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The comparison of perioperative outcomes and disease-free survival between pneumonectomy after immunochemotherapy and after isolated chemotherapy: one single center experience

Guodong Zhang[1†], Yongle Zhu[2†], Zhigang Shi[1], Zhendan Wang[1*†] and Pingping Song[1*†]

Abstract

Objective This study aims to compare the perioperative outcomes and disease-free survival (DFS) between pneumonectomy after immunochemotherapy and chemotherapy.

Methods We retrospectively identified patients who received neoadjuvant immunotherapy (n = 15) or chemotherapy alone (n = 12) in our single center between 2021 and 2023.

The primary end point was 30-day major complications. The secondary end point was major pathologic response.

Results There was no significant difference in operation time, blood loss and postoperative stay time between ICI (Received immune checkpoint inhibitor treatment including PD-1 and PD-L1 inhibitors) and Chemo cohort. There were also no difference in postoperative complications including complications > grade III, 90-day death and bronchial fistula. The pCR rate was 40.0% (6/15) in the ICI cohort versus 0.0% (0/12) in the chemo cohort ($p = 0.020$). The MPR or pCR rate was 60.0% (9/15) in the ICI cohort versus 8.3% (1/12) in the chemo cohort ($p = 0.014$). ICI cohort was associated with an improved overall 1, 2, and 3-year disease-free survival(DFS)compared with chemo cohort. At the same time, both patients received ICI and Chemo were grouped according to whether pCR occurred or not, and it was found that DFS in the pCR group was better than DFS in the non-pCR group.

Conclusions Based on our results, we argue that compared with pneumonectomy after isolated chemotherapy, pneumonectomy after immunochemotherapy not added 90-day mortality, postoperative, morbidity, but improved DFS; thus, it should be the induction therapy choice for anatomically eligible centrally located lung cancers.

Keywords Programmed cell death protein 1 inhibitors, Chemotherapy, Pneumonectomy, Disease-free survival

†Guodong Zhang, Yongle Zhu, Zhendan Wang and Pingping Song have equally contributed to this work.

*Correspondence:
Zhendan Wang
wangzhendan.love@163.com
Pingping Song
spp128@126.com
Full list of author information is available at the end of the article

Introduction

Graham's initial report of pneumonectomy (PN) for treating lung cancer in 1933 marked a pivotal moment in the evolution of surgical management for this disease [1]. This early breakthrough paved the way for further advancements, leading to the landmark research by Ginsberg et al. in the 1980s. Their study advocated for lobectomy, complemented by comprehensive lymphatic dissection of both the pulmonary hilum and mediastinum, as the gold standard for lung cancer resections, a concept initially introduced by Cahan as radical lobectomy [2, 3]. When central location or extensive size of the lesion made lobectomy impossible to guarantee a margin-free (R0) resection, PN was a primary surgical alternative. The development of sleeve lobectomy (SL) created a surgical option for those who were not candidates for PN because of their poor pulmonary function [4]. Previous studies demonstrated that sleeve lobectomy (SL) compared with PN achieved the same oncological outcome not only overall survival (OS) but disease-free survival (DFS), and with lower morbidity and mortality and improved postoperative respiratory function and quality of life [5–7].Therefore, pneumonectomy is now just used for centrally located lung cancers which are not suitable for a sleeve(bronchial, arterial, or bronchovascular) or extended sleeve resection [8]. With the development of immune checkpoint inhibitors (ICIs), treatment of advanced non-small cell lung cancer (NSCLC) has dramatically changed. Immune checkpoint inhibition alone, or combined with cytotoxic chemotherapy, has become the norm for treating advanced NSCLC [9]. Neoadjuvant immune checkpoint inhibition combined with cytotoxic chemotherapy for resectable NSCLC have also obtained satisfactory treatment results [10].However, these patients were treated with lobectomy after ICI combined with cytotoxic chemotherapy, rarely patients were treated with PN after induction therapy with ICI. This study aims to compare the perioperative outcomes and disease-free survival (DFS) between pneumonectomy after immunochemotherapy and chemotherapy.

