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Neoadjuvant immune checkpoint inhibitor reduced recurrence in operable NSCLC patients with pathological complete response: a retrospective analysis

Yanxiong Mao[1,2†], Fei Chen[3†], Zhangqun Ye[4†], Zhouyang Li[1,2], Bo Fan[3], Yimin Zou[1,2], Wen Li[1,2*] and Fen Lan[1,2*]

Abstract

Background This study aimed to evaluate if neoadjuvant immune checkpoint inhibitor (ICI) plus chemotherapy (CT) reduced tumor recurrence after surgery than neoadjuvant CT alone in non–small cell lung cancer (NSCLC) patients with pathologic complete response (pCR).

Methods From January 1st 2019 to April 30th 2022, 16 NSCLC patients with pCR who received both neoadjuvant ICI and CT were designated as ICI/CT group. Another 8 patients, who received neoadjuvant CT alone, were designated as CT group. The tumor recurrence and patients' survival status were analyzed.

Results Squamous cell carcinoma was the predominant histology type in both groups. The CT group had higher percentage of patients who received adjuvant CT than the ICI/CT group (100% vs. 75%, $p=0.046$). All patients had been followed up for at least 20 months. At 20 months after surgery, the ICI/CT group had a tumor recurrence rate of 6.25%, which was significantly lower than 37.5% recurrence rate of the CT group. One patient of the CT group died of gastrointestinal hemorrhage and severe anemia at 11 months after surgery, and no patient in the ICI/CT group died. During adjuvant therapy, the ICI/CT group had significantly lower risk of anemia (12.5% vs. 50%) than the CT group ($p=0.046$).

Conclusion The study found that in NSCLC patients with pCR, neoadjuvant ICI reduced tumor recurrence rate. This indicated that like in advanced stage NSCLC, the ICI might bring similar long-term anti-tumor effect in operable NSCLC patients.

Keywords NSCLC, Immune checkpoint inhibitor, Pathological complete response, Neoadjuvant therapy, Recurrence

†Yanxiong Mao, Fei Chen and Zhangqun Ye these authors have contributed equally to this work and share first authorship.

*Correspondence:
Wen Li
Liwen@zju.edu.cn
Fen Lan
lanfen1979@zju.edu.cn
[1]Key Laboratory of Respiratory Disease of Zhejiang Province, Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Zhejiang University School of Medicine, Wen Li, Hangzhou, Zhejiang, China
[2]Cancer Center, Zhejiang University, Hangzhou, Zhejiang, China
[3]Department of Respiratory and Critical Care Medicine, First People's Hospital of Jiashan, Jiashan, Zhejiang, China
[4]Department of Respiratory and Critical Care Medicine, Ningbo First Hospital Longshan Hospital Medical and Health Group, Ningbo, Zhejiang, China

Background

Among all cancer types worldwide, lung cancer ranks second and first respectively in incidence and mortality [1]. Non–small cell lung cancer (NSCLC) is the main type of lung cancer, which accounts for approximately 85% of lung cancer. Surgery followed by neoadjuvant platinum-based chemotherapy (CT) is the standard of care for selected patients with early-stage or locally advanced NSCLC [2]. The immunotherapy, in which immune checkpoint inhibitor (ICI) agents are the classic drugs, has arisen as a crucial element of anti-tumoral treatment [3, 4]. The feasibility of neoadjuvant ICI has increasingly been explored in operable NSCLC. Neoadjuvant pembrolizumab plus CT significantly improved event-free survival (EFS), major pathologic response (MPR), and pathologic complete response (pCR) as compared with neoadjuvant CT alone followed by surgery [5]. A meta-analysis, which included 11 randomized controlled trials of neoadjuvant ICI in operable NSCLC, showed that neoadjuvant ICI plus CT significantly improved the objective response rate (ORR), MPR and pCR rate compared with neoadjuvant CT alone [6]. These results suggested that neoadjuvant ICI plus CT have better clinical efficacy than neoadjuvant CT for operable NSCLC.

