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# Surgical perspective in neoadjuvant chemoimmunotherapy for stage II–III non-small cell lung cancer

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## Abstract

**Background:** There are many studies on neoadjuvant immunotherapy for locally advanced non-small cell lung cancer (NSCLC) patients. Expert consensus recommends neoadjuvant immunotherapy for patients with resectable stage IB–IIIA NSCLC. However, there are few clinical studies or cases to verify this.

**Methods:** Data were collected from all NSCLC patients who underwent surgical resection after neoadjuvant chemoimmunotherapy admitted to the Affiliated Hospital of Xuzhou Medical University and Xuzhou Central Hospital between September 2020 and April 2021. Data collected included patient information, relevant examination results, intraoperative parameters, postoperative complications, pathological changes, and 90-day mortality.

**Results:** In total, 25 patients achieved R0 resection. Eleven (44%) patients completed surgery by thoracotomy, and three (12%) procedures were changed from minimally invasive procedures due to dense adhesions of hilar lymph nodes, which rendered it difficult to dissect the blood vessels. Thirteen (52%) patients achieved a major pathological response (MPR) with eight (32%) of these patients having a pathological complete response (pCR). Twenty-two (88%) patients showed radiological regression, and three (12%) patients had stable disease. The median drainage time was 8.50 (3–27) days. Thirteen (52%) postoperative complications were observed, but none were above grade 3.

**Conclusions:** In this study, neoadjuvant chemoimmunotherapy was found to reduce tumor volume, cause pathological downstaging, and raise the surgical resection rate of patients with locally advanced NSCLC, and achieve a 100% R0 resection rate. There was an acceptable rate of postoperative complications. Thus, neoadjuvant chemoimmunotherapy is safe and practical.

**KEYWORDS**
neoadjuvant chemoimmunotherapy, neoadjuvant treatment, non-small cell lung cancer, surgical resection

## INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases.[1] Over 20% of patients with NSCLC are diagnosed with stage III or IV disease. Outcomes remain poor for this subset of patients, even if they have potentially operable tumors. They have been reported to have a median progression-free survival rate of 13 months, and 5-year survival rates remain unsatisfactory, ranging from 36% for stage IIIA disease to 60% for stage IIA. This is due to the high

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rates of recurrence and metastasis.[2] With the development of better surgical techniques and adjuvant therapy, these figures have shown some improvement but they are still insufficient.[3]

Surgery combined with preoperative adjuvant therapy has been the mainstay of treatment for patients with advanced stage NSCLC,[4] but complete resection is affected by the size and location of the tumor. There is a critical need to develop better therapeutic approaches to treat patients with locally advanced stage disease.[5] Increasing numbers of guidelines recommend targeted or adjuvant immunotherapy for patients with locally advanced NSCLC in order to maximize benefit to patients.[6]

Targeted therapy can specifically recognize tumor cells with known mutations and inhibit and targeted kill tumor cells by blocking the signaling pathway.[7] Great progress has been made in the study of targeted drugs. Although there is still a lack of effective adjuvant therapy for patients with EGFR(−) or ALK (−), immunotherapy has begun to fill the void.[8] Neoadjuvant immunotherapy can reduce tumor size, cause tumor downstaging, and render patients with locally advanced NSCLC operable. It has been reported that this therapy can eradicate circulating tumor cells and micrometastasis and therefore allow patients to survive longer.[9,10]

Expert consensus on neoadjuvant immunotherapy for NSCLC recommends the preoperative use of neoadjuvant immunotherapy with or without platinum-based chemotherapy for patients with resectable stage IB–IIIA NSCLC.[11] However, this consensus does not mention the influence of this therapy on the difficulty of surgery, or concerns of additional perioperative risks inherent in this approach, such as increased difficulty of surgical resection caused by diffuse fibrotic reaction, tissue edema, or lack of interstitial space, or the possible impairment of healing of the reconstructed bronchus caused by tissue damage and compromised vascularization.[12,13] An initial study performed at Memorial Sloan Kettering/Johns Hopkins Medicine performed on patients receiving preoperative nivolumab included 13 resections that were attempted with video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracic surgery (RATS), and approximately half (54%) had to switch to thoracotomy.[14] The effect of neoadjuvant immunotherapy on the difficulty of the operation still remains controversial.

