# Postoperative Chemotherapy after Pneumonectomy in PIIB-PIIIB Non-Small-Cell Lung Cancer: A Safe Treatment but Lack of Survival Benefits

**Haoxuan Wu**
Fudan University Shanghai Cancer Center https://orcid.org/0000-0002-5754-5867
**Yang Zhang**
Fudan University Shanghai Cancer Center
**Xiaoyang Luo**
Fudan University Shanghai Cancer Center
**Yawei Zhang**
Fudan University Shanghai Cancer Center
**Jiaqing Xiang**
Fudan University Shanghai Cancer Center
**Yihua Sun**
Fudan University Shanghai Cancer Center
**Hong Hu** ( huhong0997@163.com )
Fudan University Shanghai Cancer Center

**Research article**

**Keywords:** Pneumonectomy, postoperative chemotherapy, safety, survival, recurrence

**Posted Date:** December 21st, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-131038/v1

# Abstract

***Background.*** Few reports have focused on postoperative chemotherapy (POCT) in stage pIIB-pIIIB non-small-cell lung cancer (NSCLC) patients after pneumonectomy. The safety and survival benefits of POCT have not been thoroughly evaluated among these patients.

***Methods.*** Records of patients who underwent pneumonectomy for stage pIIB-pIIIB NSCLC at a single institution between Jan. 2008 and Dec. 2016 were retrospectively reviewed.

***Results.*** Among the 169 patients included, 143 cases received R0 resection and survived over 90 days postoperatively. Among these, 98 cases received POCT (Chem(+) cohort), and 45 cases did not (Chem(-) cohort). The 5-year rate of non-cancer specific death (death caused by reasons other than cancer) after pneumonectomy was 7% in all patients, 11.1% in the Chem(-) cohort and 5.5% in the Chem(+) cohort. The recurrence rate had a tendency to decrease after POCT (HR=0.95, P=0.883), both in the local recurrence and distant recurrence (HR=0.58, P=0.290; HR=0.85, P=0.645), but the change did not reach statistical significance. pTNM stage and pleural invasion were independent factors associated with the recurrence rate (HR=1.91, P=0.003; HR=1.65, P=0.027). Cancer-specific survival (CSS) was not reduced by POCT (HR=1.27, P=0.614), neither in the N2 station negative group (N2(-) group) (HR=0.55, P=0.474), nor in the N2 station positive group (N2(+) group) (P=1.64; P=0.482).

***Conclusions.*** POCT after pneumonectomy is safe among carefully selected patients in pIIB-pIIIB NSCLC. Patients who achieved R0 resection probably benefit from POCT in terms of recurrence, but not in cancer-specific survival, particularly in stage pIIIA/pIIIB-N2 patients.


# Introduction

With advances in medication and surgical techniques, cases that previously underwent pneumonectomy have alternative therapeutic strategies, such as parenchymal saving surgery and induction treatment. The percentage of patients undergoing pneumonectomy has declined to less than 2.9% of all surgeries for non-small-cell lung cancer (NSCLC)[1]. However, pneumonectomy still has its applications, and it cannot be replaced by other surgery types in cases of extension of the primary tumour or infiltrated lymph nodes.

Patients with NSCLC have a poor prognosis after pneumonectomy, with a 5-year survival of only 36% for IIIA-N0/1 and 20% for IIIA-N2[2]. Multimodal strategies, combining induction or adjuvant therapy with surgery, could distinctly improve the prognosis of NSCLC patients in stage IIB to IIIB[3–5]. However, multimodal strategies involving pneumonectomy are only performed with caution in clinical practice. It has been concluded that induction therapy before pneumonectomy is not worthwhile, considering the high postoperative mortality rate and limited survival benefits[1,6]. Meanwhile, the risk and survival benefits of postoperative chemotherapy (POCT) in pneumonectomy patients after R0 resection is uncertain. POCT after pneumonectomy is supported by a conclusion extrapolated from a series of previous clinical trials that mainly included lobectomy patients[3,7]. According to a pooled analysis by the LACE Collaborative Group, overall survival did not reached statistical significance between patients underwent or not underwent postoperative chemotherapy in a subgroup analysis of pneumonectomy[8]. Moreover, POCT is not administered to all indicated patients clinically, due to the patients' vulnerability after pneumonectomy. Clinicians concern that POCT may increase the risk of morbidity in patients after pneumonectomy.

Thus, in this study, we compared the clinicopathologic features, survival, and site-specific recurrence with or without receiving POCT in a cohort of patients undergoing pneumonectomy at a single institution. We aimed to determine the value of POCT after pneumonectomy in terms of its safety and survival benefits.

# Patients And Methods

# Patient Cohort

We retrospectively reviewed the medical records of a consecutive series of patients who underwent pneumonectomy from January 2008 to December 2016 in the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center. For each patient, preoperative evaluation included clinical history taking, physical examination, blood tests, pulmonary function tests, EKG, chest CT scan, bronchoscopy, 18-FDG PET scan or an alternative combination of bone scanning, cerebral MRI and cervical and abdominal ultrasonography. Biopsy tissues were acquired through bronchoscopy or percutaneous lung puncture, and the pathological results confirmed malignancy. For enlarged mediastinal lymph nodes found on CT scans, mediastinal staging was performed by endobronchial ultrasound transbronchial needle aspiration or 18-FDG PET scans.