The pCR of lung cancer after surgery was defined as lack of any viable tumor cells on review of pathological slides after complete evaluation of a resected lung cancer specimen including all sampled regional lymph nodes [7]. It was reported that the pCR patients after neoadjuvant therapy had an 5-year overall survival (OS)rate of 53–80.1% [8–15]. In some neoadjuvant clinical trials for operable NSCLC, pCR rate was used as a primary or secondary endpoint [5, 16, 17]. The pCR rate was used to be relatively low in operable NSCLC patients. It was reported that neoadjuvant CT had a pCR rate of 5–9%, and neoadjuvant RT plus CT had a pCR rate of 11–35% [8]. And growing body of evidence showed that compared with neoadjuvant CT alone, neoadjuvant ICI plus CT significantly increased the pCR rate. Several studies showed that neoadjuvant ICI plus CT caused the pCR rate of 17.2–40.7%, compared with a pCR rate of 1–5.7% of neoadjuvant CT alone [5, 18–20]. So in the era of immunotherapy, pCR is no longer a rare phenomenon, which warrant more attention from doctors and researchers.

Despite this proliferation of studies, the published literature on this highly selected subset of patients remains relatively sparse. The presence of pCR didn't preclude recurrence, and the recurrence rate in the literature varied wildly. Some studies reported an alarmingly high recurrence rate of 21.1–46% after surgery [8–10]. So reducing recurrence was important in pCR patients too. But this recurrence data was collected from patients with neoadjuvant CT and/or radiotherapy (RT) before the era of immunotherapy. In the era of immunotherapy, the recurrence risk might be different, which could be deduced from known data of ICI use in advanced stage lung cancer patients. It was well-known that ICI could provide durable antitumor activity in some patients, but this durable antitumor activity was mainly observed in advanced stage patients [21–24]. It was reasonable to suspect that ICI might have similar durable antitumor activity in operable NSCLC as well. The unique feature of pCR patients was ideal to test long-term antitumor activity of ICI in operable lung cancer patients. This tumor cells-free status indicated that all pCR patients had same cancer status after surgery, which provided similar subjects to test the long-term effect of ICI. So far, there was no data of recurrence in pCR patients with neoadjuvant ICI. So, we conducted a pilot retrospective study in NSCLC patients with pCR to explore if neoadjuvant ICI plus CT reduced tumor recurrence than neoadjuvant CT alone.

Methods

Study population

The operable NSCLC patients who both received neoadjuvant therapy and had pathologic assessment of pCR after surgery were identified from Electronic Medical Record System (EMRS) in the study hospital from January 1st 2019 to April 30th 2022. All patients received mediastinal lymph node dissection or systematic lymph nodes sampling on the discretion of the surgeons during surgery. Pathological response after neoadjuvant therapy was assessed by examination of hematoxylin and eosin–stained slides of resected lung tissue and lymph nodes. The pCR was defined as the absence of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes [7]. The ICI agents included programmed cell death protein 1 (PD-1) agents and programmed cell death receptor ligand-1 (PD-L1) agents. The tumor recurrence and patients' survival status were assessed by medical records and/or phone call on January 2024. At that time, all patients had been followed up for at least 20 months.

Data collection

In-depth clinical data encompassing demographic characteristics, tumor history, laboratory test alongside adverse events (AEs) were collected from EMRS. The AEs were evaluated based on medical records, using the Common Terminology Criteria for Adverse Events, version 5.0.

Data analysis

The results were analyzed using IBM SPSS Statistics (version 20). Continuous data was presented as the mean with stand deviation (SD)or median with interquartile range (IQR), depending on the distribution of data.