Under the guidance of the existing clinical research basis combined with the consensus, we completed 25 cases of NSCLC surgical resection after neoadjuvant chemoimmunotherapy over a period of 6 months. A retrospective study was then performed on these cases in order to further summarize and verify the clinical effect of neoadjuvant chemoimmunotherapy. The objective of the study was to explore the clinical safety, feasibility, and effectiveness of neoadjuvant chemoimmunotherapy.

## METHODS

According to the pathological response, we identified two groups and evaluated the association between pathological status and tumor shrinkage (Table 2 and Figure 1). We retrospective evaluated data from resected NSCLC patients who underwent 2–4 cycles of neoadjuvant chemoimmunotherapy treatment between September 2020 and April 2021 at the

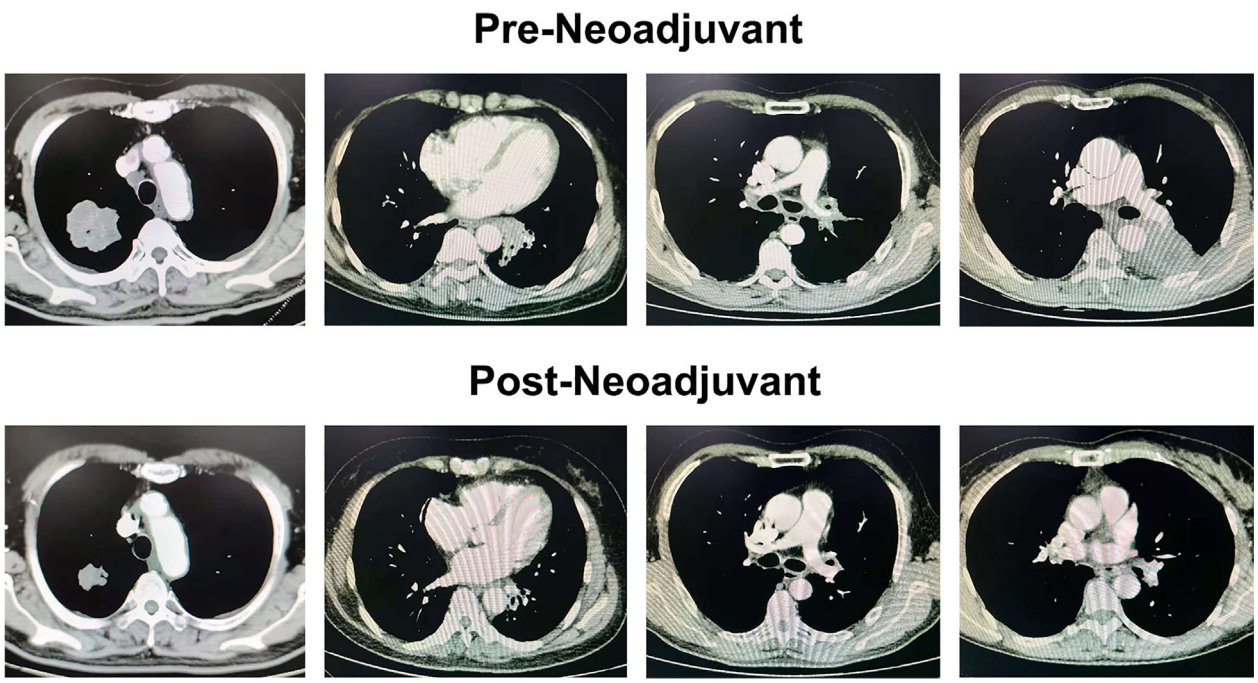


**FIGURE 1** Four typical contrast enhanced computed tomography (CT) scans in patients before and after neoadjuvant chemoimmunotherapy. Neoadjuvant chemoimmunotherapy was found to reduce tumor volume, cause pathological downstaging, and raise the surgical resection rate of patients with locally advanced NSCLC