Before performing pneumonectomy, the patients received a careful evaluation for its indication. For the cardio-pulmonary functional aspect, forced vital capacity (FVC) over 1.8 L, the forced expiratory volume in second of the predicted volume (FEV1%) over 80% and a good cardio-cerebrovascular condition was necessary. For the parenchymal saving aspect, only patients that were regarded as not suitable for lobectomy or sleeve resection were subjected to pneumonectomy.

After surgery, the utilization of adjuvant chemotherapy was determined by a multi-disciplinary team of doctors specializing in thoracic cancer, referring to the patient's postoperative performance status, cardio-pulmonary function and age. Patients received a platinum-based two drug combined regimen for one to four cycles starting one month after the surgery.

# Follow-up Protocol

Follow-ups were performed through visit records or telephone interviews as an outpatient every 3 months postoperatively for the first 2 years. Patients underwent chest CT scans and abdominal ultrasonography every 3 to 6 months. CT or magnetic resonance imaging scans of the brain and bone scintigraphy were performed every 6 months during the first 3 years. Positron emission tomography–CT scans were optional and performed if necessary. The follow-up frequency was changed to every 6 months for the third year and once per year for subsequent years.

Patients who died within 90 days after surgery and those who did not achieve R0 resection were excluded from the following analysis. The period of cancer-specific survival (CSS) was defined as the interval between the date of surgery and the date of death from lung cancer or associated complications. Cancer-specific death was defined as death caused by lung cancer or its associated complications, and non-cancer specific death was defined as death caused by reasons other than lung cancer. The time to recurrence was defined as the period between the date of surgery and the date when the recurrence was diagnosed via imaging or pathological examination. Recurrences were divided into 3 categories: local recurrence, distant recurrence, or simultaneous local and distant recurrence. We accepted the definition of local recurrence as the first recurrence found at the bronchial stump or mediastinum, which were covered in typical radiation fields in radiotherapy. The definition of a distant recurrence was the first recurrence found in the pleura, contralateral lung or extra-thorax. Simultaneous local and distant recurrence was defined as the local and distant recurrence being detected simultaneously in one follow-up and no recurrence was diagnosed previously[9].

# Statistics

Comparisons between with and without POCT were performed using chi-square tests or Mann-Whitney U tests for qualitative variables and t-tests or Mann-Whitney U tests for continuous variables. All variables possibly associated with survival ($p < 0.05$ or considered related) were entered into a multivariate Cox analysis model to identify independent prognostic factors. The Kaplan-Meier method was applied to calculate survival data, and the differences between groups were determined by the log-rank test. Competing risk regression analysis was used to evaluate the cumulative incidences of survival and recurrence, and Grey's test was used to compare groups. All data analyses were performed using R Studio (version 1.2.1335) utilizing R statistical language version 3.5.3. A p-value of $< 0.05$ was considered to indicate statistical significance.

## Results

# Patient characteristics

From Jan. 2008 to Dec. 2016, 169 non-small-cell lung cancer patients who underwent pneumonectomy were enrolled in this study, with pathological stages from IIB to IIIB according to the IASLC TNM 8th edition staging system (Fig. 1). Among them, a total of 143 patients achieved an R0 resection and survived over 90 days postoperatively with known postoperative treatment (Table 1). Patients who were administered POCT or not were divided into the Chem(+) cohort (n = 98) and Chem(-) cohort (n = 45), respectively. Patients with POCT were administered a combination of a platinum drug (cis-platinum or carboplatin) and an additional drug, gemcitabine in 56.34% patients, pemetrexed in 14.08% patients, docetaxel in 12.68% patients, vinorelbine in 12.68% patients or paclitaxel in 4.23% patients for one to four cycles, and 54.90% patients completed all four cycles of POCT.

Table 1
Clinicopathological characteristics.