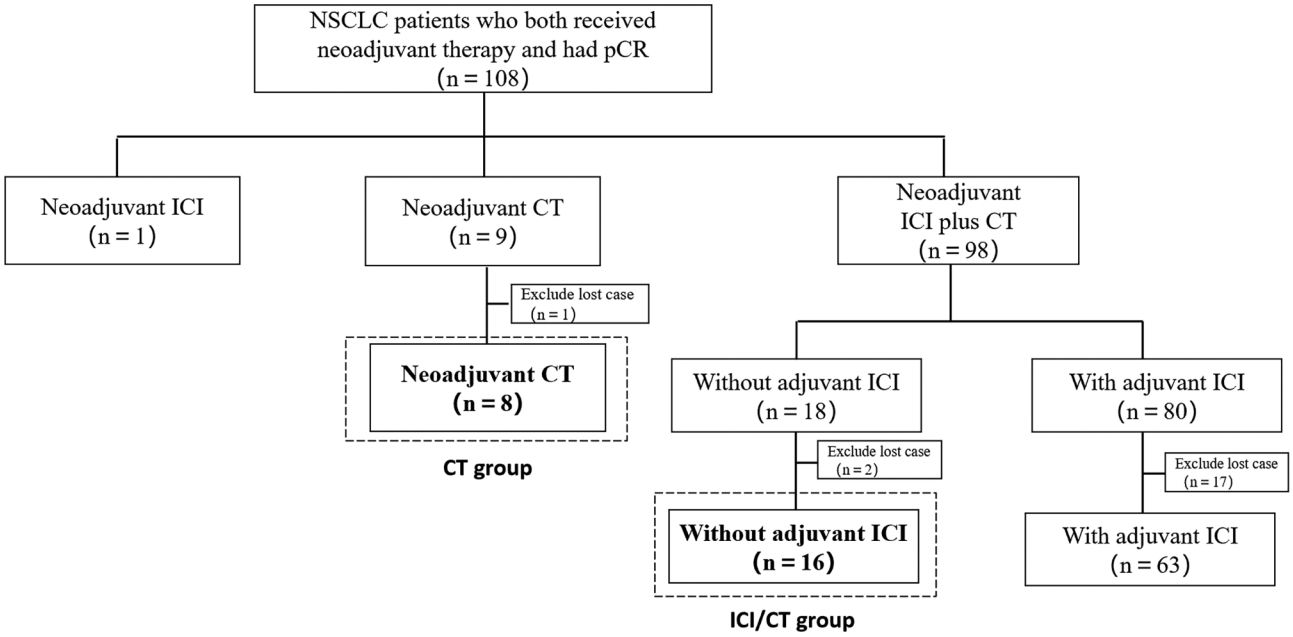

Fig. 1 Flow chart of study population. NSCLC: non-small cell lung carcinoma; ICI: immune checkpoint inhibitor; CT: chemotherapy

Table 1 Baseline feature and comorbidity profile

Variables	CT group (*n*=8)	ICI/CT (*n*=16)	*p*
Age	60.63 (7.96)	62.06 (7.17)	0.659
Male	7(87.5%)	16(100%)	0.149
BMI, kg/m2	21.39(2.95)	23.47(3.50)	0.163
Smoking history			0.205
Ever	6 (75.0%)	8(50.0%)	
Current	0	5(31.2%)	
Never	2 (25.0%)	3 (18.8%)	
Pack-years	30 (16.88, 45.00)	40 (20.00, 52.50)	0.407
Comorbidities			
COPD	0	2 (12.5%)	0.296
Asthma	0	0	—
Hepatic disease	1 (12.5%)	0	0.149
Hypertension	2 (25.0%)	5 (31.2%)	0.751
Diabetes mellitus	1 (12.5%)	2 (12.5%)	1.000
Cerebrovascular disease	0	1 (6.2%)	0.470
Renal insufficiency	0	0	—
Heart insufficiency	0	0	—

All data are presented as No. (%), median (interquartile range), or mean(standard deviation)

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease

Variables were compared using the unpaired Student's t-test, Welch t-test or the Wilcoxon rank sum test with continuity correction, depending on data normality and homogeneity of variance. Categorical data were presented as absolute value and percentage, and analyzed using Chi-square test or Fisher's exact test according to test assumptions. Statistical significance was set at $p<0.05$.

