients with stage III NSCLC (2). A phase III clinical trial, CheckMate-816, showed that three cycles of neoadjuvant immunotherapy combined with chemotherapy, compared with three cycles of neoadjuvant chemotherapy, resulted in longer progression-free survival (PFS), higher rates of complete pathological remission, and reduced influence for surgery in patients with stage IB–IIIB NSCLC (3). The results of the KEYNOTE-671 trial (4) suggest that a full course of neoadjuvant immunotherapy in combination with surgery and adjuvant therapy may lead to an increase in event-free survival (EFS) in patients with NSCLC. Overall, these studies attest to the efficacy of neoadjuvant immunotherapy in combination with chemotherapy. In our study, unlike the above-mentioned prospective studies, the scope of patients included was wider; however, the patient screening process might not have been as rigorous, as it encompassed patients with target mutations and those who did and did not receive adjuvant therapy. Thus, the comparisons between groups were more intuitive and may offer valuable insights to the wider clinical community.

Objective

The aim of this study was to investigate and analyze the effect of neoadjuvant immunotherapy combined with chemotherapy on surgery, PFS, and safety in patients with resectable stage II–IV NSCLC. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1276/rc).

Highlight box

Key findings

- Neoadjuvant immunotherapy combined with chemotherapy induced fewer adverse effects and demonstrated better efficacy; surgery and adjuvant therapy can improve patient prognosis.

What is known and what is new?

- Neoadjuvant immunotherapy combined with chemotherapy has a low incidence of adverse events and demonstrates better efficacy. Operation and adjuvant therapy can improve patient prognosis.
- Patients with target mutations may benefit from immunochemotherapy.

What is the implication, and what should change now?

- Further research involving a follow-up of patient prognosis should be conducted with overall survival used as the study endpoint.
- More effective biomarkers should be identified to assess immunotherapy.

Methods

Based on the collected patient data, this study classified patients according to two criteria: (I) those who did and not receive surgical treatment and (II) those who did and did not receive adjuvant therapy. Further classification was completed based on the degree of pathological remission observed, with patients divided into pathological complete response (pCR), major pathological response (MPR), and partial response (PR) groups. This allowed for an analysis of both PFS and survival rates.

Participants

This study enrolled 78 patients with stage II to IV NSCLC who received neoadjuvant immunotherapy combined with chemotherapy at the Department of Thoracic Surgery, First Medical Center, General Hospital of Chinese People Liberation Army, between January 2019 and May 2022. Tumors were staged according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system (eighth edition) and histologically classified according to the World Health Organization (WHO) lung cancer diagnostic criteria established in 2021. Patient inclusion criteria for the study were as follows: (I) age ≥18 years, Eastern Cooperative Oncology Group (ECOG)

Table 1 Radiological staging

Stage	Preneoadjuvant therapy	Postneoadjuvant therapy
0	0	3
IA	0	9
IB	0	12
IIA	15	3
IIB	7	4
IIIA	32	30
IIIB	10	3

Values are presented as n.

score 0–1; (II) NSCLC diagnosed via pathology (histology or cytology); (III) administration of at least one cycle of immunotherapy combined with chemotherapy in our hospital or other hospitals before surgery; and (IV) cardiac function and pulmonary function assessed as being able to tolerate the lobectomy before treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of General Hospital of Chinese People Liberation Army (No. S2023-499-01). Individual consent for this retrospective analysis was waived.

Methods of assessment

Imaging assessment

Chest computed tomography (CT) or positron emission tomography (PET)-CT images and reports were collected before and after neoadjuvant immunotherapy combined with chemotherapy, and the efficacy of the imaging results was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The maximum diameter (mm) of the main body of the primary tumor foci was measured before and after treatment, and the results were translated into the staging described in *Table 1*.

Pathological assessment

The pathological assessment was performed on surgically resected specimens, and the results were classified as a MPR, pCR, PR, stable disease (SD), or progressive disease (PD). MPR was defined as neoadjuvant therapy with ≤10% residual live tumor cells on pathology, PCR was defined as neoadjuvant therapy with no residual live tumor cells on pathology or in drained lymph nodes, PR was defined as neoadjuvant tumor foci with >10% residual live tumor cells at the pathological level but smaller than the size measured in the pretreatment image, SD was defined as neoadjuvant tumor foci of the same size as that in the pretreatment image, and PD was defined as a neoadjuvant tumor foci size larger than that in the pretreatment image.