| Variable | | Total(143) | Chem(-)(45) | Chem(+)(98) | P-Value |
|---|---|---|---|---|---|
| Gender | | | | | |
| | Male | 128(89.5) | 41(91.1) | 87(88.8) | 0.897 |
| | Female | 15 (10.5) | 4 (8.9) | 11 (11.2) | |
| Age (y) | | 57.44 ± 7.57 | 58.66 ± 7.18 | 56.89 ± 7.71 | 0.195 |
| Performance status | | | | | |
| | 0 | 22(15.4) | 5(11.1) | 17(17.3) | 0.478 |
| | >=1 | 121 (84.6) | 40 (88.9) | 81 (82.7) | |
| Smoking status | | | | | |
| | Non-smoker | 26(18.2) | 7(15.6) | 19(19.4) | 0.750 |
| | Smoker | 117 (81.8) | 38 (84.4) | 79 (80.6) | |
| Pulmonary function | | | | | |
| | FVC(L) | 2.34 ± 0.52 | 2.13 ± 0.56 | 2.42 ± 0.50 | 0.087 |
| | FEV1% | 84.78 ± 14.34 | 78.54 ± 12.39 | 86.92 ± 14.48 | 0.068 |
| | MVV% | 74.02 ± 14.71 | 73.92 ± 19.83 | 74.05 ± 12.84 | 0.978 |
| Side | | | | | |
| | Left | 123(86.0) | 38(84.4) | 85(86.7) | 0.915 |
| | Right | 20 (14.0) | 7 (15.6) | 13 (13.3) | |
| Pathologic type | | | | | |
| Large cell carcinoma | | 4 (2.8) | 1 (2.2) | 3 (3.1) | 0.833 |
| Squamous carcinoma | | 102 (71.3) | 33 (73.3) | 69 (70.4) | |
| Adenocarcinoma | | 28 (19.6) | 7 (15.6) | 21 (21.4) | |
| Adenosquamous carcinoma | | 5 (3.5) | 2 (4.4) | 3 (3.1) | |
| Others | | 4 (2.8) | 2 (4.4) | 2 (2.0) | |
| Pleural invasion | | 28 (20.4) | 7 (15.6) | 21 (22.8) | 0.444 |
| Neural invasion | | 32 (25.2) | 10 (26.3) | 22 (24.7) | 1.000 |
| Vessel invasion | | 44 (34.9) | 12 (31.6) | 32 (36.4) | 0.754 |
| No. of lymph nodes resected | | 22.04 ± 9.66 | 22.73 ± 11.98 | 21.72 ± 8.43 | 0.564 |
| No. of lymph nodes invaded | | 3.34 ± 3.67 | 3.49 ± 4.11 | 3.28 ± 3.47 | 0.748 |
| Pathologic TNM stage | | | | | |
| IIB | | 35 (24.5) | 12 (26.7) | 23 (23.5) | 0.082 |
| IIIA | | 72 (50.3) | 27 (60.0) | 45 (45.9) | |
| IIIB | | 36 (25.2) | 6 (13.3) | 30 (30.6) | |
| Postoperative complication | | 10 (7.0) | 4 (8.9) | 6 (6.1) | 0.803 |

Among these patients, 128 (128/143, 89.5%) were male and 117 (117/143, 81.8%) were smokers (Table 1). In the pathological analyses, squamous carcinoma was the most frequently diagnosed (102/143, 71.3%), and adenocarcinoma came in second (28/143, 19.6%). The pathological stage constituted 24.5% of IIB, 50.3% of IIIA and 25.2% of IIIB. The Chem(-) cohort and Chem(+) cohort demonstrated similarities across the clinicopathological characteristics.

# Risk of POCT

The pattern of death was analysed through a cumulative competing risk analysis model (Fig. 2; Table 2). The median duration of follow-up was 41.43 months. Four and 5 patients died of non-cancer causes in the Chem(-) cohort and Chem(+) cohort, respectively, who all died of cardiopulmonary insufficiency. The five-year cancer non-cancer specific death was 7% in the total cohort, with 11.1% and 5.5% in the Chem(-) cohort and Chem(+) cohort, respectively. Most non-cancer specific deaths happened before the end of the first year, and the one-year death rate was 5.4%.

Table 2
Cumulative incidence of death and recurrence

| | | | Cumulative competitive incidence rate(%) | | | |
|---|---|---|---|---|---|---|
| | | | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years |
| Death | | | | | | | |
| | Cancer specific death | | 6.2 | 20.3 | 28.7 | 31.7 | 33.8 |
| | | Chem(-) | 2.9 | 21.7 | 21.7 | 21.7 | 21.7 |
| | | Chem(+) | 7.5 | 19.8 | 31.4 | 35.7 | 39.2 |
| | Non-cancer specific death | | 5.4 | 7 | 7 | 7 | 7 |
| | | Chem(-) | 8.1 | 11.1 | 11.1 | 11.1 | 11.1 |
| | | Chem(+) | 4.3 | 5.5 | 5.5 | 5.5 | 5.5 |
| Recurrence | | | | | | | |
| | Total | | | | | | |
| | | Local | 6.1 | 8.7 | 8.7 | 8.7 | 8.7 |
| | | Distant | 19 | 28.5 | 31.3 | 33.8 | 35.9 |
| | | Local&Distant | 5.5 | 8.1 | 8.9 | 8.9 | 10.7 |
| | N2(-) | | | | | | |
| | | Local | 5.7 | 7.3 | 7.3 | 7.3 | 7.3 |
| | | Distant | 12.8 | 20.5 | 22.2 | 26.6 | 26.6 |
| | | Local&Distant | 1.5 | 3 | 4.5 | 4.5 | 4.5 |
| | N2(+) | | | | | | |
| | | Local | 6.6 | 10.4 | 10.4 | 10.4 | 10.4 |
| | | Distant | 26.3 | 38.2 | 42.6 | 42.6 | 47.3 |
| | | Local&Distant | 10 | 14.1 | 14.1 | 14.1 | 18.8 |

# Effect of POCT on recurrence

The recurrence pattern after pneumonectomy is shown in Fig. 3 and Table 2. The five-year rate was 8.7% for local recurrence, 35.9% for distant recurrence and 10.7% for simultaneous local and distant recurrence. The curve of recurrence, both local and distant, rose quickly in the 18-month period after surgery, and then started to flatten. Then, the patients were divided into the

N2(-) group (n = 79) and N2(+) group (n = 72) for the N2 station lymph node negative and positive in pathological analyses. The N2(-) group included patients of pIIB and pIIIA-N0/1, and the N2(+) group included patients of pIIIA-N2 and pIIIB. The N2(+) group had significantly higher rates of total distant recurrence (distant + simultaneous local and distant) than the N2(-) group (66.1% vs 31.1%, P < 0.001), as well as the total local recurrence (local + simultaneous local and distant) (29.2% vs 11.8%, P = 0.021). The recurrence sites are listed in Supplementary Table 1.