Materials and methods

Patients selection

Data were retrospectively harvested from the Shandong Cancer Hospital and Institute's database for the period 2021 to 2023, focusing on non-small cell lung cancer patients who underwent induction therapy, encompassing both immunochemotherapy and chemotherapy. A total of 135 patients achieved complete (R0) resection post-induction therapy. This cohort included 20 (14.8%) sleeve lobectomy cases, 70 (51.9%) instances of isolated lobectomy, 18 (13.3%) patients receiving combined lobectomy (excluding pneumonectomy), and 27 (20.0%) undergoing pneumonectomy. Subsequent categorization based on induction therapy divided these patients into two groups: 15 patients in the ICI with chemo group, and 12 patients in the chemotherapy-only (Chemo) group, as illustrated in Fig. 1. The Institutional Review Board / Ethics Committee granted approval for this study. Due to the retrospective nature of the research and pre-existing consent for data usage at the time of surgery, the requirement for individual data consent was exempted.

Treatment and follow-up

All patient treatment plans are discussed through multidisciplinary consultations.Between two to four cycles of induction therapy were administered to patients, which included the use of programmed cell death protein 1 (PD-1) inhibitors alongside a dual chemotherapy regimen incorporating platinum in ICI group, while only a dual chemotherapy regimen incorporating platinum in chemo group as per established guidelines, with treatments occurring tri-weekly. Patients with squamous cell carcinoma received albumin paclitaxel combined with carboplatin regimen, while patients with adenocarcinoma received pemetrexed combined with carboplatin regimen. In the ICI group, 13 patients received 3 cycles of treatment, 1 patient received surgical treatment in advance due to unclear remission of the lesions in 2 cycles, and 1 patient did not undergo the third cycle of treatment due to severe bone marrow suppression.

In the chemotherapy group, 11 patient received 3 cycles of treatment, and 1 patient received one more cycle treatment due to the large lesion.Subsequent to the completion of the induction phase, surgical interventions were scheduled to occur between three to six weeks later. Across the treatment continuum, patients were subjected to a total of four chemotherapy cycles, both preceding and following surgery, with an additional recommendation for the continued application of the same PD-1 inhibitor over a span of one year as part of adjuvant therapy. Diagnostic and preparatory evaluations prior to surgery encompassed comprehensive computed tomography (CT) scans of the chest, abdomen, and brain, supplemented by bone scans for all patients. In instances of ambiguous brain CT outcomes, magnetic resonance imaging (MRI) was employed to ascertain clarity. Bronchoscopies were systematically conducted to facilitate tissue diagnosis and to aid in the meticulous planning of surgical procedures. In scenarios where CT scans proved insufficient for the definitive determination of lymph node metastasis, positron emission tomography (PET) scans, along with endobronchial ultrasound, were predominantly utilized. A complete removal of the mediastinal lymph nodes was carried out in a methodical manner. The histological grading of