Assessment of adverse events

Any adverse reaction occurring within 1 month after the start of neoadjuvant immunotherapy combined with chemotherapy until the end of treatment, regardless of being causally related to the use of therapeutic agents, was considered an adverse event. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.1.

Follow-up

Patients were followed up by telephone or at the outpatient clinic, and patients who underwent surgery were followed up every 3 months for the first year after surgery and every 6 months from the second year onward. Follow-up to October 2022 ranged from 5 to 33 months, with a median follow-up of 10.3 months, and no cases were lost to follow-up.

Statistical methods

Statistical analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine whether patients' age, intraoperative bleeding, operation time, postoperative hospital stay, and PFS followed a normal distribution. The PFS and survival of the two groups were calculated using the Kaplan-Meier method. The rank-sum test was used to test the PD-L1 expression status and the degree of pathological response of the tumor. Statistical disparities between subgroups were assessed by means of chi-squared tests, with a test level of α=0.05.

Results

Clinical characteristics of patients

Among 78 included patients, 64 patients received surgical treatment and 14 patients received no surgical treatment. The number of neoadjuvant treatment cycles of patients who received surgical treatment ranged from one to nine, and the median number of cycles was two. The neoadjuvant regimen of 53 cases was paclitaxel + platinum + PD-L1/

Table 2 Baseline data of all patients

Characteristics	Value (n=78)
Age (years)	60 [34, 72]
Sex	
Male	67 [86]
Female	11 [14]
Surgery	
Yes	64 [82]
No	14 [18]
Pathology	
Adenocarcinoma	22 [28]
Squamous carcinoma	52 [67]
Neuroendocrine cancer	1 [1]
Large-cell carcinoma	1 [1]
Adenosquamous carcinoma	2 [3]
Smoking status	
Never smoked	21
Current or former smoker	53
Comorbidity	
No	36 [46]
Yes	42 [54]
Hypertension	24 [31]
Diabetes	9 [12]
Cerebrovascular disease	6 [8]
Cardiac infarction	1 [1]
Coronary disease	7 [9]
Hepatitis B	2 [3]
Rheumatoid arthritis	1 [1]
Peripheral vascular disease	2 [3]
Allergic asthma	1 [1]
Lymph node staging	
N0	29 [37]
N1	6 [8]
N2	42 [54]
N3	1 [1]
Stage	
II	22 [28]
IIIa	40 [51]
IIIb	12 [15]
IV	1 [1]
No record	3 [4]

Values are presented as median [first quartile, third quartile] or n [%].

PD-1 inhibitor. The most prevalent treatments included albumin-bound paclitaxel at a dose of 300 mg administered intravenously on day 1; cisplatin or carboplatin at doses of 80 and 50 mg, respectively, administered intravenously on days 1 and 2; and pembrolizumab at a dose of 200 mg, on day 4 or 5. Five cases were administered pemetrexed + platinum + PD-L1/PD-1 inhibitor. The treatment regimen consisted of pemetrexed at a dosage of 800 mg via intravenous injection on day 1, carboplatin at a dosage of 400 mg along with Lopressor at a dosage of 100 mg via intravenous injection on day 1, and pembrolizumab at a dosage of 100 mg or sindilizumab at a dosage of 200 mg on day 4. In six cases, other regimens were applied. Other details are shown in *Table 2*.

Surgical treatment

Of the 64 patients who underwent surgery, 59 underwent R0 resection and 4 underwent exploratory surgery only. Details of the surgical treatment received are shown in *Tables 3*,*4*.

Postoperative pathological response

Of the 60 patients who underwent surgical treatment (excluding those who underwent exploratory surgery), postoperative pathology indicated PCR in 17 patients (26.25%), MPR in 14 patients (21.87%), and PR in 29 patients (45.31%).