Affiliated Hospital of Xuzhou Medical University and Xuzhou Central Hospital. A total of 25 cases were evaluated (stage IIA–IIIC according to the American Joint Committee on Cancer eighth edition lung cancer staging system.[15] These patients underwent surgical resection after neoadjuvant therapy following Chinese Medical Association guidelines for clinical diagnosis and treatment of lung cancer.[16] The demographic and clinical characteristics of the overall cohort are listed in Table 1. Extracted clinical data included examination results, intraoperative parameters, postoperative recovery outcomes, and oncological response evaluation, which included radiological and pathological regression. The major pathological response (MPR) rate was defined as 10% or less of viable tumor tissue remaining on postoperative pathological review, which was identified on routine hematoxylin and eosin staining. A complete lack of residual tumor cells in dissected tissues and lymph nodes was defined as pathological complete response (pCR). In the data analysis phase, we divided the cases into two groups according to the definition of MPR to explore the correlation between different factors and pathological reactions.

The patients' median age at the time of the surgery was 62 years (range, 51–83 years). In total, 23 of the patients were male (92.0%) and two were female (8.0%). Squamous cell carcinoma ($n = 19$, 76.0%) was the most common histological subtype and adenocarcinoma ($n = 5$, 20.0%) the second most common. In total, the majority of patients had stage IIIA disease (14, 56.0%), seven patients (28.0%) had stage IIIB disease, one patient (4.0%) had stage IIIC disease, two (8.0%) had stage IIB disease, and one (4.0%) had stage IIA disease and was treatment naive. The most commonly prescribed checkpoint inhibitor was camrelizumab (15, 60%), and the others were sintilimab (6, 24%) and pembrolizumab (4, 16%). The frequencies of the most commonly used drugs and drug classes are shown in Table 2. The median tumor diameter was 4.9 cm (range 3.4–7.1). Details of surgical intervention and tumor location for the patients are listed in Table 3.

Preoperative examination data, operation records, postoperative course of disease, and other medical records were reviewed. The radiological changes before and after chemoimmunotherapy, pathological stage, MPR, and details related to the operation were summarized. These also included surgical approach, resection range, duration of surgery, reasons for conversion to thoracotomy if necessary, drainage time, hospitalization time, postoperative complications, follow-up after discharge, which itself included adverse reactions and 90-day survival rate.

The main outcome of the study was the R0 resection rate after neoadjuvant therapy and the pathological remission rate

**TABLE 1** Demographic and clinical characteristics of the overall cohort

| Characteristic | ≤10% viable tumor ($n = 13$) | >10% viable tumor ($n = 12$) | *p*-value |
|---|---|---|---|
| Mean age (range), years | 62.35(51–83) | 57.62(49–74) | 0.674 |
| Sex | | | 0.955 |
| Female | 1(4%) | 1(4%) | |
| Male | 12(48%) | 11(44%) | |
| Histological subtype | | | 0.718 |
| Adenocarcinoma | 3(12%) | 2(8%) | |
| Squamous cell | 9(36%) | 10(40%) | |
| Adenosquamous | 0 | 0 | |
| Others | 1(4%) | 0 | |
| Clinical stage | | | 0.815 |
| IIA | | | |
| T2bN0 | 2(8%) | 0 | |
| IIB | | | |
| T2bN1 | 0 | 1(4%) | |
| IIIA | | | |
| T1cN2 | 1(4%) | 0 | |
| T2aN2 | 1(4%) | 4(16%) | |
| T2bN2 | 2(8%) | 3(12%) | |
| T3N1 | 1(4%) | 1(4%) | |
| T4N0 | 1(4%) | 0 | |
| IIIB | | | |
| T3N2 | 2(8%) | 3(12%) | |
| T4N2 | 2(8%) | 0 | |
| IIIC | | | |
| T4N3 | 1(4%) | 0 | |
| Smoking history | | | 0.214 |
| Never | 5(20%) | 3(12%) | |
| Former | 8(32%) | 7(28%) | |
| Current | 0 | 2(8%) | |