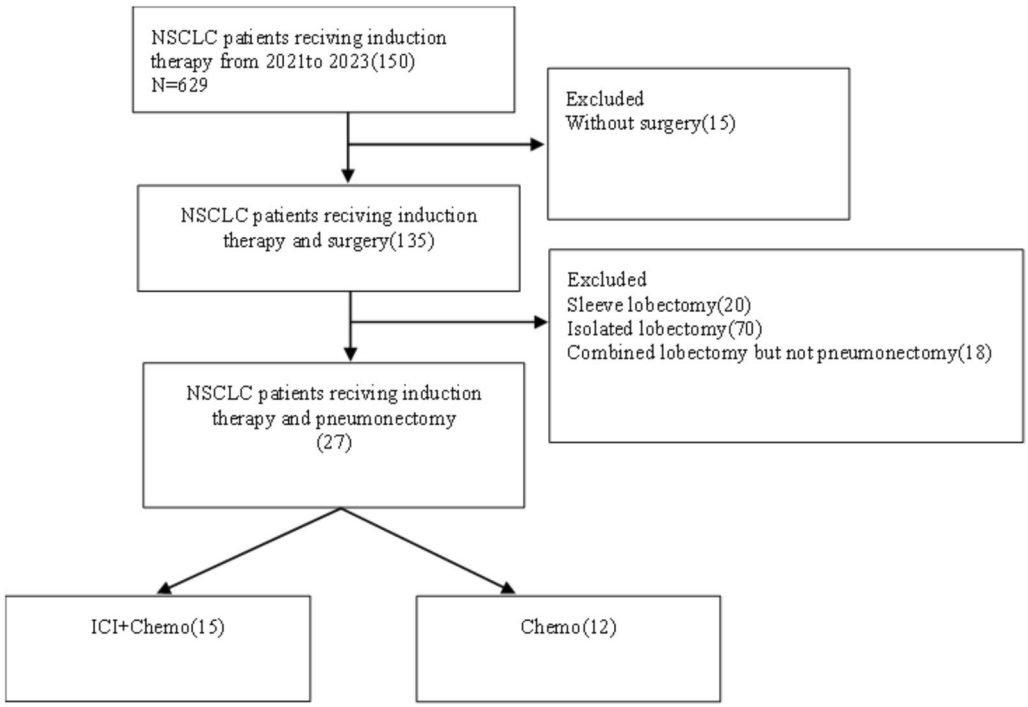

Fig. 1 Patient selection flowchart. *chemo* chemotherapy; *ICI* immune checkpoint inhibitor

tumors was done according to the latest criteria given by the WHO and staging of the tumors was decided carefully as per the eighth edition of TNM classification system by International Association for the Study of Lung Cancer. Postoperative follow-up was strictly organized, with regular scheduled outpatient consultations at 1, 3, 6, and 12 months after the surgery, and biannual thereafter during three or five years in case of stage III patients, and then annual afterwards. Chest-CT scan was ordered for each visit to track progress of the patient. The follow-up of patients who were not able to come for these consultations was also done through telephone in which comprehensive data on the patients' current status, the recurrence patterns and mortality was closely extracted from these telephone calls as well as the records of the clinic.

Outcome measures

Surgical complications were meticulously classified according to the Clavien-Dindo system, identifying those of grade III or above as significant [1]. Documented pulmonary issues encompassed a range of conditions from pneumonia and empyema to acute respiratory distress syndrome, necessitating reintubation for respiratory failure, as well as pleural effusion and pulmonary embolism. Cardiac-related complications included arrhythmias, demand ischemia, and heart attacks. Challenges related to anastomosis featured leaks, separation, and the formation of fistulas. Other notable complications covered chyle leaks, deep vein thrombosis, infections at the surgical site, and injuries to the recurrent laryngeal nerve. The period from the completion of neoadjuvant therapy to the surgical procedure was precisely measured, as was the duration of the surgery itself, from the initial cut to the final suture. The main focus was on identifying major complications occurring within 30 days following the operation. Secondary outcomes concentrated on the pathological responses, including complete pathologic response (PCR) and major pathologic response (MPR), using the TNM staging from the eighth edition of the American Joint Committee on Cancer's staging manual for cancer, and the mediastinal lymph node mapping adhered to the 2009 guidelines set by the International Association for the Study of Lung Cancer. The effectiveness of the therapeutic interventions was evaluated based on the percentage of tumor cells that remained viable, utilizing routine hematoxylin and eosin staining techniques, in accordance with the methodology proposed by Hellmann et al. [11].

Statistical analysis

For the analysis of discrete data, the utilization of percentage metrics was standard, while the assessment of continuous data relied on the calculation of mean values and their standard deviations, employing one-way analysis of variance with the application of Scheffe's method

for post-hoc adjustment when required. The evaluation of binary outcomes such as OS, DFS, post-surgical mortality, and incidences of complications was conducted through the computation of hazard ratios (HRs). To chart the progression of OS and DFS, the Kaplan–Meier method was employed, facilitating the generation and comparison of survival curves via the log-rank test. Estimations of HRs were refined using Cox proportional hazards models. The comprehensive statistical analysis was carried out using the SPSS software, version 24.0, developed by IBM-SPSS Inc., Armonk, NY, and the GraphPad Prism software, version 7.0d, from GraphPad Software, San Diego, California. The approach to hypothesis testing was bidirectional, ensuring a comprehensive assessment of the data.