To analyse the effect of POCT on recurrence, we built a Cox proportional hazard model incorporating gender, age, performance status, side, pathological TNM stage, pleural invasion, vessel invasion, number of metastatic lymph nodes, postoperative complications and POCT for multivariate analysis of site-specific recurrence (Table 3). pTNM stage and pleural invasion were independent factors associated with the total recurrence rate (HR = 1.91, P = 0.003; HR = 1.65, P = 0.027), local recurrence rate (HR = 2.66, P = 0.018; HR = 2.91, P = 0.004) and distant recurrence rate (HR = 1.9, P = 0.008; HR = 1.78, P = 0.018). POCT slightly reduced the rate of total recurrence (HR = 0.95, P = 0.883), local recurrence (HR = 0.58, P = 0.290) and distant recurrence (HR = 0.85, P = 0.645), but it did not reach statistical significance.

Table 3
Multivariate analysis for site-specific recurrence

| | Total recurrence | | | Local recurrence | | | Distant recurrence | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Hazard Ratio | 95% confidence interval | P-value | Hazard Ratio | 95% confidence interval | P-value | Hazard Ratio | 95% confidence interval | P-value |
| Gender (Female vs Male) | 0.55 | 0.22–1.37 | 0.199 | 0 | 0-Inf | 0.998 | 0.71 | 0.28–1.81 | 0.471 |
| Age | 0.98 | 0.95–1.02 | 0.385 | 0.97 | 0.91–1.04 | 0.456 | 0.99 | 0.95–1.04 | 0.756 |
| Performance status ( > = 1 vs = 0) | 0.91 | 0.44–1.91 | 0.811 | 1.36 | 0.29–6.26 | 0.695 | 0.81 | 0.37–1.78 | 0.6 |
| Side (Right vs Left) | 1.08 | 0.49–2.4 | 0.841 | 1.3 | 0.34–4.96 | 0.7 | 1.25 | 0.53–2.99 | 0.611 |
| Pathologic TNM stage | 1.91 | 1.25–2.92 | 0.003 | 2.66 | 1.19–5.99 | 0.018 | 1.9 | 1.18–3.03 | 0.008 |
| Pleural invasion | 1.65 | 1.06–2.57 | 0.027 | 2.91 | 1.42–5.97 | 0.004 | 1.78 | 1.1–2.88 | 0.018 |
| Vessel invasion | 1.24 | 0.81–1.88 | 0.322 | 1.16 | 0.57–2.37 | 0.681 | 1.27 | 0.79–2.03 | 0.323 |
| No. of metastatic lymph nodes | 1.02 | 0.93–1.12 | 0.647 | 1.05 | 0.89–1.23 | 0.559 | 1.02 | 0.92–1.13 | 0.665 |
| Postoperative complication | 1.04 | 0.48–2.25 | 0.928 | 1.48 | 0.46–4.73 | 0.506 | 0.88 | 0.35–2.19 | 0.778 |
| Postoperative chemotherapy | 0.95 | 0.51–1.77 | 0.883 | 0.58 | 0.21–1.6 | 0.290 | 0.85 | 0.43–1.68 | 0.645 |

# Effect of POCT on cancer-specific survival

CSS between the Chem(-) cohort and the Chem(+) cohort had no statistical significance both in the N2(-) group (P = 0.66) and the N2(+) group (P = 0.98) (Fig. 4). The five-year CSS was 85.64% in the Chem(-) versus 75.27% in the Chem(+) in the N2(-) group, and it was 50.00% in the Chem(-) versus 41.81% in the Chem(+) in the N2(+) group. In the N2(-) group, the Chem(+) cohort

showed a tendency towards a survival advantage over the Chem(-) cohort in the first 3 years postoperatively, but the survival curves intersected afterward. We built a Cox proportional hazard model for multivariate analysis (Table 4). The pTNM stage was an independent factor associated with CSS (HR = 2.06, P = 0.001), whereas POCT was not (HR = 1.27, P = 0.614), neither in the N2(-) group (HR = 0.55, P = 0.474) and in the N2(+) group (HR = 1.64, P = 0.482).

