Original Article

Neoadjuvant therapy bridging percutaneous coronary intervention (PCI) and video-assisted thoracoscopic (VATS) lobectomy: a retrospective study

Lin Guo^, Songlei Ou, Shaoyan Zhang, Dong Li, Xuchen Ma

Department of Thoracic Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China

Contributions: (I) Conception and design: L Guo, S Ou, X Ma; (II) Administrative support: X Ma; (III) Provision of study materials or patients: D Li, S Zhang; (IV) Collection and assembly of data: L Guo, S Ou, X Ma; (V) Data analysis and interpretation: L Guo, D Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xuchen Ma, MD. Department of Thoracic Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, 2 Anzhen Road, Chaoyang District, Beijing 100029, China. Email: maxunchenanzhen@126.com.

Background: Currently, there is no unified standard for the treatment of coronary artery disease (CAD) in non-small cell lung cancer (NSCLC), and the treatments have their own advantages and disadvantages. Thus, this study aimed to analyze the safety and feasibility of neoadjuvant therapy during the dual antiplatelet therapy (DAPT) period before surgery in patients with NSCLC coexisting with CAD after percutaneous coronary intervention (PCI) treatment.

Methods: We retrospectively included 13 patients with T2aN0M0 (stage IB) NSCLC who also had concomitant CAD. After PCI treatment, neoadjuvant targeted or immunotherapy was administered based on the type of lung cancer, and the effects on treatment and impact on surgery were observed.

Results: The objective response rate (ORR) after neoadjuvant treatment in 13 patients was 53.8% [95% confidence interval (CI): 25.1–80.8%], and the disease control rate (DCR) reached 100%. Ten patients (76.9%) experienced adverse events (AEs) ≤ grade 2. All patients underwent standard VATS lobectomy with lymph node dissection. One case (7.7%) required conversion to open thoracotomy, and all cases achieved R0 resection. The median operative time was 150 [interquartile range (IQR) 125–250] minutes, median intraoperative blood loss was 180 (IQR 150–235) mL, median postoperative drainage tube placement time was 4 (IQR 3–5) days, median total drainage volume was 1,310 (IQR 780–1,705) mL, and the median postoperative hospitalization was 7 (IQR 7–8) days. One patient (7.7%) experienced rapid atrial fibrillation. No deaths occurred. Postoperative pathological evaluation in three cases achieved major pathological response (MPR) (23.1%, 95% CI: 5–53.8%), with two cases achieving pathological complete response (pCR) (15.4%, 95% CI: 1.9–45.4%).

Conclusions: The study presents initial evidence suggesting for the safety and feasibility of performing PCI treatment followed by neoadjuvant therapy during the DAPT period for patients with T2aN0M0 (IB) stage NSCLC coexisting with CAD. This approach presents a potential treatment option to control the disease while eliminating concerns about tumor progression and metastasis.

Keywords: Coronary artery disease (CAD); non-small cell lung cancer (NSCLC); percutaneous coronary intervention (PCI); neoadjuvant therapy; video-assisted thoracoscopic lobectomy

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^ ORCID: 0009-0003-5009-202X.

Introduction

Cancer and cardiovascular diseases are two major threats to human health. Global cancer epidemiological statistics (GLOBOCAN) indicate that in 2020, there were approximately 2.207 million new cases of lung cancer worldwide, with about 1.796 million new deaths, accounting for 11.4% and 18.0% of all new and fatal malignant tumor cases, respectively. Globally, lung cancer is the leading cause of cancer-related death in males and the second leading cause in females (1). In 2022, China reported around 871,000 new cases of lung cancer and approximately 767,000 new deaths, constituting 18.1% and 23.9% of all malignant tumor incidence and mortality cases, respectively (2). The treatment of non-small cell lung cancer (NSCLC) involves personalized comprehensive approaches such as surgery, targeted therapy, immunotherapy, chemotherapy, and radiotherapy. Neoadjuvant therapy for resectable NSCLC has various potential benefits, including better tolerability compared to traditional chemotherapy (3) and early systemic treatment controlling micro-metastases, reducing the scope of surgical resection, and achieving complete removal (4). Coronary artery disease (CAD) is also a common cardiovascular disease with high global incidence and mortality rates. According to the "China Cardiovascular Health and Disease Report 2022", there are 11.39 million existing CAD patients in China, and its mortality rate is the highest among all diseases (5). Tumors and cardiovascular diseases share some common risk factors and biological pathways, leading to an increasing incidence of NSCLC combined with CAD (6,7). Data show that 20.9% of NSCLC patients requiring surgical treatment also have CAD (8). The incidence and mortality rates of perioperative cardiovascular-related diseases, such as acute coronary syndrome (ACS), significantly increase (9,10).