Results

During the years 2021 to 2023, our facility observed a cohort of 27 patients who underwent PN after receiving induction therapy. This cohort was subdivided into two groups: one consisting of 15 patients who were administered induction therapy with ICIs and the other comprising 12 patients who received solely neoadjuvant chemotherapy. Post-surgical evaluation revealed that all individuals in both the ICI and Chemo groups had clear bronchial margins, indicating successful removal of the tumor. Detailed patient demographics and operative data are systematically outlined in Table 1. Predominantly, the ICI + Chemo group was male, while the Chemo group primarily consisted of female patients($P < 0.001$). In terms of histological types, the ICI + chemotherapy group had more patients with squamous cell carcinoma, while the chemotherapy group had more patients with adenocarcinoma($P < 0.001$).The average age across both groups was around 57 years, with the majority being in the clinical stage IB to IIIA–B, specifically 74.1% falling within the IIIA–B category. Analysis revealed no significant differences in tumor location, duration of surgery, blood loss during surgery, or the length of postoperative hospital stays between the ICI + Chemo and Chemo groups. Similarly, rates of postoperative complications, including severe complications (grade III or above), mortality within 30 days, and the occurrence of bronchial fistulas, were comparable between the groups. Notably, the ICI + Chemo cohort experienced one death within 30 days post-operation and reported two instances of bronchial fistula formation (Table 2).

In the comparison between the ICI and chemo cohorts, a notable superiority was observed in the ICI group concerning pathologic complete response (pCR) and the combined rate of major pathologic response (MPR) or pCR, as detailed in Table 3. Specifically, the ICI cohort achieved a pCR rate of 40.0% (6 out of 15 patients), significantly outperforming the chemo cohort, which had no cases of pCR (0 out of 12 patients), with a p-value of 0.020. Furthermore, the combined rate of MPR or pCR in the ICI group was 60.0% (9 out of 15 patients), substantially higher than the 8.3% (1 out of 12 patients) observed in the chemo group, with a *p*-value of 0.014. Nevertheless, the rate of MPR alone did not show a significant difference between the groups, with the chemo cohort at 8.3% (1/12) and the ICI cohort at 20.0% (3/15), resulting in a *p*-value of 0.605, as depicted in Fig. 2.

The analysis also revealed that the ICI group exhibited improved DFS rates at 1, 2, and 3 years when compared to the chemo cohort, as illustrated in Fig. 3a.

Table 1 Clinical characteristics of two cohorts

	ICI (15)	Chemo (12)	*P*
Age, mean (SD), y	57.2(6.4)	56.9(6.0)	0.901
Male	14(93.3)	2(16.7)	
Female	1(0.7)	10(83.3)	0.000
Comorbidity/yes	3(20.0)	1(8.3)	
Comorbidity/no	12(80.0)	11(81.7)	0.605
Smoking history/current	9(60.0)	8(66.7)	
Smoking history/never	6(40.0)	4(33.3)	1.000
Serum albumin, mean (SD), g/L	42.0(5.0)	43.7(4.1)	0.494
Adenocarcinoma (n, %)	2 (13.3)	10(83.3)	
Squamous cell carcinoma (n, %)	13(86.7)	2(16.7)	0.000
C Stage (n, %)			
IB	1(6.7)	0(0)	
IIA	0(0)	1(8.3)	
IIB	2(13.3)	3(25.0)	
IIIA	11(73.3)	6(50.0)	
IIIB	1(6.7)	2(16.7)	0.335

Values are n (%) of patients unless indicated otherwise. Comorbidity is defined as chronic cardiovascular and respiratory diseases or diabetes mellitus. *c-* clinical-; *chemo* chemotherapy; *ICI* immune checkpoint inhibitor

Table 2 Perioperative outcome

Items	ICI (15)	Chemo (12)	*P*
Mini-invasive VATS	1(6.7)	1(8.3)	1.000
Operation time, mean (SD), min	126.6(54.5)	124.8(60.2)	0.960
Blood loss, mean (SD), mL	220.8(78.2)	200.7(68.9)	0.562
Complications > grade III	4(26.7)	2(16.7)	0.662
90-day death	1(6.7)	0(0)	1.000
Total complications	3(20.0)	0(0)	0.231
Fistula	2(13.3)	0(0)	0.487
Postoperative stay, mean (SD), d	14.7(6.5)	13.4(2.4)	0.528