Results

From January 1st 2019 to April 30th 2022, a total number of 108 operable NSCLC patients who both received neoadjuvant therapy and had pathologic assessment of pCR after surgery were identified from EMRS (Fig. 1). Of these 108 patients, one patient received neoadjuvant ICI alone, 9 patients neoadjuvant CT alone, and 98 patients both neoadjuvant ICI and CT. After excluding one patient who was lost to follow-up, the 8 patients, who received neoadjuvant CT alone, were designated as CT group. Of these 98 patients with both neoadjuvant ICI and CT, 18 patients received no adjuvant ICI after operation. After excluding 2 patients who was lost to follow-up, the rest 16 patients were designated as ICI/CT group. The rest 80 patients, who also received adjuvant ICI after operation, were excluded in order to rule out the potential interference of adjuvant ICI.

Baseline features and comorbidity profile

The baseline features and comorbidities were compared (Table 1). No difference in baseline features was noted between two groups. The included patients in both groups were mainly male (87.5% in CT group and 100% in ICI/CT group respectively). The comorbidity profile was similar between groups as well. Hypertension was the most common comorbidity across groups, with a proportion of 25.0% in CT group and 31.2% in ICI/CT group respectively.

History of lung cancer and neoadjuvant therapy

The history of lung cancer was similar across groups (Table 2). There was no difference in whole blood cell

Table 2 Characteristics of lung cancer and perioperative treatment

Variables	CT group (*n*=8)	ICI/CT (*n*=16)	*p*
Baseline blood test results			
White blood cell count, x109/L	6.46 (2.82)	6.00 (2.28)	0.669
Eosinophil count, x109/L	0.08 (0.07)	0.10 (0.09)	0.567
Neutrophil count, x109/L	4.01 (2.99)	3.92 (2.04)	0.872
Lymphocyte count, x109/L	1.67 (0.53)	1.44 (0.52)	0.325
Hemoglobin	119.63 (14.60)	118.44 (11.00)	0.825
Platelets	198.00 (161.00, 215.75)	184.50 (167.75, 252.00)	0.645
Albumin, g/L	39.79 (3.37)	38.13 (3.13)	0.246
Histology			0.741
Adenocarcinoma	2 (25.0%)	3 (18.8%)	
Squamous cell carcinoma	6 (75.0%)	12 (75.0%)	
Other NSCLC	0	1 (6.2%)	
Stage			0.181
I	0	2 (12.5%)	
II	3 (37.5%)	1 (6.2%)	
IIIA	4 (50.0%)	8 (50.0%)	
IIIB	1 (12.5%)	5 (31.2%)	
Neoadjuvant cycles	2 (2, 2)	2 (2, 2)	0.492
Neoadjuvant immunotherapy agents			—
Pembrolizumab	—	2 (12.5%)	
Tislelizumab	—	4 (25.0%)	
Camrelizumab	—	4 (25.0%)	
Sintilimab	—	4 (25.0%)	
Durvalumab	—	1 (6.2%)	
Teprotumumab	—	1 (6.2%)	
Length of hospital stay during surgery, days	13.00 (7.75, 14.00)	12.50 (9.25, 18.00)	0.498
Concurrent therapy with adjuvant immunotherapy			
Adjuvant chemotherapy	100 (100.0%)	10 (75.0%)	0.046
Adjuvant Immunotherapy	0	0	—
Adjuvant radiotherapy	0	1 (6.2%)	1
Adjuvant tyrosine kinase inhibitors	0	0	—
Follow-up, months	52.50 (47.50, 57.75)	36.00 (32.00, 41.75)	<0.001