The primary methods for CAD surgery are percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Currently, there is no unified standard for the treatment of CAD in NSCLC, including staged PCI, staged CABG, and simultaneous CABG. But for patients with of concurrent lung cancer and cardiovascular disease, these approaches have their own advantages and disadvantages. PCI has advantages such as minimal trauma and faster recovery. With improvements in intervention techniques, the application of drug-eluting stents (DESs), and the use of radial artery access, the occurrence of postoperative complications and other adverse events (AEs) has significantly decreased, which making it the preferred method for treating CAD (11). However, lung cancer surgery needs to be delayed until the completion of dual antiplatelet therapy (DAPT). The current optimal duration for DAPT is 6–12 months, although some literature reports a possible reduction to 3 months (12,13). During this period, there is a risk of lung cancer progression and metastasis, impacting patient staging, surgical treatment, and prognosis. Patients have experienced failure or infeasibility of PCI may opt for CABG. Staged CABG, which involves two separate surgeries for CABG and lung cancer resection, can result in two wounds and increase pain and pressure on patients, meanwhile is associated with various complications, potential disease progression due to delayed treatment, patient anxiety, elevated treatment costs and prolonged hospitalization. Simultaneous CABG has one or two surgical incisions under general anesthesia and effectively avoids the delay in lung cancer treatment, but carries a higher risk of perioperative mortality and complications, and presents technical difficulties in removing mediastinal lymph nodes. Therefore, the selection of surgical methods should be determined based on the patient's condition and requirement (14). Therefore, exploring a new treatment method that is minimally invasive, with fewer complications, and simultaneously adheres to the principles of oncology treatment has certain clinical significance.

In this study, we retrospectively included 13 patients with T2aN0M0 (stage IB) NSCLC who also had concomitant CAD, performing PCI as an initial treatment followed by

Highlight box

Key findings

- This study presents initial evidence suggesting that for patients with T2aN0M0 (stage IB) non-small cell lung cancer (NSCLC) who also have concomitant coronary artery disease, after performing percutaneous coronary intervention (PCI), treatment followed by neoadjuvant therapy during the dual antiplatelet therapy (DAPT) period is safe and feasible, which presented a potential treatment option to control the disease and eliminated concerns about tumor progression and metastasis.

What is known and what is new?

- Targeted therapy and immunotherapy have made significant progress in advanced NSCLC and neoadjuvant strategies for NSCLC have received widespread attention.
- There are currently no relevant trials that consider neoadjuvant therapy as a bridging treatment between PCI and lobectomy.

What is the implication, and what should change now?

- This strategy presents a potential treatment option for lung cancer patients with severe coronary artery disease.

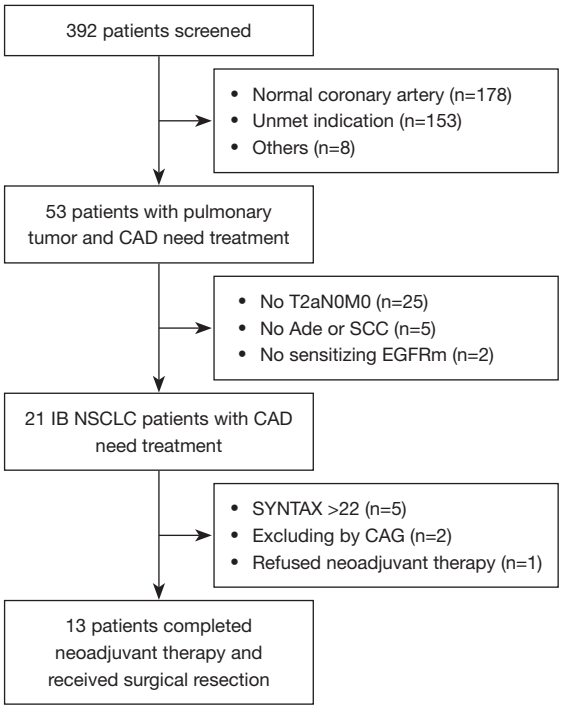

Figure 1 Screening flow diagram. CAD, coronary artery disease; Ade, adenocarcinoma; SCC, squamous cell carcinoma; EGFRm, epidermal growth factor receptor mutation; NSCLC, non-small cell lung cancer; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery; CAG, coronary angiography.

neoadjuvant therapy during the DAPT period and analyzed the safety and feasibility of neoadjuvant therapy. This article is presented in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-132/rc).