Table 4
Multivariate analysis for cancer-specific survival

| | Local Advanced | | | N2(-) | | | N2(+) | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Hazard Ratio | 95% confidence interval | P-value | Hazard Ratio | 95% confidence interval | P-value | Hazard Ratio | 95% confidence interval | P-value |
| Gender (Female vs Male) | 0.67 | 0.2–2.22 | 0.508 | 0 | 0-Inf | 0.998 | 1.35 | 0.36–5.1 | 0.66 |
| Age | 1.01 | 0.96–1.07 | 0.598 | 1.08 | 0.97–1.2 | 0.17 | 1.02 | 0.95–1.08 | 0.651 |
| Performance status ( > = 1 vs = 0) | 1.72 | 0.5–5.94 | 0.393 | 0.4 | 0.04–3.91 | 0.428 | 1.89 | 0.38–9.48 | 0.44 |
| Side (Right vs Left) | 1.24 | 0.4–3.85 | 0.708 | 4.26 | 0.75–24.29 | 0.103 | 0.57 | 0.06–5.23 | 0.619 |
| Pathologic TNM stage | 2.06 | 1.17–3.6 | 0.012 | 3.96 | 0.86–18.3 | 0.078 | 0.64 | 0.21–1.93 | 0.428 |
| Pleural invasion | 1.54 | 0.84–2.83 | 0.165 | 0.76 | 0.22–2.57 | 0.656 | 1.31 | 0.61–2.82 | 0.49 |
| Vessel invasion | 1.55 | 0.9–2.68 | 0.115 | 3.48 | 1.02–11.92 | 0.047 | 1.62 | 0.78–3.37 | 0.194 |
| No. of metastatic lymph nodes | 1.09 | 0.97–1.23 | 0.154 | 0.83 | 0.54–1.28 | 0.404 | 1.03 | 0.89–1.21 | 0.663 |
| Postoperative complication | 1.03 | 0.4–2.66 | 0.953 | - | - | - | 0.71 | 0.25–2.01 | 0.524 |
| Postoperative chemotherapy | 1.27 | 0.5–3.19 | 0.614 | 0.55 | 0.11–2.8 | 0.474 | 1.64 | 0.41–6.49 | 0.482 |

# Discussion

For pIIB-pIIIB NSCLC patients, the incidence of non-cancer specific death of POCT subsequent to pneumonectomy was low among carefully selected patients. The recurrence rate slightly reduced by POCT, but it did not reach statistical significance. POCT did not prolong cancer-specific survival in those who underwent R0 resection with pneumonectomy, particularly in stage pIIIA/pIIIB-N2 patients.

The safety of chemotherapy after pneumonectomy is an important issue in clinical practice. It is generally known that, in addition to the intraoperative risks, pneumonectomy has a high postoperative morbidity and mortality. Removal of an entire lung leads to a dramatic reduction in pulmonary volume, an increase in pulmonary vascular resistance and an increased right ventricle workload, rendering patients vulnerable[10]. Moreover, drugs used for NSCLC chemotherapy have toxic effects and can cause deaths in 0.8% of treated patients[11]. Whether a combination of pneumonectomy and POCT will increase the postoperative mortality is unclear. It has been reported that pulmonary and cardiac complications are the factors that negatively influence

overall survival after pneumonectomy[12], and patients with these complications are more likely to die from the severe toxicity of POCT than those without these complications. Actually, in clinical practice, not all individuals after pneumonectomy indicated for POCT receives it. Even for those who start POCT, the completion rate is significantly lower after pneumonectomy than after lobectomy[13].

In this study, all patients included were in stage pIIB to pIIIB, and they should receive POCT theoretically, but only 68.53% (98/143) of them did and only 54.90% of them completed the four cycles of chemotherapy. Some patients in the study complained of frequent shortness of breath in their daily life and they had to rest in bed most of the time, even several months postoperatively. Thus, they did not receive POCT and their five-year non-cancer specific death rate was 11.1%.

On the other hand, we carefully selected patients to receive POCT based on performance status, age, cardio-pulmonary function and subjective willingness, that was also adopted in a previous study[1]. The patients who received POCT all tolerated it well, and the five-year non-cancer specific death was only 5.5%. Thus, our results indicate that POCT after pneumonectomy is a safe process in carefully selected patients.

As for the site-specific recurrence pattern, we found that distant recurrence (46.6%) was the main reason for treatment failure after pneumonectomy, followed by local recurrence (19.4%). This was consistent with the recurrence patterns of a previous study that recruited stage pIII-N2 NSCLC patients for chemoradiotherapy subsequent to pneumonectomy, that the distant recurrence (the rate was 48.7%) was the main cause of treatment failure, and the local-regional recurrence rate accounted for 32.8%[14].

In this study, POCT slightly reduced the rate of recurrence, and the effect was insignificant, while pathologic TNM stage and pleural invasion played a crucial role in predicting recurrence. Our study did not find a significant difference, but it was likely underpowered to detect any such differences, particularly considering that with the strong impact of TNM stage and pleural invasion on recurrence, the effect of POCT could not be revealed in a retrospective cohort design. A specific analysis of the risk for developing local and distant recurrence after pneumonectomy may be useful to identify the best candidates for adjuvant therapies[15].

A series of studies have proven that patients with resected stage IIB to IIIB NSCLC could earn survival benefits from receiving chemotherapy[3,4,11]. However, most patients in these studies recruited cases of lobectomy. Pignon et al. conducted a pooled analysis in which the benefit of POCT on overall survival was not significant in a subgroup analysis of pneumonectomy[8]. Asad et al. found that adjuvant therapy predicted improved survival in pneumonectomy of stage IIIA NSCLC, but he also proposed that it was uncertain that the result was due to the oncologic effect of POCT or selection bias because patients selected to receive POCT were in a good performance status. Ramnath et al. suggested that POCT should only be prescribed for those who were unable to achieve R0 resection in pneumonectomy and were in good physical condition[16]. In this study, we found that survival was not prolonged by POCT after R0 resection in pneumonectomy, after excluding patients who died of non-cancer causes. The trend is more obvious in the analysis of the N2(+) group. This is a retrospective analysis, so there is inevitable bias and no robust conclusion could be drawn. A large-scale, prospective study focusing on pneumonectomy is urgently needed to verify these results and to confirm the best candidates to receive POCT.