All data are presented as No. (%), median (interquartile range), or mean(standard deviation)

Abbreviations: NSCLC: non-small cell lung carcinoma

count and albumin. Squamous cell carcinoma was the predominant histology type, with a proportion of 75.0% in both groups. The tumor stage at diagnosis were similar between groups, and stage IIIA was most common, which account for 75.0% in both groups. The cycles of neoadjuvant therapy were similar between two groups, which both have a median neoadjuvant cycle of 2. There were six ICI agents used in the current study, which included five PD-1 agents (pembrolizumab, tislelizumab, camrelizumab, sintilimab and teprotumumab) and PD-L1 agents (durvalumab). The proportion of ICI used in ICI/CT group were as follows: tislelizumab (25.0%), sintilimab (25.0%), camrelizumab (25.0%), pembrolizumab (12.5%), teprotumumab (6.2%) and durvalumab (6.2%).

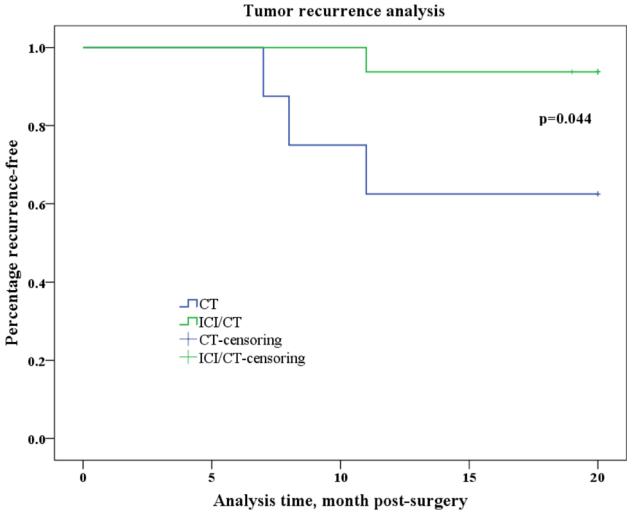

Fig. 2 Kaplan-Meier analysis of tumor recurrence between two groups. The Kaplan–Meier curves showed significantly difference in tumor recurrence between two groups (ICI/CT group vs. CT group: 6.25% vs. 37.5%) (log rank: $p=0.044$)

Hospital stay and follow-up

During surgery, the CT group had a median length of hospital stay of 13.00 (7.75, 14.00) days, which was similar to 12.50 (9.25, 18.00) days of ICI/CT group (Table 2). After the surgery, the majority of patients received adjuvant CT. But the CT group had significantly higher percentage of patients who received adjuvant CT than the ICI/CT group (100% vs. 75%, $p=0.046$). One patient in the ICI/CT group received adjuvant radiotherapy. All patients had been followed up for at least 20 months. The median follow-up time of the CT group was 52.50 (47.50, 57.75) months, which was significantly longer than 36.00 (32.00, 41.75) months of the ICI/CT group ($p<0.001$).

Tumor recurrence

At 20 months after surgery, the ICI/CT group had a tumor recurrence rate of 6.25% (1 out of 16 patients), compared with 37.5% (3 out of 8 patients) in the CT group. And the difference in tumor recurrence rate was statistically significant (log rank, $p=0.044$) (Fig. 2). One patient of the CT group died of gastrointestinal hemorrhage and severe anemia at 11 months after surgery, and no patient in the ICI/CT group died.