Methods

Clinical information

From January 2021 to December 2022, a total of 392 patients with screening for lung tumors and concomitant cardiovascular high-risk factors were identified, with 13 patients ultimately included in the study. The median age was 68 [interquartile range (IQR) 62–73] years, with 9 male patients (69.2%) and 4 female patients (30.8%) (*Figure 1*). All patients underwent staged PCI followed by video-assisted thoracoscopic surgery (VATS) lobectomy. Inclusion criteria: patients under 75 years of age with concomitant cardiovascular high-risk factors, chest computed tomography (CT) indicating a solitary lesion >3 and ≤4 cm, preoperative tissue cytology diagnosis obtained through bronchoscopy or CT-guided puncture confirming lung adenocarcinoma or squamous cell carcinoma. According to the Eighth Edition of the International Association for the Study of Lung Cancer (IASLC) lung cancer Tumor Node Metastasis (TNM), classification was T2aN0M0 (IB). Epidermal growth factor receptor (EGFR) 19 exon deletion (ex19Del) or 21 exon mutation (leu858Arg) in lung adenocarcinoma confirmed by allele-specific PCR (AS-PCR). Coronary CTA indicating a single or double lesion, CT-FFR <0.8, coronary angiography SYNTAX score ≤22, ECOG score ≤1. Exclusion criteria: Complex coronary lesions not suitable for PCI, heart function ≥2, FEV1 <1.5L, concomitant severe functional diseases in other systems. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (Ethics Approval No: 2020022X), and all participants provided informed consent.

Treatment planning

Before treatment, all patients underwent positron emission tomography (PET)-CT examination to assess clinical staging, excluding lymph node and distant metastasis. Coronary angiography was performed through radial artery by local anesthesia to confirm the location, type, and degree of vascular stenosis. DESs were implanted. DAPT protocol: after PCI, aspirin 0.1 g + clopidogrel 75 mg were taken 12 weeks for antiplatelet therapy. Clopidogrel was discontinued 5 days before lung cancer surgery, and aspirin continued to be taken perioperatively. Depending on drainage, clopidogrel was resumed 24–72 hours after surgery. Patients with lung adenocarcinoma received neoadjuvant targeted therapy: gefitinib 250 mg QD for 12 weeks. Surgery was performed after a one-week drug withdrawal. After surgery, oral gefitinib 250 mg QD was continued for 2 years. Patients with lung squamous cell carcinoma received neoadjuvant immunotherapy combined with chemotherapy: tislelizumab (200 mg, D1) combined with albumin-bound paclitaxel (260 mg/m^2, D2) and cisplatin (AUG5, D3), Q3W, for 3 cycles. Surgery was made after observing 4 weeks. After surgery, tislelizumab (200 mg) was administered every 3 weeks for maintenance therapy for 2 years.

Before surgery, all patients underwent PET-CT examination again to assess the therapeutic effect and

clinical staging. Evaluation of imaging responses was done according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), including:

- Complete response (CR): all target lesions disappear, no new lesions appear, and tumor markers are normal, maintained for at least 4 weeks.
- Partial response (PR): the sum of the longest diameters of target lesions decreases by ≥30%, maintained for at least 4 weeks.
- Progressive disease (PD): the sum of the longest diameters of target lesions increases by ≥20%, or new lesions appear.
- Stable disease (SD): the sum of the longest diameters of target lesions does not reach PR shrinkage or PD enlargement.

Disease control rate (DCR): the proportion of patients with CR + PR + SD.

Objective response rate (ORR): the proportion of patients with CR + PR.

After general anesthesia and double-lumen endotracheal intubation, patients underwent standard VATS lobectomy with lymph node dissection. We carried out 2 incisions, one of 3–4 cm in the 4th or 5th intercostal space on the anterior axillary line and another of 1 cm in the 7th intercostal space on median axillary line. The right-side operation should clear groups 2R, 4R, 7, 8, and 9, with an attempt to remove as much as possible from group 3A. The left-side should clear groups 5, 6, 7, 8, and 9, with an attempt to remove as much as possible from group 4L. Lymph nodes in the hilar (group 10) and pulmonary (groups 11, 12) regions were removed in all operations. R0 resection rate was the proportion of patients undergoing curative surgery for lung cancer. Pathological response evaluation was performed on the resected specimens, including:

- Major PR (MPR): the proportion of patients with residual viable tumor cells not exceeding 10%.
- Pathological CR (pCR): the proportion of patients with no residual viable tumor cells.