Postoperative PFS

The median PFS for patients with PCR, MPR, and PR

was not reached. Follow-up was conducted as of October 30, 2022.

Perioperative adverse events

Approximately 19% of patients experienced grade II or lower adverse events during the perioperative period, and 1 patient (1.56%) died as a result of a serious adverse event (immune pneumonitis). There were no grade III or higher adverse events in any of the patients who underwent surgery. Details are shown in *Table 5*.

Patients who did not undergo surgery

Of the 13 patients after receiving the neoadjuvant immunochemotherapy, 1 patient was admitted to medical oncology after 2 cycles of neoadjuvant therapy due to disease progression (cervical lymph node metastasis), and the remaining 12 patients were continued on medical treatment because their relatives considered that the patients were not physically fit to undergo surgery after neoadjuvant therapy. The median PFS of patients who did not undergo surgery was 23 months. The details are shown in *Table 6*.

Table 3 Details of operation data

Characteristics [2019–2022]	Value (n=64)
Thoracoscopic lobectomy	34 [53]
Thoracoscopic complex surgery	21 [33]
Sleeve lobectomy	8 [13]
Combined lobectomy	7 [11]
Pneumonectomy	6 [9]
Conversion from thoracoscopic surgery to an open approach	5 [8]
Thoracoscopy exploration	4 [6]
Bleeding volume (mL)	50 [50, 50]
Operation time (min)	150 [120, 180]

Values are presented as n [%] or median [first quartile, third quartile].

Comparison between the surgical and non-surgical groups

The tumor responses of the two groups after neoadjuvant immunochemotherapy are shown in Figure S1. The neoadjuvant and postneoadjuvant tumor therapies and postoperative pathological grading of the patients in the surgical group are described in Figure S2. The patients in the surgery group had a 91.7% PFS rate over a 23-month period, while the median PFS for patients in the non-surgical group was 23 months. The difference in PFS between the two groups was statistically significant according to the log-rank test (χ^2=16.15; P<0.05). The 23-month survival rate was 100% for patients who underwent surgery, and the median survival in the non-surgical group was 23 months. The difference in survival between the two groups was statistically significant according to the log-rank test (χ^2=28.38; P<0.05). See Figures S3,S4 for details.

Discussion

In this study, 17% of patients had grade II and below adverse reactions, only one patient died, and one patient failed to undergo surgery as planned. In the CheckMate-816 study (3), patients with stage IB–IIIA NSCLC in the neoadjuvant immunotherapy combined with chemotherapy group demonstrated a lower incidence of adverse reactions and cancellation or postponement of surgery due to adverse reactions compared to the chemotherapy-alone group. In a study by Bott *et al.* (5), the mean bleeding volume in patients operated on after neoadjuvant immunotherapy was 98 mL, the mean operating time was 168 minutes,

Table 4 Details of different styles of operation

Perioperative outcomes	Pneumonectomy	Combined lobectomy	Lobectomy (including sleeve)
Operation time (min)	165 [135, 210]	150 [120, 178]	150 [120, 195]
Intraoperative bleeding volume (mL)	175 [80, 200]	50 [45, 100]	50 [50, 50]
Postoperative hospital stay (day)	6 [5.75, 7.75]	4.5 [3, 6.75]	4 [3, 6]

Values are presented as median [first quartile, third quartile]. The above data on intraoperative bleeding, operative time, and postoperative hospital stay were tested with the Kolmogorov-Smirnov test. P<0.01, which is less than 0.05, indicating that the data did not conform to normal distribution.