Safety profile

The safety profile of both groups was recorded (Table 3). During neoadjuvant therapy, the most common AEs in

Table 3 Adverse events

Variables	CT group (*n*=8)	ICI/CT (*n*=16)	*p*
Neoadjuvant			
Leukopenia	2(25.0%)	6(37.5%)	0.540
Thrombocytopenia	0	3(18.8%)	0.190
Anemia	2(25.0%)	7(43.8%)	0.371
Hepatic insufficiency	0	4(25.0%)	0.121
Renal insufficiency	0	0	—
Rash	0	0	—
Adrenocortical insufficiency	0	0	—
Hypothyroidism	0	0	—
Hyperthyroidism	0	4(25.0%)	0.121
Adjuvant			
Leukopenia	2(25.0%)	4(25.0%)	1.000
Thrombocytopenia	0	0	—
Anemia	4(50.0%)	2(12.5%)	0.046
Hepatic insufficiency	0	1(6.2%)	0.470
Renal insufficiency	0	0	—
Rash	0	0	—
Adrenocortical insufficiency	0	1(6.2%)	0.470
Hypothyroidism	0	0	—
Hyperthyroidism	0	0	—

All data are presented as No. (%), median (interquartile range), or mean(standard deviation)

both groups were anemia and leukopenia. The ICI/CT group had higher risk of thrombocytopenia (18.8% vs. 0), hepatic insufficiency (25% vs. 0) and hyperthyroidism (25% vs. 0) than the CT group during neoadjuvant therapy, but without statistical significance. During adjuvant therapy the overall safety profile was mostly similar except for anemia. The ICI/CT group had significantly lower risk of anemia (12.5% vs. 50%) than the CT group ($p=0.046$).

Discussions

ICI could provide durable antitumor activity in advanced stage NSCLC patients [21–24]. It was reasonable to stipulate that ICI could have similar durable antitumor activity in operable NSCLC as well. The unique feature of pCR patients was ideal to test long-term antitumor activity of ICI in operable NSCLC. Our pilot retrospective study preliminarily compared tumor recurrence between neoadjuvant ICI/CT and neoadjuvant CT alone in the pCR patients. We found that in NSCLC patients with pCR, neoadjuvant ICI reduced tumor recurrence rate after surgery. Our finding suggested that like in advanced stage NSCLC, neoadjuvant ICI may exert similar long-term antitumor activity in operable NSCLC.

The principal finding of the current study was that in NSCLC patients with pCR, neoadjuvant ICI reduced tumor recurrence rate after surgery. To the best of our knowledge, there was no previous report. This reduced recurrence might be caused by the long-term antitumor activity of ICI, which was mainly observed in advanced NSCLC. Before the advent of immunotherapy, patients with advanced lung cancer had poor prognosis, with a 5-year OS rate of only 6.9% in America between 2010 and 2016 [22]. After the advent of immunotherapy, a growing body of evidence showed that ICI with/without CT brought long-term antitumor activity in some patients with advanced NSCLC [22–25]. For example, results from the phase III KEYNOTE-024 study suggested that the 5-year OS rate in the pembrolizumab group (31.9%) was approximately double of that in the CT group (16.3%) in previously untreated NSCLC patients with high PD-L1 expression [22]. Similarly in previously untreated, metastatic squamous NSCLC, the 5-year OS rate of the pembrolizumab plus CT group was much higher than that of CT group (18.4% versus 9.7%) [23]. In pretreated patients with advanced NSCLC, nivolumab treatment resulted in a 5-year OS rate of 16% [24]. And the long-term durable anti-tumor effect of ICI might lie in their abilities to induce long-lasting anticancer immune responses, resulting in long-term complete responses [26]. Now evidence altogether suggested that the long-lasting anticancer immune responses of ICI therapies might be related to the generation of anticancer memory T cells. Although the follow-up time of our study was relatively short, our study provided preliminary evidence to show that there might be long-term antitumor activity of ICI in operable lung NSCLC as well. To further verify this finding, prospective studies with longer follow-up time were warranted.