There are a few limitations of the present study. First, the results probably could not be generalized as it is a retrospective study extending over a period of 8 years. However, the study was performed in a single institution with a regular follow-up schedule. Second, cases were not randomized to POCT, suggesting that selection bias may have existed. Third, the number of patients recruited was relatively small, because of the strict indications for pneumonectomy over the past decade. On the other hand, cases in this study could represent the current features of pneumonectomy well, as the included patients were all treated in the last 15 years.

## Conclusions

POCT was safe after pneumonectomy with careful selection of patients. Patients may benefit from POCT in terms of reducing the rate of recurrence in stage pIIB-pIIIB. The CSS may not prolonged by POCT in those who achieved an R0 resection, especially in pIIIA/pIIIB-N2 patients. Our study may serve as a reference for performing POCT for pneumonectomy patients.

## Abbreviations

POCT
postoperative chemotherapy
NSCLC
non-small-cell lung cancer
CSS
cancer-specific survival
FVC
forced vital capacity
FEV1%
the forced expiratory volume in second of the predicted volume

## Declarations

Ethics approval and consent to participate: Informed consent of the included patients was waived because the study was retrospective.

Consent for publication: Not applicable.

Availability of data and materials: The datasets of the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported, in part, by the Shanghai Anticancer Association EYAS Project (SACA-CY1C10).

Authors' contributions: Haoxuan Wu performed the data analyses and wrote the manuscript. Yang Zhang and Xiaoyang Luo contributed significantly to analysis and manuscript preparation. Yawei Zhang, Jiaqing Xiang and Yihua Sun helped perform the analysis with constructive discussions. Hong Hu contributed to the conception of the study. All authors read and approved the final manuscript.

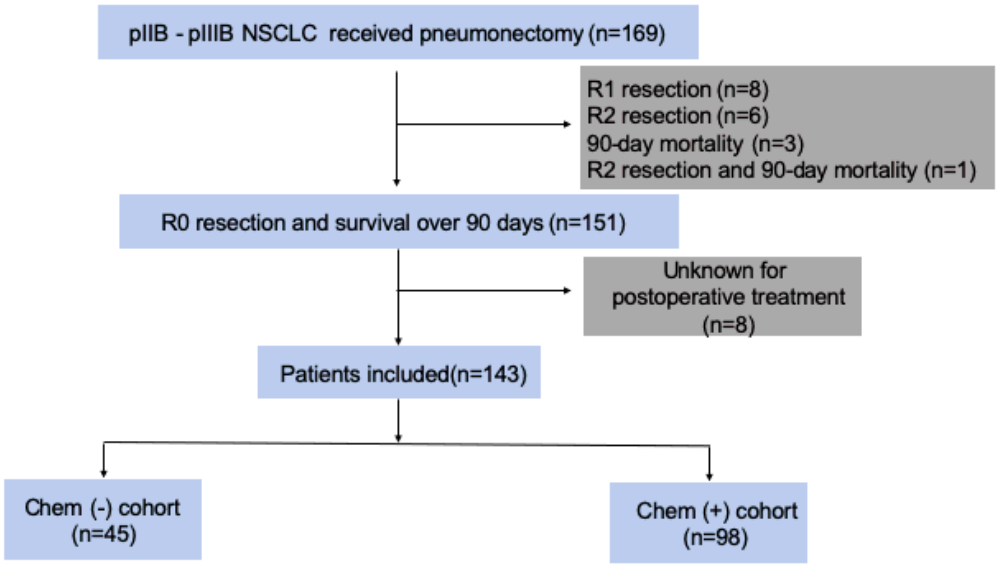
Acknowledgements: Not applicable.

## References

1. Speicher PJ, Ganapathi AM, Englum BR, Onaitis MW, D'Amico TA, Berry MF. Survival in the elderly after pneumonectomy for early-stage non-small cell lung cancer: a comparison with nonoperative management. J Am Coll Surg. 2014;218(3):439–49.
2. Shah AA, Worni M, Kelsey CR, Onaitis MW, D'Amico TA, Berry MF. Does pneumonectomy have a role in the treatment of stage IIIA non-small cell lung cancer? Ann Thorac Surg. 2013;95(5):1700–7.
3. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7(9):719–27.
4. Pisters KM, Vallieres E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol. 2010;28(11):1843–9.