**TABLE 2** Neoadjuvant characteristics of the overall cohort

| Characteristic | ≤10% viable tumor ($n = 13$) | >10% viable tumor ($n = 12$) | *p*-value |
|---|---|---|---|
| Chemoimmunotherapy | | | |
| Chemotherapy | | | |
| Taxol + cisplatin (carboplatin) | 13(52%) | 12(48%) | |
| Prescribed checkpoint inhibitor | | | 0.716 |
| Pembrolizumab | 2(8%) | 2(8%) | |
| Sintilimab | 4(16%) | 2(8%) | |
| Camrelizumab | 7(28%) | 8(32%) | |
| Median doses (range) | 3(2–4) | 3(2–3) | 0.613 |
| Median duration from final treatment to surgery (range), days | 36(30–61) | 34(28–48) | 0.418 |
| Radiographic response assessment | | | 0.511 |
| PR | 12(48%) | 10(40%) | |
| SD | 1(4%) | 2(8%) | |
| PD | 0 | 0 | |

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

**TABLE 3** Surgical and postoperative characteristics of the overall cohort

| Characteristic | ≤10% viable tumor ($n = 13$) | >10% viable tumor ($n = 12$) | $p$-value |
|---|---|---|---|
| Approach | | | 0.866 |
| Open thoracotomy | 5(20%) | 4(16%) | |
| VATS | 2(8%) | 4(16%) | |
| RATS | 5(20%) | 3(12%) | |
| Transit thoracotomy | 1(4%) | 1(4%) | |
| Tumor location | | | 0.170 |
| LUL | 2(8%) | 0 | |
| LLL | 4(16%) | 2(8%) | |
| RUL | 3(12%) | 4(16%) | |
| RML | 1(4%) | 2(8%) | |
| RLL | 3(12%) | 4(16%) | |
| Extent of resection | | | 0.404 |
| Lobectomy | 3(12%) | 4(16%) | |
| Sleeve lobectomy | 7(28%) | 6(24%) | |
| Left pneumonectomy | 1(4%) | 0 | |
| Bilobectomy | | | |
| RML and RLL | 2(8%) | 1(4%) | |
| RUL and RML | 0 | 1(4%) | |
| Median operative time (range), min | 143 (87–243) | 152(76–237) | 0.814 |
| Median estimated blood loss (range), ml | 110 (60–230) | 120(80–200) | 0.143 |
| Drainage time (days) | 5.50(3–27) | 6.8(5–23) | 0.633 |
| Median hospital length of stay after surgery (range), days | 6.7 (4–27) | 7.8(5–24) | 0.724 |
| Pathological complete response | 8(32%) | 0 | 0.001 |
| Postoperative complications | | | 0.372 |
| Prolonged air leak | 3(12%) | 4(16%) | |
| Wound infection | 0 | 0 | |
| Arrhythmia | 1(4%) | 0 | |
| Pneumonia | 3(12%) | 2(8%) | |
| Broncho-obstruction | 0 | 1(4%) | |
| Surgical margin | | | 1 |
| R0 | 13(52%) | 12(48%) | |
| R1 | 0 | 0 | |
| R2 | 0 | 0 | |

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; RATS: robot-assisted thoracic surgery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; VATS, video-assisted thoracoscopic surgery; Unless otherwise indicated, data are n (%).

(pCR/MPR rate). The secondary observation indexes were the rate of radiological-regression and postoperative complications.

All patients were monitored for adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events. TNM staging was based on the eighth edition of the American Joint Committee on Cancer staging manual. Mediastinal lymph node staging was based on the 2009 International Association of the Study of Lung Cancer lymph node map.

## Statistical analysis

Data are expressed as median and range unless otherwise indicated, and $p < 0.05$ was considered statistically significant. Statistical calculations were conducted with SPSS software (IBM SPSS Statistics for Windows, version 22.0., IBM Corp.).

# RESULTS

## Pathological remission assessment

After surgical resection, 13 of 25 resected tumors experienced a MPR (52%), and eight patients achieved pCR (32%) (Table 3). Postoperative pathology usually showed hyperplasia of bronchial and peribronchial fibrous tissue with transparent degeneration, necrosis, and a large number of foam cells in some areas; lipid crystallization and multinucleated giant cell reaction in other areas; and a small or nonexistent residual tumor.

## Radiological regression

According to the imaging evaluation before and after neoadjuvant therapy and the Response Evaluation Criteria in Solid Tumors [17] 22 (88%) patients achieved partial remission (PR) (Figure 1), 3 patients had stable disease, and no disease progression (PD) occurred in any patient (Table 2). No differences were found between the two groups in terms of tumor shrinkage ($p = 0.511$).