Studies suggested that pCR should not be thought as a complete cure. Recurrences detected during follow-up might be caused by either tumor metastases before or during neoadjuvant therapy or technically undetected living tumor cells. The recurrence rate of pCR patients in the literature varied wildly. Some studies reported alarmingly high recurrence rate of 21.1–46% after surgery [8–10]. In pCR patients, recurrence was a major risk factor affecting survival. The 5-year OS rate of pCR patients with recurrence was significantly lower than that of patients without recurrence (19.3% vs. 78.2%) [9]. The time from the end of the neoadjuvant therapy to the surgery and the type of neoadjuvant treatment were the independent risk factors affecting the recurrence [9]. Compared with neoadjuvant CT or RT alone, neoadjuvant RT plus CT had lower recurrence. This was similar to our finding which showed that neoadjuvant ICI plus CT had lower recurrence. This indicated that addition of new neoadjuvant modality to CT could reduce tumor recurrence after surgery.

One major strength of current study was that the pCR patients were our study population. In operable NSCLC patients, the pCR rate after surgery was used to be relatively low, and the neoadjuvant use of ICI significantly increased the rate. Neoadjuvant ICI plus CT had the pCR

rate varying from 17.2 to 40.7% among different studies, compared with a pCR rate of 1–5.7% brought by neoadjuvant CT alone [5, 18–20]. A meta-analysis showed that pCR rate of neoadjuvant ICI/CT was significantly superior to neoadjuvant CT alone [6]. In the past, the small size of pCR patients made it unfeasible to conduct conclusive study in this specific population. Now the increasing number of pCR patients provided golden opportunity for us to conduct in-depth research and answer some question. By definition, after thorough evaluation of resected specimens, the pCR patients were considered to lack of any viable tumor cells [7]. This tumor cells-free status indicated that all included patients in the current study had same cancer status after surgery, which provided similar subjects to test the long-term effect of ICI. Another strength of current study was that patients who received adjuvant ICI after operation were excluded from current study. The exclusion of those patients eliminated the potential bias brought by adjuvant ICI. So the selection of pCR patients and exclusion of patients with adjuvant ICI increased the credibility of our research results.

Our study revealed that the ICI/CT group had significantly lower percentage of patients who received adjuvant CT than CT group (75% vs. 100%). In pCR patients, it was still unclear if adjuvant therapy after surgery could improve survival. Lococo et al. reported that the pCR patients who underwent adjuvant treatment had better 5-year OS rate, long-term survivals and disease-free survival [8]. In another study of 62 pCR patients, the death risk was estimated to be 3 times higher for patients who did not receive adjuvant therapy [11]. On the contrary, in the review of 759 stage I-III NSCLC patients who achieved pCR after multimodal therapy, the authors did not observe a statistically significant difference in terms of long-term survival between patients with adjuvant treatments and those without [12]. Similarly, Melek et al. and colleagues reported that in a series of 72 pCR NSCLC patients, adjuvant therapy did not influence the long-term outcome [13]. Although the adjuvant treatment in patients with pCR remained controversial in terms of theoretically having no viable tumor cells, the majority of patients in the current received adjuvant CT therapy. In our study, although the ICI/CT group were less likely to receive adjuvant CT than the CT group, the ICI/CT group still had lower tumor recurrence. This disparity lend further support to the long-lasting anti-tumor effect of ICI in operable like in advance stage NSCLC. Moreover, in order to rule out the potential interference of adjuvant ICI, all patients receiving adjuvant ICI were excluded from current study. So whether adjuvant ICI could reduce the recurrence was not within the scope of this article.

Our study also found that the ICI/CT group had significantly lower risk of anemia than the CT group. This may be partly explained by the fact that the ICI/CT group were less likely to received adjuvant CT. The majority of cancer patients would develop anemia during the course of their disease or treatment, and patients receiving CT are especially at risk [27]. By a study of European cancer patients, 75% of patients treated with CT were anemic at least once during the 6-month follow-up, compared to 67% of all patients included [28]. The incidence of anemia in patients receiving their first cancer treatment was 62.7% in patients treated with CT compared to 53.7% in patients overall [28]. Moreover, treatment with platinum, which was essential for CT in lung cancer, was an independent risk factor for patients with CT [27]. So in current study, patients of ICI/CT group might have lower risk of anemia because they were less likely to receive platinum-based adjuvant CT.