AEs were monitored throughout the entire treatment period. Physical examinations, vital signs, electrocardiograms, echocardiograms, and laboratory tests were conducted at specific time points and compared with baseline values. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Observational items

Coronary artery lesion status, number of stents implants, DCR, ORR, AEs, surgical approach, R0 resection rate, operative time, intraoperative blood loss, postoperative drainage tube placement time, total drainage volume, postoperative hospitalization, MPR, pCR, complications, and follow-up time were observed.

Statistical analysis

Continuous variables are presented as median (IQR). Categorical variables are expressed as n (%). The Clopper-Pearson method is used to calculate the 95% confidence intervals (CI) for ORR, MPR, and pCR. Statistical analysis is conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

From January 2021 to December 2022, a total of 392 patients with lung tumors and concomitant cardiovascular high-risk factors were screened and identified, with 13 patients ultimately included in the study. The median age was 68 (IQR 62–73) years, with 9 male patients (69.2%) and 4 female patients (30.8%). Among them, 5 had lung adenocarcinoma, and 8 had lung squamous cell carcinoma. The median fractional flow reserve (FFR) was 0.69 (IQR 0.67–0.72), median ejection fraction (EF) was 60% (IQR 56.5–65), median forced expiratory volume in 1 second (FEV1) was 2.13 (IQR 1.90–2.39) L, and the median SYNTAX score was 11.0 (IQR 6.5–15.5) (*Table 1*). Coronary angiography indicated single-vessel disease in 9 cases (69.2%) and double-vessel disease in 4 cases (30.8%). A total of 27 DESs were implanted, and postoperative TIMI blood flow grades all reached level 3. During the neoadjuvant treatment period, 10 patients (76.9%) experienced AEs of grade ≤2, all of which were managed symptomatically without affecting the treatment process (*Table 2*). After completion of treatment, 7 cases (53.8%) achieved a PR, and 6 cases (46.2%) maintained SD. The ORR was 53.8% (95% CI: 25.1–80.8%). The DCR reached 100% (*Figure 2*).

All patients underwent standard VATS lobectomy with lymph node dissection. One case (7.7%) required conversion to open thoracotomy, and all cases achieved R0 resection. The distribution of VATS lobectomy is as follows: right upper lobe (2 cases, 15.4%), right middle lobe (2 cases, 15.4%), right lower lobe (5 cases, 38.5%), left upper lobe (3 cases, 23.1%), and left lower lobe (1 case, 7.7%). The median operative time was 150 (IQR

Table 1 Clinical information

Category	Patients
Age (years)	68 [62–73]
Sex	
Male	9 (69.2)
Female	4 (30.8)
Smoking	
Current	8 (61.5)
Never	5 (38.5)
Comorbidity	
Diabetes	5 (38.5)
Hypertension	8 (61.5)
Hyperlipidemia	9 (69.2)
ECOG scale	
0	7 (53.8)
1	6 (46.2)
Tumor histology	
Adenocarcinoma	5 (35.8)
Squamous cell carcinoma	8 (61.5)
Fractional flow reserve	0.69 [0.67–0.72]
EF%	60 [56.5–65]
FEV1 (L)	2.13 [1.90–2.39]
SYNTAX scores	11.0 [6.5–15.5]

Data are presented as n (%) or median [IOR]. ECOG, eastern cooperative oncology group; EF, ejection fraction; FEV1, forced expiratory volume in one second; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery; IQR, interquartile range.

Table 2 Treatment-related adverse events during neoadjuvant therapy

Adverse events	Grade 1	Grade 2	Grade 3	Total
Skin and mucosa	3	1	0	4
Gastrointestinal problems	4	0	0	4
Cardiotoxicities	0	0	0	0
Nephrotoxicity	0	0	0	0
Hepatotoxicity	5	1	0	6
Neurotoxicity	1	0	0	1
Others	1	0	0	1
Total number	14	2	0	16

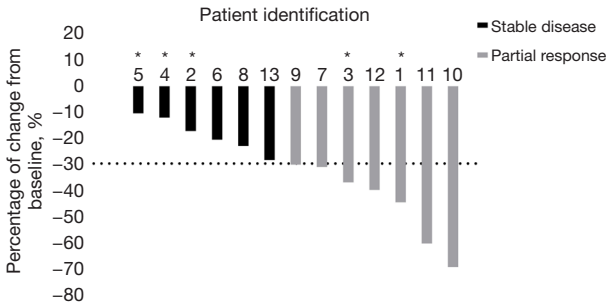

Figure 2 Waterfall plot of target lesion changes in the 13 patients after neoadjuvant treatment. *, represents adenocarcinoma patients.