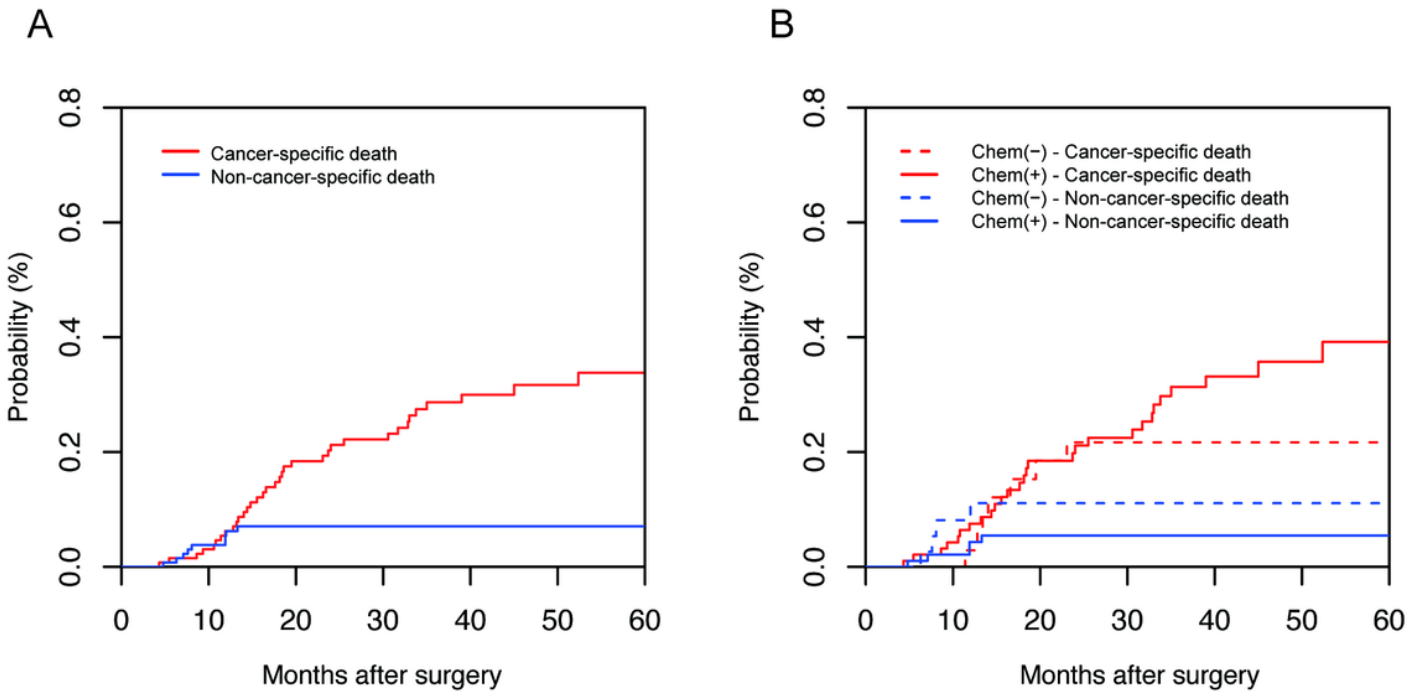
5. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008;9(7):636–48.
6. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374(9687):379–86.
7. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. The New England journal of medicine. 2005;352(25):2589–97.
8. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008;26(21):3552–9.
9. Kelsey CR, Marks LB, Hollis D, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer. 2009;115(22):5218–27.
10. Petrella F, Spaggiari L. Therapeutic options following pneumonectomy in non-small cell lung cancer. Expert review of respiratory medicine. 2016;10(8):919–25.
11. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351–60.
12. Tabutin M, Couraud S, Guibert B, Mulsant P, Souquet PJ, Tronc F. Completion pneumonectomy in patients with cancer: postoperative survival and mortality factors. J Thorac Oncol. 2012;7(10):1556–62.
13. Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. Lung cancer. 2005;47(3):385–94.
14. Wang W, Men Y, Wang J, et al. Postoperative radiotherapy is effective in improving survival of patients with stage pIII-N2 non-small-cell lung Cancer after pneumonectomy. BMC Cancer. 2019;19(1):478.
15. Janet-Vendroux A, Loi M, Bobbio A, et al. Which is the Role of Pneumonectomy in the Era of Parenchymal-Sparing Procedures? Early/Long-Term Survival and Functional Results of a Single-Center Experience. Lung. 2015;193(6):965–73.
16. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e314S–340S.

## Figures



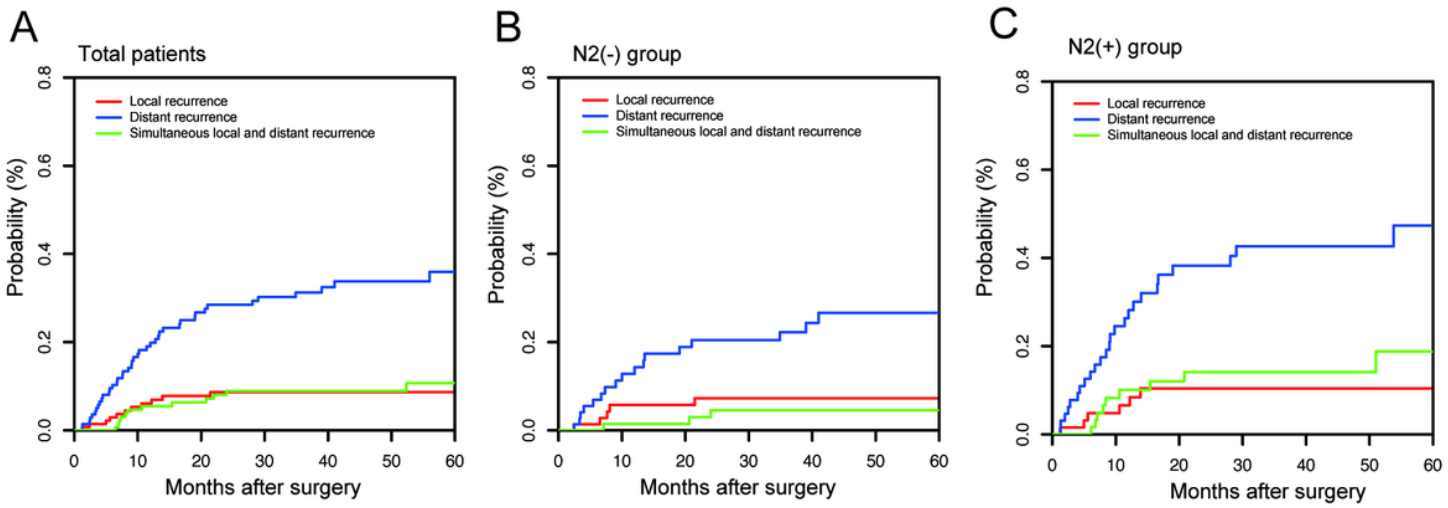
## Figure 1

Flowchart of patients recruited to the study.