## Operation and recovery outcome

No death or serious side effects occurred during neoadjuvant therapy. One patient experienced a long interval without drug treatment—61 days—because of the Chinese Lunar New Year Holiday. A total of 25 patients achieved R0 resection. Among them, lobectomy was performed in seven cases (28%), sleeve lobectomy in 13 cases (52%), left pneumonectomy in one case (4%), and bilobectomy in four cases (16%). The median drainage time was 8.50 days (3–27). One or more postoperative complications occurred in 13 of these 25 patients (overall morbidity, 52%) (Table 3). There was no significant difference in complication rates between the two groups ($p = 0.372$).

## Recurrence and survival outcome

No early deaths (within 90 days) were reported in this cohort, and the recurrence rate was 0% in 90 days.

**TABLE 4** Comparison with previous studies on neoadjuvant therapy for NSCLC

| Study | Size (cases) | Stage | Neoadjuvant therapy | R0 rate | MPR |
|---|---|---|---|---|---|
| Our study | 25 | IIA–IIIC | Chemoimmunotherapy | 100% | 52% |
| NADIM | 46 | IIA–IV | Chemoimmunotherapy | 100% | 83% |
| NCT02716038 | 22 | IB–IIIA | Chemoimmunotherapy | 86.4% | 54.5% |
| CM159 | 21 | I–IIIA | Immunotherapy | 95% | 45% |
| LCMC3 | 101 | IB–IIIB | Immunotherapy | 89% | 19% |
| TOP1501 | 35 | IB–IIIA | Immunotherapy | 83% | 28% |

Abbreviation: MPR, major pathological response.

The survival statuses were obtained from clinical medical records or telephone follow-up.

## DISCUSSION

The biggest question for locally advanced NSCLC patients is whether surgery is a suitable option. The surgical techniques available involve great difficulty. Ordinarily, these patients can choose to undergo bilobectomy or pneumonectomy to achieve R0 resected by thoracotomy for long-term survival, which may lead to a poor quality of life, or can undergo R1/R2 resection for a better quality of life but leaving the residual tumors. These patients and their doctors face a dilemma. The 25 patients retrospectively analyzed in this study were considered difficult and risky for surgery before neoadjuvant therapy, and unable to undergo lobectomy or sleeve lobectomy without the risk of residual tumors. After neoadjuvant chemoimmunotherapy, the R0 resection rate reached 100%. In total, 20 (80%) patients underwent lobectomy and sleeve lobectomy, and 14 (56%) underwent minimally invasive surgery (including VATS and RATS). Only one patient underwent pneumonectomy (4%), which is much lower compared with previous studies.[18] This proved that neoadjuvant chemoimmunotherapy can improve the resection rate and R0 resection rate of patients with locally advanced NSCLC.[19]

Many studies have been published on neoadjuvant therapy for NSCLC (Table 4): Checkmate-159 research showed that neoadjuvant nivolumab was associated with few side effects, did not delay surgery, and induced MPR in 45% of resected tumors.[20] The NADIM study was the first to evaluate the potential therapeutic effect of neoadjuvant PD-1 inhibitors in combination with chemotherapy in stage IIIA NSCLC patients.[14] A high MPR rate of 85.36% and 100% R0 resection rate suggested that combination neoadjuvant strategy might be a new option for patients with locally advanced NSCLC. Similar to Checkmate-159, the MPR rate of our study is 52%, which indicates neoadjuvant chemoimmunotherapy led to considerable pathological remission. As a research focus, MPR was chosen as the grouping criteria to study the predictive value of pathological indexes in this study.

Neoadjuvant administration was not associated with delays in surgery in this study. All surgical operations were successfully completed without adverse events such as intraoperative hemorrhage. The middle chest tube duration was 8.50 days (3–27). Treatment-related adverse events occurred in 13/25 (52%) patients. There were similar rates of complications in the present neoadjuvant group and in those from previous reports without neoadjuvant cohorts: 42.5%–68.3%.[21] This suggests that the method is safe and feasible. The patients who benefited according to the consensus had stage IB–IIIA resectable NSCLC. However, a significant effect was also found in patients with stage IIIB or IIIC NSCLC after neoadjuvant chemoimmunotherapy in this study. These patients ultimately achieved R0 resection. The research team at our institution expect that these benefits will be expanded to IIIB–IIIC NSCLC patients in the future.