125–250) minutes, median intraoperative blood loss was 180 (IQR 150–235) mL, median postoperative drainage tube placement time was 4 (IQR 3–5) days, median total drainage volume was 1,310 (IQR 780–1,705) mL, and the median postoperative hospitalization was 7 (IQR 7–8) days. During the perioperative period, one patient (7.7%) experienced rapid atrial fibrillation, which improved after antiarrhythmic treatment. No deaths occurred (*Table 3*). All postoperative pathology results were consistent with preoperative pathology, and no lymph node metastasis was found. Three cases (23.1%) achieved MPR based on postoperative pathology assessment (95% CI: 5–53.8%). Among them, two cases (15.4%) achieved pCR (95% CI: 1.9–45.4%) (*Figure 3*). The current median follow-up time for the patients is 21 (IQR 19–26) months. The medical condition remains stable, and there have been no indications of disease recurrence or metastasis.

Discussion

Patients with NSCLC who are eligible for surgical resection often have cardiovascular high-risk factors. These factors include age over 65, a history of CAD or clinical manifestations of myocardial ischemia, abnormal electrophysiology (such as arrhythmias, conduction blocks), cardiovascular complications (such as hypertension, diabetes, peripheral vascular disease), etc. Many of these patients also have varying degrees of coronary artery stenosis. In this trial, 54.6% (214/392) of patients had coronary artery stenosis, and 13.5% (53/392) had severe coronary artery stenosis. The most significant cardiovascular complication in these patients during the perioperative period is ACS, which is a common and serious complication after non-cardiac surgery, especially in the presence of coronary artery stenosis (15). The mortality rate

Table 3 Outcomes of treatment

Category	Patients
Coronary lesion	
One	9 (69.2)
Two	4 (30.8)
Stent number	
One	5 (38.5)
Two	4 (30.8)
Three	2 (15.4)
Four	2 (15.4)
Curative response	
ORR	7 (53.8)
DCR	13 (100.0)
VATS lobectomy	
RUL	2 (15.4)
RML	2 (15.4)
RLL	5 (38.5)
LUL	3* (23.1)
LLL	1 (7.7)
Operative time (minutes)	150 [125–250]
Intraoperative bleeding loss (mL)	180 [150–235]
Postoperative drainage tube placement (days)	4 [3–5]
Total drainage volume (mL)	1,310 [780–1,705]
Postoperative hospitalization duration (days)	7 [7–8]
Pathological assessment	
MPR	3 (23.1)
pCR	2 (15.4)
Complication	1 (7.7)
Follow-up (months)	21 [19–26]

Data are presented as n (%) or median [IQR]. *, one patient transferred to open lobectomy. ORR, objective response rate; DCR, disease control rate; VATS, video-assisted thoracoscopic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; MPR, major pathological response; pCR, pathological complete response; IQR, interquartile range.

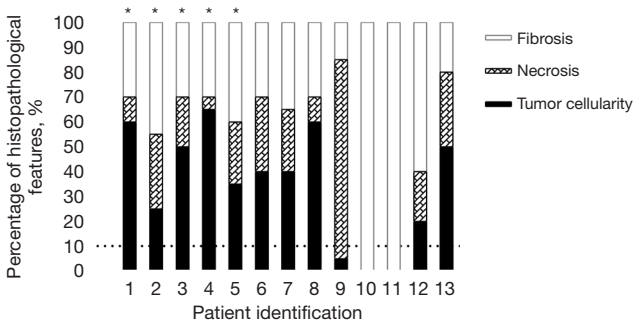

Figure 3 Postoperative pathological assessment in the 13 patients after neoadjuvant treatment. *, represents adenocarcinoma patients.

of perioperative acute myocardial infarction is significantly higher than that during non-surgical treatment (16). Lung cancer, once diagnosed, requires timely surgery to prevent disease progression and loss of the opportunity for surgery. However, malignant tumors themselves can trigger a hypercoagulable state, exacerbating CAD. Additionally, lung resection surgery can reduce the pulmonary vascular bed, leading to hypoxia and hemodynamic instability. This can cause coronary artery spasm, exacerbation of stenosis, and reduced blood flow. Performing lung cancer resection in patients with unstable severe CAD may lead to fatal ACS. Therefore, for patients with cardiovascular high-risk factors before surgery, it is recommended to conduct comprehensive assessments, including coronary CT angiography, myocardial scintigraphy, FFR, and other relevant examinations to determine the presence of coronary artery stenosis. If there are indications of left main trunk ≥50% or non-left main trunk ≥70% stenosis, ischemic area ≥10%, FFR <0.8, etc., further coronary angiography evaluation is needed. The decision to choose PCI or CABG for revascularization should be based on the SYNTAX score (17).