Unlike prospective clinical trials, the AEs in the current study were retrospectively evaluated based on medical records, and the underestimation of AEs was unavoidable. This made the comparison with other studies troublesome. Several prospective clinical trials reported the safety profile of neoadjuvant ICI. The results of KEYNOTE-671 revealed that neoadjuvant pembrolizumab plus CT had similar AEs risk to neoadjuvant CT alone (96.7% vs. 95.5%) [5]. The pembrolizumab group had higher risk of alanine aminotransferase level increased (12.9% vs. 7.8%) and similar thrombocytopenia (18.7% vs. 18.5%). The Neotorch study preliminarily reported that the incidence of Grade≥3 AEs was 63.4% in the toripalimab arm and 54.0% in the placebo arm, but the details of AEs profile had not been released [19]. The RATIONALE-315 study also reported that the neoadjuvant tislelizumab plus CT had similar incidence of AEs (99.1% vs. 99.6%) and Grade≥3 AEs (69.5% vs. 69.6%), but the details of AEs profile were unknown [20]. A meta-analysis also found that neoadjuvant ICI plus CT and neoadjuvant double-immunotherapy did not increase the incidence of AEs and Grade≥3 AEs [6]. So far the data of AEs of neoadjuvant ICI was limited, and the release of detailed AEs profile would be helpful.

The current study revealed that squamous cell carcinoma was the predominant histology type of pCR patients. Whether squamous cell carcinoma was associated with pCR was still debatable in the published literature. In a study including 38 NSCLC patients with pCR, 60.5% of patients had squamous cell carcinoma [10]. Similarly, in the study of 72 pCR patients, Melek et al. reported that squamous cell carcinoma accounted for 54.2% [13]. Mouillet et al. [12] also noted squamous cell carcinoma as the sole predictor of pCR [14]. Another study which included 39 pCR patients reported that 69.2% of patients with pCR had squamous cell carcinoma [15]. On the other hand, in the review of 759 stage I-III

NSCLC patients with pCR, adenocarcinoma was the predominant histology type [12].

There were a few limitations in this study. First, the minimum follow-up time of 20 months was relatively short for lung cancer patients receiving surgery, and longer follow-up time was needed. Second, the present study was a retrospective study, which came with many inherent limitations including selection bias. The retrospective nature of this study was also prone to biases from missing data and reliance on documentation available for review. Third, the dose modifications of chemotherapy agents were based on the discretion of the attending doctors and therefore, not standardized among the patients. Forth, data were missing regarding PD-L1 expression and tumor mutation burden for the majority of the study patients, so we were unable to evaluate these factors as biomarkers.

Conclusions

Our study found that in NSCLC patients with pCR, neoadjuvant ICI reduced disease recurrence rate after surgery. This indicated that like in advanced stage NSCLC, the ICI might bring similar long-term anti-tumor effect in operable NSCLC patients. Future prospective studies with larger sample size are needed.

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Author contributions
All authors contributed to the study conception and design. Material preparation and data collection were performed by YXM, FC and ZQY. Data analysis was performed by ZYL, BF and YMZ. The first draft of the manuscript was written by YXM, FC and ZQY, and revised by FL and WL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available due patients' individual privacy could be compromised, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The retrospective study was performed in a tertiary Chinese hospital (Second Affiliated Hospital of Zhejiang University School of Medicine). The Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine reviewed the study and granted approval (Approval Number: 2023 – 1094). The need for consent to participate was also waived by the Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine which approved the study, because it found the non-interventional retrospective study to entail minimal risk. The ethical standards of the Declaration of Helsinki were adhered to ensure the maintenance of patient data privacy and confidentiality throughout the course of this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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