## Figure 2

Death pattern analyses. (A) Cumulative competing risk analysis of cancer-specific death and non-cancer-specific death. (B) Influence of postoperative chemotherapy on the death pattern (Chem(+) cohort, patients who received postoperative chemotherapy; Chem(-) cohort, patients who did not receive postoperative chemotherapy).




## Figure 3

Cumulative competing risk analysis of the recurrence pattern after pneumonectomy in total patients (A), the N2 station negative group (N2(-) group) (B), and the N2 station positive group (N2(+) group) (C). The recurrence patterns include local recurrence, distant recurrence and simultaneous local and distant recurrence.

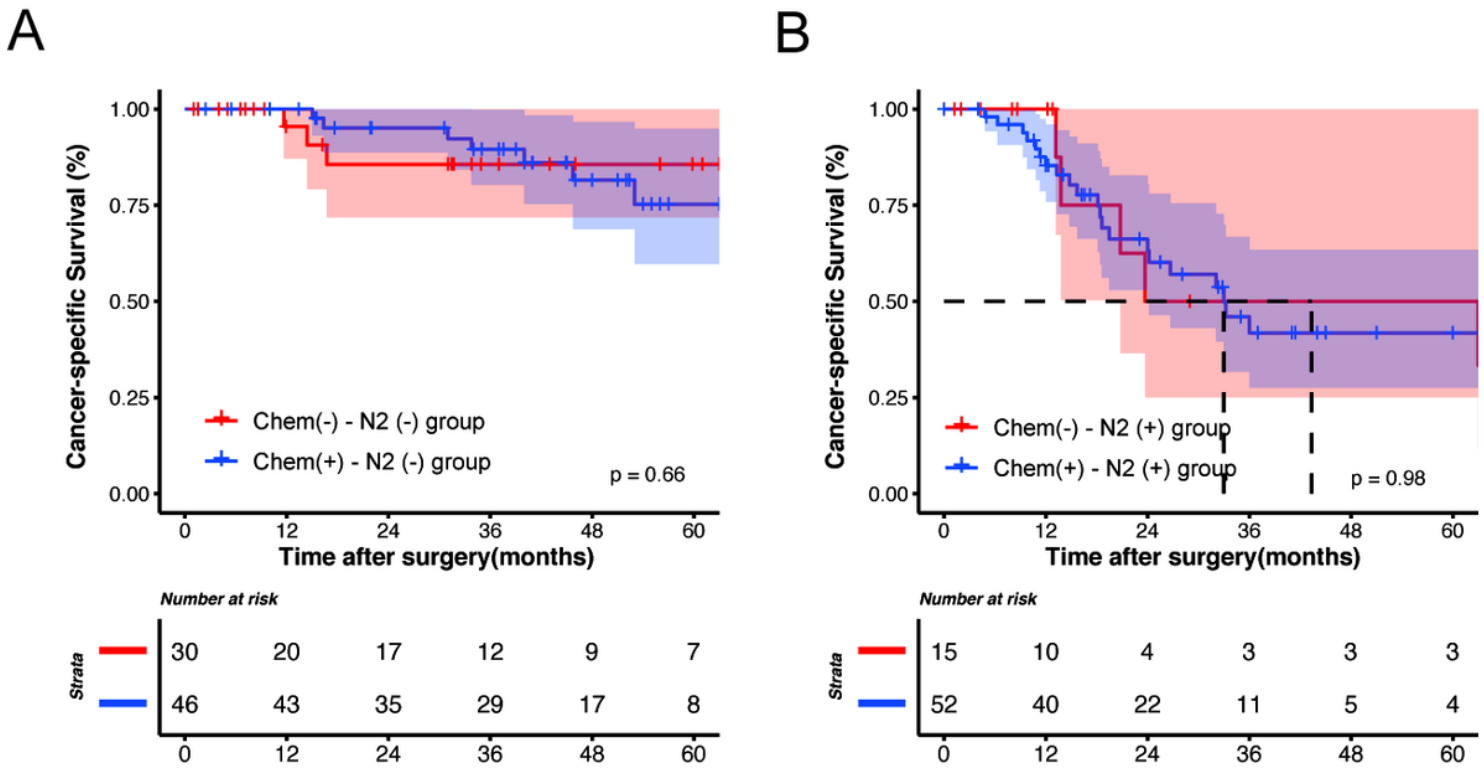



**Figure 4**

Comparison of cancer-specific survival (CSS) between patients with or without postoperative chemotherapy (Chem(+) cohort or Chem(-) cohort) after pneumonectomy in the N2 station negative group (N2(-) group) (A) and in the N2 station positive group (N2(+) group) (B).

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.docx