The treatment of NSCLC combined with CAD includes staged PCI, staged CABG, and concurrent CABG. Each of these treatment methods has its advantages and disadvantages. PCI has the benefits of small trauma and quick recovery, but the curative surgery for NSCLC needs to be delayed until the end of DAPT, which generally requires 6–12 months for DESs and at least 3 months (12,13). In recent years, with the widespread use of CT imaging examinations, many early lung cancers presenting as ground-glass nodules (GGN) have been discovered, especially non-invasive adenocarcinomas with T≤2 cm and a consolidation-to-tumor ratio (CTR) ≤25%, reaching a non-invasive rate of 98.7%, with slow progression (18,19). For such lung cancer patients with severe CAD, we believe that staged treatment, especially staged PCI, is more

advantageous. However, for NSCLC with T>3 cm or CTR >50%, there are concerns when considering staged PCI due to the risk of tumor progression and metastasis (20). Of course, in clinical practice, bare-metal stents (BMSs) can be chosen, and the DAPT time can be shortened to 1 month (21). However, the restenosis rate within 6 months of BMSs is 30%, significantly higher than that of DESs (22). This will significantly increase the long-term ACS risk for early lung cancer patients. For patients unsuitable for PCI, staged CABG has a low short-term surgical risk but requires two surgeries, increasing psychological burden and length of hospitalization, with a surgery interval generally of 2–4 weeks. Concurrent CABG can remove lung tumors while dealing with complex coronary artery lesions, without delaying lung cancer treatment. However, it has a large short-term surgical trauma, numerous complications, a high perioperative mortality rate (23), and clearing mediastinal lymph nodes through the midline incision can be challenging, often requiring a change in body position before lung surgery. Therefore, for NSCLC patients with concomitant CAD, a more precise personalized treatment plan should be formulated.

Neoadjuvant therapy is typically aimed at potentially resectable tumors, involving preoperative treatments such as chemotherapy, targeted therapy, immunotherapy, and radiation to increase the chances of curative resection by reducing tumor volume, eliminating micro-metastases, and lowering the risk of tumor recurrence. As targeted therapy and immunotherapy have made significant progress in advanced NSCLC, and with a growing awareness of the importance of improving survival outcomes in early-stage NSCLC, new adjuvant strategies for NSCLC have received widespread attention (24). Moreover, neoadjuvant therapy can directly influence the pathological response rates. For instance, chemotherapy often works by damaging DNA or disrupting cell division, leading to tumor cell death. Targeted therapies, on the other hand, aim to interfere with specific molecular pathways critical for tumor growth and survival. Immunotherapy agents, such as immune checkpoint inhibitors, work by enhancing the activity of the immune system against cancer cells. The extent of immune cell infiltration into the tumor microenvironment and the presence of pre-existing anti-tumor immune responses can impact the likelihood of achieving a pathological response. Additionally, immunotherapies may induce immune-mediated tumor destruction, leading to varying degrees of pathological responses. CT, PET-CT, and MRI are commonly used to assess the response of NSCLC patients to neoadjuvant therapy. However, there is a significant discrepancy in results. Literature reports inconsistency rates between tumor pathological remission and CT response of 41% (25). Inflammatory lesions and fibrotic components of tumors may affect the radiographic interpretation of tumor size, leading to inaccurate prediction of neoadjuvant therapy efficacy via CT. Therefore, histology becomes the only more accurate method for assessing the response to neoadjuvant therapy. With the clinical application of neoadjuvant therapy for lung cancer, pathological evaluation of surgical specimens after neoadjuvant therapy becomes increasingly important. It is recommended to standardize sampling according to the International Association for the Study of Lung Cancer multidisciplinary recommendations for pathological evaluation of post-neoadjuvant therapy lung cancer resection specimens, to optimize the assessment of postoperative pathological response. The tumor bed refers to the area where the tumor was located before treatment and is described as follows: residual tumor, necrotic tissue, and stroma (including inflammatory lesions and fibrosis), with the sum of these components totaling 100% (26). For NSCLC patients with driver gene mutations, new adjuvant targeted therapy has shown good tolerance and a high response rate. A retrospective literature showed that preoperative tyrosine kinase inhibitor (TKI) targeted therapy was well tolerated in patients with clinical stage I to III NSCLC with actionable EGFR and ALK alterations. In addition, radiographic response strongly correlated with pathologic response, and preoperative targeted therapy, even when used alone, was associated with good RFS and OS (27). A Phase II trial evaluating preoperative gefitinib in early-stage NSCLC patients with EGFR-positive mutations demonstrated that preoperative gefitinib as adjuvant targeted therapy combined with surgery is a safe and feasible approach. This trial design also provides better predictive information for treatment response or sensitivity (28). Another single-arm phase II clinical study included 33 EGFR-positive mutation patients with stage II–IIIA NSCLC, and after 42 days of preoperative gefitinib adjuvant targeted therapy, ORR was 55%, MPR was 24%, evaluating the effectiveness of gefitinib as adjuvant therapy (29). Moreover, Apple trial revolves around the time until progression with direct use of osimertinib versus using a first-generation followed by a third-generation until progression. Ultimately, the results show a high degree of similarity in survival outcomes between the two treatment groups, with no statistically significant