Values are n (%) of patients unless indicated otherwise. Postoperative 30-day major complications were all graded IIIa according to Clavien-Dindo Classification. *chemo* chemotherapy; *ICI* immune checkpoint inhibitor; *VATS* video-assisted thoracic surgery

Table 3 Pathologic stage and response between ICI cohort and chemo cohort

Pathologic findings	ICI cohort (15)	Chemo cohort (12)	*P*
Pathologic stage Tx	5(33.3)	0(0)	
IA	2(13.3)	0 (0)	
IIA	0(0)	2(16.7)	
IIB	3(20.0)	2(16.7)	
IIIA	5(33.3)	8(66.7)	0.046
MPR	3(20.0)	1(8.3)	0.605
PCR	6(40.0)	0(0)	0.020
MPR or PCR	9(60.0)	1(8.3)	0.014

Values are n (%) of patients. Tx refers to cancer cells not found pathologically, indicating pCR. *chemo* chemotherapy; *ICI* immune checkpoint inhibitor; *MPR* major pathologic response; *pCR* pathologic complete response

Additionally, when classifying patients based on the occurrence of pCR, regardless of whether they received chemotherapy or immunotherapy, it was determined that the DFS in the pCR group significantly surpassed that of the non-pCR group, as shown in Fig. 3b.

Discussion and conclusion

In the subset of individuals diagnosed with non-small-cell lung cancer (NSCLC), approximately 20 to 25% present with tumors that are candidates for surgical removal. However, among these surgically treated patients, 30 to 55% experience a recurrence of their disease and eventually succumb to it [12]. Neoadjuvant chemotherapy is considered for patients at stages that would benefit from adjuvant chemotherapy post-surgery, yet the improvement in 5-year recurrence-free survival and overall survival when compared to surgery alone is modest, at about 5 to 6% [13]. The addition of ICIs to neoadjuvant chemotherapy does not significantly alter the risk of major perioperative complications or mortality. Similarly, induction ICIs do not lead to an increase in toxicities that could delay surgical intervention. Based on the CheckMate-816 findings, immunochemotherapy is recommended as a neoadjuvant strategy in the guidelines. The question of whether pneumonectomy is safe or feasible following induction ICIs remains open. This study aimed to explore the perioperative outcomes and DFS in patients with centrally located NSCLC who underwent pneumonectomy after being treated with induction ICIs, compared to a similar cohort that received only neoadjuvant chemotherapy [14].

The main issues of concern in induction immunotherapy may consist of technical challenges, toxicities, and postoperative risks. No objective findings in our research attributed neoadjuvant immunotherapy to increased technical difficulty associated with pneumonectomy. There was no significant difference operation time, intraoperative blood loss, postoperative major complication rate, and length of hospital stay between the ICI and

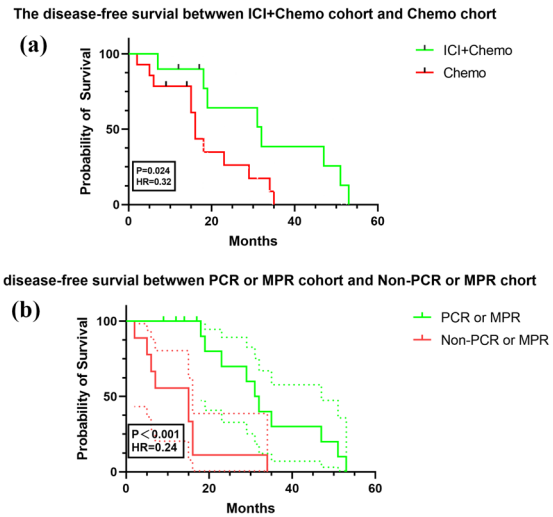

Fig. 3 (**a**) Disease-free survival (DFS) was significantly better for the ICI group. This effect was constant. *HR* hazard ratio; *CI* confidence interval. (**b**) Disease-free survival (DFS) was better in pCR group than non-pCR group