The effect of neoadjuvant chemoimmunotherapy on the difficulties associated with surgery is unclear. Through the analysis of 25 cases, researchers at our center have attempted to analyze the difficulty of surgery in two respects. First, for some patients with large tumors, direct resection is very difficult, and neoadjuvant therapy helps to shrink the tumor, create space for surgery, and reduce the difficulties associated with surgery. Second, during clinical practice, we also found that neoadjuvant chemoimmunotherapy caused thickening of the tunica vaginalis, thickening of tissue around tumor edema, and compromised vascularization. Shrinkage of lymph nodes led to a lack of interstitial space in most cases in this study and increased the difficulty and risk of surgery, as in previous clinical studies.[22]A greater destruction of elastic fiber of the blood vessels, vascular wall degeneration, fibrinoid necrosis and fibrosis, and greater pulmonary interstitial exudation were found in neoadjuvant immunotherapy patients compared to the neoadjuvant chemotherapy patients according to a recent study,[13] and researchers should pay more attention to this in the future. These will increase the difficulties associated with surgery, which is manifested in an increase in the thoracotomy rate. Just as is reported in the study by Yang et al. which used preoperative chemotherapy plus ipilimumab, 12 of 13 patients had initially been scheduled for a minimally invasive approach, and the conversion rate was 25%.[18]

Pathological complete response is the most commonly used alternative endpoint in the design of clinical trials evaluating neoadjuvant therapy.[23] The FDA has reported that pCR is an effective predictor of event-free survival (EFS),

disease-free survival (DFS), and overall survival (OS). With the development of neoadjuvant therapy in recent years, patients with pCR have gradually expanded to a group that cannot be ignored in neoadjuvant therapy. Three questions come to mind on the management of patients with pCR. First, the diagnosis of pCR in clinical settings relies on the pathological examination of the tumor after resection. We should try to establish a system to determine whether to achieve pCR after neoadjuvant therapy and before surgery. It is of great significance to evaluate the curative effect of neoadjuvant therapy, formulate treatment plans, and assess the prognosis of different patients. Then, after identifying patients with pCR, the treatment team must determine whether it is necessary for them to undergo surgical treatment. We evaluated different patients with locally advanced NSCLC in clinical practice. Whether surgery is necessary, or not, according to the patient's age, complications, family members' wishes and expectations, and other factors should ultimately be determined.

Third, we must determine whether pCR means that there are in fact no surviving tumor cells. It is unclear whether achieving pCR can lead to an improvement in overall survival. In May 2012, the FDA approved pCR as an alternative endpoint for accelerated drug approval. It has served as an alternative endpoint in clinical research for many years. PCR is a widely used index, but some studies have questioned its predictive value in recent years. Some researchers claim that pCR may be correlated with OS, but note that statistical correlation is not equal to causality. Cortazar et al.[24] analyzed data from 12 identified international trials and 11 955 patients and recorded little association between increases in frequency of pCR and EFS (R [2] = 0.03, 95% CI: 0.00–0.25) and OS (R[2] = 0.24, 0.00–0.70). Furthermore, a meta-analysis reported by Berruti et al.[25] (29 trials, 59 arms, and 30 comparisons with a total of 14 641 patients) did not support the use of pCR as a surrogate endpoint for DFS and OS. Whether pCR means there are actually no surviving tumor cells remains to be determined. The definition and criteria of pCR have not been updated for many years. The increasing proportion of patients with pCR in clinical research suggests that the relevant indicators and detection should be improved. The previous definition of pCR is based on pathomorphology alone. We should define pCR in many dimensions, including gene target, histochemistry, second generation sequencing, and liquid biopsy. This should be an important direction for future research, and a beneficial supplement for the accurate management of patients with locally advanced NSCLC and pCR after neoadjuvant therapy.

In conclusion, based on the findings from the analysis of the cases in this study, neoadjuvant chemoimmunotherapy has been shown to achieve pathological response and pathological downstaging and increase R0 resection rate with no increase in perioperative adverse events and surgical difficulty. For patients with locally advanced NSCLC, this therapy is safe, effective, and feasible.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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