difference (30). Therefore, in this study, we opted for the first-generation targeted drug gefitinib. For NSCLC patients without driver gene mutations, several clinical studies suggest that neoadjuvant immunotherapy can significantly increase the pathological response rate and R0 resection rate, especially when combined with neoadjuvant immunotherapy and chemotherapy. The NADIM trial (31) was the first Phase II clinical study reporting neoadjuvant immunotherapy combined with chemotherapy for resectable stage IIIA NSCLC. After three cycles of neoadjuvant therapy with nivolumab combined with paclitaxel/carboplatin, 41 patients completed R0 surgical resection, and 37 patients showed downstaging after neoadjuvant treatment, with an MPR of 83% and a pCR of 63%. The subsequent NADIM II trial (32) demonstrated that maintaining adjuvant treatment with nivolumab for one year after surgery resulted in a 91% overall survival (OS) rate in the planned treatment group for 36 months. This provides strong support for the safety, feasibility, and effectiveness of nivolumab combined with platinum-containing chemotherapy as neoadjuvant therapy for resectable stage IIIA NSCLC. The latest data from the CheckMate816 trial in 2022 showed that neoadjuvant nivolumab combined with chemotherapy significantly prolonged event-free survival (EFS) compared to chemotherapy alone, with a higher percentage of patients achieving pCR (24% *vs.* 2.2%). The addition of nivolumab in neoadjuvant chemotherapy did not increase the incidence of AEs or hinder the surgery, further highlighting the superiority of immunotherapy combined with chemotherapy in neoadjuvant treatment (33). Based on this, the FDA approved the use of nivolumab in combination with platinum-based doublet chemotherapy as neoadjuvant treatment for adult patients with resectable NSCLC in 2022, marking a significant milestone in the history of lung cancer treatment. However, there are currently no relevant trials that consider neoadjuvant therapy as a bridging treatment between PCI and lobectomy. In this trial, different neoadjuvant regimens were developed for different types of NSCLC, taking into account the duration of DAPT, neoadjuvant cycle length, and preoperative drug withdrawal period (12,13,31,33,34). The duration of neoadjuvant targeted therapy was 12 weeks, with a one-week preoperative drug withdrawal period; neoadjuvant immunotherapy combined with chemotherapy was administered for three cycles, with a one-month interval before surgery. All patients completed neoadjuvant treatment, and the post-treatment ORR was 53.8% (95% CI: 25.1–80.8%), with DCR reaching 100%. No severe AEs (> grade 2) occurred during neoadjuvant treatment. Postoperative pathological assessment revealed that three cases achieved MPR (23.1%, 95% CI: 5–53.8%), including two cases with pCR (15.4%, 95% CI: 1.9–45.4%), and no lymph node metastasis was found. The neoadjuvant treatment during the DAPT period exerted control over lung diseases, and no disease progression was observed, further confirming the effectiveness of neoadjuvant therapy.

Simultaneously, some scholars have pointed out that neoadjuvant targeted therapy and immunotherapy may induce changes in the primary tumor vasculature and microenvironment, leading to tissue and cellular edema, disappearance of tissue interstitium, local adhesions, and fibrosis. This could result in increased vascular fragility, making surgery more challenging and raising the rate of conversion to open thoracotomy (35-37). However, when compared with data from studies on neoadjuvant chemotherapy, relevant researches have found that the impacts of new adjuvant targeted therapy and immunotherapy on surgical implementation are manageable. Lv *et al.* (38), for instance, reported that the differences in surgery time, intraoperative blood loss, drainage tube placement time, postoperative drainage volume, postoperative hospitalization, and postoperative complications were not statistically significant in patients with stage II–IIIA NSCLC treated with neoadjuvant EGFR-TKI compared to chemotherapy. Yang *et al.* (39) evaluated the safety and feasibility of neoadjuvant ipilimumab combined with chemotherapy in patients with stage II–III A NSCLC. They found that the adverse surgical outcome rate did not significantly increase in the immunotherapy combined with chemotherapy group compared to the chemotherapy-only group. Although the conversion to open thoracotomy was slightly higher in the immunotherapy combined with chemotherapy group, the difference was not statistically significant (23% *vs.* 17%). There were no deaths within 30 days after surgery in both groups, and there was no difference in postoperative hospitalization and drainage tube placement time. In our study, the rate of complications was low, and blood loss was minimal in most cases. the median operative time was 150 (IQR 125–250) minutes and median intraoperative blood loss was 180 (IQR 150–235) mL, which were consistent with literature reports. For instance, in Bott's report, the median [range] operative time was 228 [132–312] minutes, estimated blood loss was 100 [25–1,000] mL and length