Table 5 Adverse events and grade

Adverse events	All	Grade 3 or 4
Treatment-related adverse event (n=78)		
Total	15 (19.23)	–
Fever	2 (2.56)	–
Anemia	1 (1.28)	–
Alanine/alkaline aminotransferase increase	1 (1.28)	–
Pneumonia	2 (2.56)	–
Decreased white blood cell count	2 (2.56)	–
Muscle weakness of the lower limbs	1 (1.28)	–
Hyperkalemia	1 (1.28)	–
Abdominal pain	1 (1.28)	–
Alopecia	1 (1.28)	–
Hypothyroidism	1 (1.28)	–
Hyperthyroidism	1 (1.28)	–
Thromboembolic event	2 (2.56)	–
Death	1 (1.28)	1 (1.28)
Surgery-related adverse event (n=64)		
Total	29 (45.31)	–
Anemia	25 (39.06)	–
Pneumonia	1 (1.56)	–
Pneumothorax	1 (1.56)	–
Pancreatic enzyme increase	1 (1.56)	–
Hyperkalemia	1 (1.56)	–
Nausea	1 (1.56)	–
Decreased white blood cell count	1 (1.56)	–
Hypothyroidism	1 (1.56)	–

Values are presented as n (%).

Table 6 Basic data of nonoperation patients

Characteristics (2019.1–2022.5)	Value (n=13)
Age (years)	63.9±6.2
Sex	
Male	11 [85]
Female	2 [15]
Tumor response	
CR	2 [15]
PR	1 [8]
SD	2 [15]
PD	7 [54]
Metastasis	1 [8]
Status at follow-up	
Recheck	4 [31]
Continued treatment	4 [31]
Dead	5 [38]
mPFS (months)	23

Values are presented as mean ± standard deviation, n (%), or median. Age and PFS were analyzed with the Kolmogorov-Smirnov test, with P values of 0.20, 0.20, and >0.05 indicating conformity to a normal distribution. CR, complete response (defined as neoadjuvant therapy with no residual live tumor cells or in lymph nodes in imaging); PR, partial response (defined as a size of neoadjuvant tumor smaller than the size measured in the pretreatment image); SD, stable disease (defined as neoadjuvant tumor foci of the same size as that in the pretreatment image); PD, progressive disease (defined as a neoadjuvant tumor foci size larger than that in the pretreatment image); mPFS, median PFS (defined as the time to tumor progression or death present in 50% of patients); PFS, progression-free survival.

and the percentage of open thoracotomy was 17%. In the CheckMate-816 (3) trial, the mean operating times in the neoadjuvant immunotherapy combined with chemotherapy and neoadjuvant chemotherapy groups were 185 minutes and 213.5 minutes, respectively, while the percentage of open thoracotomy was 59% and 63% respectively. In this study, the median bleeding volume in the neoadjuvant immunotherapy combined with chemotherapy group was 50 mL, the median operation time was 150 minutes, and the percentage of open thoracotomy was 7%. Open thoracotomy was performed because important intraoperative anatomical structures, such as pulmonary arteries and bronchioles, were so tightly adherent that they were difficult to separate. The cause of adhesions may be due to the cytotoxic effect of platinum drugs, which interfere with cellular DNA synthesis, and albumin-bound paclitaxel, which promotes microtubule aggregation into microtubule protein dimers and inhibits stabilization of the microtubule system via microtubule depolymerization (6). However, currently, there is no clinical system for objectively evaluating the acceptability of neoadjuvant immunochemotherapy or establishing a standardized dosing

regimen, and this should be urgently addressed.

In this study, we found that in patients treated with neoadjuvant immunotherapy combined with chemotherapy, postoperative pathology showed a pCR rate of 26.25%, an MPR rate of 21.87%, a PR rate of 45.31%, and an R0 resection rate of 92.19% (see Figures S1,S2 for details). Moreover, for 26 patients in whom lymph node metastasis was highly suspected, there was no tumor cell residue in lymph nodes as confirmed pathologically after neoadjuvant therapy. Previous research (7) indicates that neoadjuvant immunochemotherapy can eradicate tumor cells by impacting the tumor microenvironment. The concomitant use of immunotherapy with chemotherapy could stimulate the immune system, enhancing the efficacy of the body's T and B cells in eliminating tumor cells for an extended period. In practice, patients receiving this approach may experience long-term benefits. The complete pCR rate for the neoadjuvant chemotherapy group in the CheckMate-816 trial was a mere 2.2%. In contrast, the neoadjuvant immunotherapy group had a pCR rate of approximately 26.25%, which supports this hypothesis.