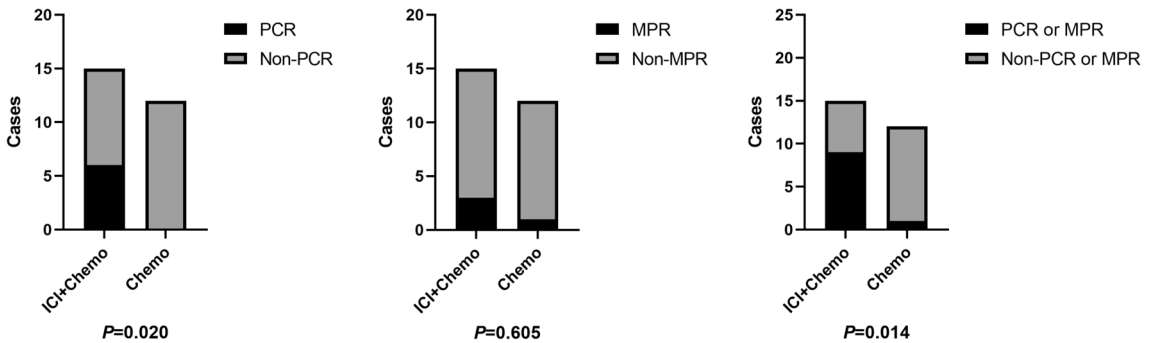

Fig. 2 Pathologic response between ICI cohort and chemo cohort

chemo cohorts. But 30-day death and postoperative anastomotic fistula occurred in ICI cohort, although it is not statistically significant, it still needs to be taken seriously.

Because pCR survival rates in the ICI cohort were greater than those in the chemo cohort after surgery, it seems to indicate that induction ICIs may have better effects than induction chemotherapy. Our study demonstrated that ICI was associated with an improved overall 1, 2, and 3-year DFS compared with chemo cohort. At the same time, both chemotherapy and immunotherapy were grouped according to whether pCR occurred or not, and it was found that DFS in the pCR group was better than DFS in the non pCR group. Our research results are consistent with the results of isloated lobectomy or sleeve lobectomy after neoadjuvant immunotherapy therapy [10, 15].

To our knowledge, this is presently the earliest study comparing the patients with NSCLC receiving induction ICIs and isolated chemotherapy before pneumonectomy. However, several limitations of our study should be recognized. The first and most important limitation of this study was its descriptive nature, using a relatively small cohort of patients at a single institution. In addition, due to the short follow-up time, there is a lack of overall survival evaluation, and further extension of the follow-up time is needed. Additionally, there are some issues that need further research and resolution. Firstly, for patients with complete pathological remission, can compromise surgery be performed instead of total lung resection to preserve more lung function, and does it have an impact on survival. Secondly, there is currently no consensus on whether immunotherapy can continue and the duration of immune maintenance therapy in patients undergoing complete pathological remission and total lung resection.

Conclusions

Based on our results, we argue that compared with pneumonectomy after isolated chemotherapy, pneumonectomy after immunochemotherapy not added 900-day mortality, postoperative, morbidity, but improved DFS; thus, it should be the induction therapy choice for anatomically eligible centrally located lung cancers.

Abbreviations

NSCLC	Non-small cell lung cancer
ICIs	Immune checkpoint inhibitors
PET-CT	Positron emission tomography-computed tomography
CT	Computed tomography
MDT	Multidisciplinary team

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Not applicable

Author contributions

Pingping Song and Zhendan wang are the corresponding authors. Guodong Zhang and Yongle Zhu conceived of the study and participated in its design and coordination. Guodong Zhang and Yongle Zhu draft the manuscript. Zhigang Shi prepared Figs. 1, 2, 3.All authors reviewed the manuscript.

Availability of data and materials

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Shandong Cancer Hospital. We obtained patient consent before the study.

Consent for publication

Manuscript is approved by all authors for publication.

Competing interests

The authors declare no competing interests.

Author details

[1]Thoracic Surgery Department, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Science, Jinan 250117, China. [2]Pharmacy Department, The People's Hospital of Pingyi County, Linyi, China.

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