of hospital stay was 4 [2–17] days, and the most common postoperative complication was atrial arrhythmia (36). The surgical radical resection rate in this group reached 100%, with one case (7.7%) of conversion to open thoracotomy due to inflammatory lymph node adhesion between the pulmonary artery branches and trachea during the separation process, which led to bleeding. Here are some of our experiences and recommendations. First, we suggest using scissors for sharp dissection as much as possible, as this allows for better differentiation of tissue layers and helps avoid inadvertent vascular injury. Second, if encountering tight adhesions between the trachea and vessels which cannot be separated, it may be necessary to cut the trachea firstly, then manage the vessels with staples before dealing with the remaining tracheal stump. Third, if there is a significant risk of vascular injury during the dissection process, preemptive vessel blockage should be performed.

Preoperative neoadjuvant treatment and continued oral aspirin therapy during the perioperative period did not have a significant impact on the surgery. Only one patient experienced rapid atrial fibrillation postoperatively, which improved after antiarrhythmic treatment. For patients in this group, it is recommended to continue targeted or immune maintenance therapy for 2 years postoperatively, primarily based on clinical staging in IB stage and the goal of improving OS (31,34). In a retrospective clinical cohort of patients with advanced NSCLC who were treated with immunotherapy and were progression-free at 2 years, approximately only 1 in 5 discontinued treatments. The lack of statistically significant OS advantage for the indefinite-duration cohort on adjusted analysis provides reassurance to patients and clinicians who wish to discontinue immunotherapy at 2 years (40). The ADJUVANT study suggests that the risk of recurrence in the gefitinib group stabilizes and begins to rise steadily after 12 months. The first peak of recurrence typically occurs around 21 months after surgery, with a second peak around 30 months post-surgery. This indicates that at least 24 months of EGFR-TKI adjuvant therapy may be a good option for delaying recurrence in lung cancer (41). As of now, the follow-up results for patients in this group are satisfactory, with a median follow-up time of 21 months, and no recurrence or metastasis has been observed.

We can draw clinical implications from this study. Despite the relatively frequent occurrence of AEs, the majority were graded as ≤ grade 2, indicating manageable toxicity levels. Therefore, clinicians should emphasize vigilant monitoring and proactive management of AEs in patients undergoing comparable treatment protocols. Early detection and intervention can help mitigate potential complications and optimize patient outcomes.

Because this was a single-center, retrospective study, the generalizability of our findings might be limited. First, as a retrospective study, the number of cases in our group was relatively small, so the feasibility of this treatment method could not be fully confirmed. Second, our clinical data selection was very strict, only including T2aN0M0 (stage IB) and SYNTAX score ≤22. Because this was a new exploratory treatment method, we hoped that the conditions of the patients enrolled in the study were relatively simple and stable. This approach excluded complex CAD and allows for better assessment and comparison of neoadjuvant treatment effects in lung cancer patients of the same stage, and did not introduce additional prognostic evaluation impacts for patients undergoing concomitant coronary intervention and lung cancer resection. As a result of this, it remained unclear whether this treatment approach was effective for patients with lung cancer and coronary heart disease at other stages and conditions. Therefore, further studies with larger sample sizes covering other stages are needed for validation. Third, the median follow-up time for patients in our group was only 21 months, and longer-term follow-up data were needed to validate efficacy, including disease-free survival, progression-free survival and OS, etc.

Conclusions

This study presents initial evidence suggesting that for patients with T2aN0M0 (stage IB) NSCLC who also have concomitant CAD, performing PCI as an initial treatment followed by neoadjuvant therapy during the DAPT period is safe and feasible. By controlling the disease and eliminating concerns about tumor progression and metastasis, this strategy presents a potential treatment option for lung cancer patients with severe CAD.

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Footnote

Reporting Checklist: The authors have completed the

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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-24-132/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 parts 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 Beijing Anzhen Hospital, Capital Medical University (Ethics Approval No: 2020022X), and all participants provided informed consent.

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