In a study by Zhai *et al.* (8), it was shown that neoadjuvant immunochemotherapy had a strong downstaging effect on the regionally draining lymph nodes. In another study (1), neoadjuvant immunochemotherapy was demonstrated to work via the synergistic proliferation of B cells and $CD4^+$ T cells acting on lymph nodes and primary tumor. The NADIM study (2) conducted on patients with from stage III NSCLC reported a pCR rate of 36.8% in the group receiving neoadjuvant immunochemotherapy. In this group, patients with pCR did not reach the median PFS while the patients without pCR reached a median PFS of about 20 months. In the CheckMate-816 study (3), the group receiving neoadjuvant immunochemotherapy had a pCR rate of 24%. Moreover, the patients with pCR did not reach the median EFS, while the patients without pCR achieved a median EFS of around 30 months. This indicates that neoadjuvant immunotherapy in combination with chemotherapy has a more favorable effect on the short-term prognosis of patients with resectable NSCLC. The median PFS of the patients with pCR in our study was comparable with the aforementioned findings. Furthermore, we observed that the median PFS was not reached for the MPR and PR groups. This could be attributable to the fact that the majority of patients underwent adjuvant therapy postsurgery, thereby diminishing the likelihood of recurrence and metastasis, or to the brevity of the follow-up period. Similar to the abovementioned studies, we found no significant association between the degree of PD-L1 expression and the degree of pathological remission (P=0.925>0.05). One study reported heterogeneity in the PD-L1 expression within the primary lesion of the same patient with NSCLC (9). In the CheckMate-816 trial (3), EFS was 31.6 months in the neoadjuvant immunochemotherapy group and 20.8 months in the chemotherapy-alone group. In the NADIM trial (2), the 12- and 24-month PFS rates in the immunotherapy combined with chemotherapy group were 89.3% and 66.6%, respectively, whereas the 12- and 24-month PFS rates in the chemotherapy-alone group were 60.7% and 42.3%, respectively. This suggests that neoadjuvant immunochemotherapy has a better impact on the short-term prognosis of patients with resectable NSCLC. The primary objective of neoadjuvant immunochemotherapy is to enable R0 resection following surgery, when feasible. Consequently, patients without underlying ailments or with insignificant underlying ailments are more inclined to benefit from treatment. Nevertheless, there are no reliable metrics available to predict the efficacy of neoadjuvant therapy, and, unfortunately, no standard medication regimens exist that achieve the desired efficacy while reducing the potential for adverse events.

The CheckMate-816 trial (3) found that complete pathological remission after surgery may be associated with a long-term survival benefit, which is in line with our results. In addition, we found a better survival benefit in patients who underwent surgery (see Figures S3,S4 for details). Findings from the IMpower 010 trial (10) suggest that adjuvant treatment with atirizumab results in longer disease-free survival in patients with NSCLC and PD-L1 ≥50% free of target mutations compared to best supportive care. The KEYNOTE-671 trial (4) found that adjuvant immunotherapy in combination with chemotherapy improved patients' EFS compared to adjuvant chemotherapy. In our study, patients who underwent surgery after neoadjuvant therapy were followed up for a median of 19.7 months, and 46 continued to receive treatment after surgery, including immunomonotherapy, chemotherapy combined with immunotherapy, radiotherapy combined with immunotherapy, etc.; there was only one case of recurrent metastasis in these patients, and four cases did not receive any treatment after surgery and were only followed up periodically, with metastases being found in three of them. This suggests that postoperative adjuvant therapy may reduce the likelihood of recurrence (χ^2=7.183; P=0.007<0.05).

Patients with epidermal growth factor receptor (*EGFR*) mutations were not screened in this trial. For a variety of reasons, these patients were unable to undergo genetic testing in time for treatment, so neoadjuvant immunotherapy was administered in combination with chemotherapy. With the exception of one patient whose postoperative review suggested brain metastases, the remaining three patients were successfully downstaged, with pathology suggesting complete remission. Whether patients with target mutations can benefit from immunotherapy is currently unclear. A subgroup analysis of the CheckMate-057 trial (11) suggested that patients with *EGFR* mutations may not benefit from nivolumab treatment. A study (12) found that atezolizumab in combination with erlotinib for the treatment of *EGFR*-mutated NSCLC has a good safety profile with a low adverse reaction rate, while a different study (13) showed that PD-L1 expression was suppressed in patients with mutations in *EGFR* targets when an *EGFR*-tyrosine kinase inhibitor (TKI) was used. In another clinical trial (14), pembrolizumab was more effective in patients who had not been treated with a targeted agent than in those who had been treated with a targeted agent. Another study suggested that patients with *EGFR*-TKI resistance had a better response to immunotherapy (15). The results of this retrospective study suggest that patients with target mutations may benefit from immunotherapy.

Limitations

Some limitations to this study should be acknowledged. First, the number of cases enrolled in this trial was small. and the proportion of patients with squamous cell carcinoma was large, which may bias the results to a degree. Second, overall survival could not be assessed in this study, so further clarification of the effect of neoadjuvant immunotherapy combined with chemotherapy on overall survival is needed. The results of the current study suggest that there is still a lack of biological markers to guide the use of neoadjuvant immunotherapy when combined with chemotherapy in clinical practice. Third, the analyses performed might have been additionally biased due to the small number of patients who did not undergo surgical treatment for various reasons. Moreover, neoadjuvant immunochemotherapy regimens for patients with target mutations represent an area of uncertainty, as small sample sizes preclude decisive evaluation of patient benefit. Consequently, large phase III clinical trials are required to validate these regimens. Furthermore, a precise evaluation of the differential effects of neoadjuvant immunochemotherapy on metastatic lymph nodes versus the original lesion necessitates comparison across a broad sample size.

Conclusions

The results of this study indicate that neoadjuvant immunochemotherapy has more significant efficacy for advanced NSCLC and that surgery and adjuvant therapy can increase patients' PFS. This approach thus warrants further clinical application and research.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1276/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 Ethics Committee of General Hospital of Chinese People Liberation Army (No. S2023-499-01). Individual consent for this retrospective analysis was waived.

References

1. Hui Z, Zhang J, Ren Y, et al. Single-cell profiling of immune cells after neoadjuvant pembrolizumab and chemotherapy in IIIA non-small cell lung cancer (NSCLC). Cell Death Dis 2022;13:607.
2. Provencio M, Serna-Blasco R, Nadal E, et al. Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA Non-Small-Cell Lung Cancer (NADIM phase II trial). J Clin Oncol 2022;40:2924-33.
3. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
4. Wakelee H, Liberman M, Kato T, et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer. N Engl J Med 2023;389:491-503.
5. Bott MJ, Yang SC, Park BJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:269-76.
6. Topalian SL, Taube JM, Anders RA, et al. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer 2016;16:275-87.
7. Cai W, Jing M, Gu Y, et al. Tumor microenvironment features decipher the outperformance of neoadjuvant immunochemotherapy over chemotherapy in resectable non-small cell lung cancer. Front Immunol 2022;13:984666.
8. Zhai WY, Zhao ZR, Chen S, et al. Response of primary tumor and lymph node in non-small cell lung cancer after neoadjuvant immunotherapy: a pooled analysis. J Immunother Cancer 2022;10:e005160.
9. Bassanelli M, Sioletic S, Martini M, et al. Heterogeneity of PD-L1 Expression and Relationship with Biology of NSCLC. Anticancer Res 2018;38:3789-96.
10. Atezolizumab Extends DFS after NSCLC Relapse. Cancer Discov 2021;11:OF3.
11. Borghaei H, Gettinger S, Vokes EE, et al. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. J Clin Oncol 2021;39:723-33.
12. Rudin C, Cervantes A, Dowlati A, et al. P3. 02c-046 Safety, Clinical Activity and Biomarker Results from a Phase Ib Study of Erlotinib plus Atezolizumab in Advanced NSCLC: Topic: IT. J Thorac Oncol 2017;12:S1302-3.
13. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 2013;3:1355-63.
14. Lisberg A, Cummings A, Goldman JW, et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC. J Thorac Oncol 2018;13:1138-45.
15. Lu S, Wu L, Jian H, et al. Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med 2023;11:624-36.

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