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Surgical Attrition After Neoadjuvant Chemoimmunotherapy for Non–Small Cell Lung Cancer: Real-World Experience and Predictors

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Abstract:	Objective Despite the increasing adoption of neoadjuvant chemoimmunotherapy (nCIT) in resectable non–small cell lung cancer (NSCLC), a substantial proportion of patients do not complete the planned surgical resection. Although surgical attrition has been reported in randomized trials, its real-world incidence and determinants remain insufficiently defined. This study aimed to determine the incidence, causes, and pre-treatment predictors of surgical attrition following neoadjuvant nCIT in patients with resectable stage II–III NSCLC. Methods We conducted a single-institution cohort study of 100 consecutive patients with stage II–III NSCLC treated with nCIT between November 2022 and December 2023. Baseline clinical, functional, and radiologic variables were analyzed to identify

	predictors of attrition using multivariable logistic regression with multiple imputation. Event-free survival (EFS) was compared according to final treatment strategy. Results Eighty-two patients (82%) proceeded to surgery, whereas 18 (18%) experienced surgical attrition. Attrition was more frequently associated with functional deterioration rather than tumor progression, despite clinical downstaging in 52% of patients. Older age, reduced diffusion capacity for carbon monoxide (<60% predicted), tumor cavitation, and main bronchus abutment were independently associated with surgical attrition. Patients who underwent surgery demonstrated superior 1- and 2-year EFS compared with those managed non-surgically (77.7% vs. 58.8% and 64.5% vs. 41.1%, respectively; P = 0.028). Conclusions Successful oncologic response after nCIT does not ensure surgical completion. Baseline physiologic reserve and airway involvement are critical determinants of resectability. Comprehensive pre-treatment assessment integrating functional and radiologic parameters is essential to optimize surgical completion and long-term outcomes.

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Editor-in-Chief
Lung cancer

Dear Editor,

We are submitting our manuscript entitled "**Surgical Attrition After Neoadjuvant Chemoimmunotherapy for Stage II–III Non–Small Cell Lung Cancer: A Real-World Experience and Predictors**", for consideration for publication as an original article in *Lung Cancer.*

Neoadjuvant chemoimmunotherapy followed by surgery has become a standard treatment strategy for resectable stage II–III non–small cell lung cancer. However, a clinically meaningful proportion of patients do not ultimately undergo the planned surgical resection, limiting the benefit of multimodality treatment. Surgical attrition remains poorly characterized in real-world practice, where patient heterogeneity and multidisciplinary decision-making differ from clinical trial settings.

In this real-world cohort study, approximately 18% of patients failed to proceed to surgery after neoadjuvant chemoimmunotherapy despite frequent clinical downstaging. Surgical attrition was primarily driven by functional deterioration rather than tumor progression alone. Reduced diffusion capacity and older age were associated with increased attrition risk, and specific radiologic features—particularly tumor cavitation and abutment to the main bronchus—emerged as independent anatomic predictors. These findings have direct implications for patient selection and multidisciplinary treatment planning in contemporary surgical oncology practice.

This manuscript is original, has not been published previously, and is not under consideration elsewhere. All authors have approved the final version of the manuscript and have declared no competing interests. We believe that our findings will be of interest to the readership of Lung Cancer, particularly clinicians involved in multidisciplinary management of locally advanced lung cancer.

Thank you for your consideration.

Sincerely,

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Highlights

- Surgical attrition occurred in 18% after neoadjuvant chemoimmunotherapy.
- Functional decline was a more frequent cause of attrition than progression.
- Older age and reduced DLCO were associated with failure to proceed to surgery.
- Tumor cavitation and main bronchus abutment predicted surgical attrition.
- Surgery was associated with improved event-free survival.

Surgical Attrition After Neoadjuvant Chemoimmunotherapy for Non–Small Cell Lung Cancer: Real-World Experience and Predictors

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Running Head: Predictors of Surgical Attrition After nCIT

Abstract

Objective

Despite the increasing adoption of neoadjuvant chemoimmunotherapy (nCIT) in resectable non–small cell lung cancer (NSCLC), a substantial proportion of patients do not complete the planned surgical resection. Although surgical attrition has been reported in randomized trials, its real-world incidence and determinants remain insufficiently defined. This study aimed to determine the incidence, causes, and pre-treatment predictors of surgical attrition following neoadjuvant nCIT in patients with resectable stage II–III NSCLC.

Methods

We conducted a single-institution cohort study of 100 consecutive patients with stage II–III NSCLC treated with nCIT between November 2022 and December 2023. Baseline clinical, functional, and radiologic variables were analyzed to identify predictors of attrition using multivariable logistic regression with multiple imputation. Event-free survival (EFS) was compared according to final treatment strategy.

Results

Eighty-two patients (82%) proceeded to surgery, whereas 18 (18%) experienced surgical attrition. Attrition was more frequently associated with functional deterioration rather than tumor progression, despite clinical downstaging in 52% of patients. Older age, reduced diffusion capacity for carbon monoxide (<60% predicted), tumor cavitation, and main bronchus abutment were independently associated with surgical attrition. Patients who underwent surgery demonstrated superior 1- and 2-year EFS compared with those managed non-surgically (77.7% vs. 58.8% and 64.5% vs. 41.1%, respectively; P = 0.028).

Conclusions

Successful oncologic response after nCIT does not ensure surgical completion. Baseline physiologic reserve and airway involvement are critical determinants of resectability. Comprehensive pre-treatment assessment integrating functional and radiologic parameters is essential to optimize surgical completion and long-term outcomes.

Keywords:

Non–small cell lung cancer; Neoadjuvant chemoimmunotherapy; Surgical attrition; Event-free survival; Pulmonary function; Radiologic predictors; Multidisciplinary treatment

Introduction

Neoadjuvant chemoimmunotherapy (nCIT) has reshaped the therapeutic landscape for resectable non-small cell lung cancer (NSCLC). Pivotal phase III trials, such as CheckMate 816, have demonstrated that integrating immune checkpoint inhibitors to platinum-based chemotherapy results in superior pathological responses and improved survival compared with chemotherapy alone, thereby establishing nCIT followed by surgery as a new standard of care.[1]

Despite these advances, a significant clinical dilemma persists: a substantial proportion of patients, approximately 20% even within controlled clinical trials, failed to undergo the planned surgical resection after nCIT.[1] This phenomenon, termed *surgical attrition*, limits the realization of the full therapeutic potential of multimodality treatment. Although recent randomized controlled trials have reported surgical attrition rates and their causes, it remains uncertain whether these trial-based findings accurately reflect the patterns observed in real-world clinical practice, where patient heterogeneity and multidisciplinary decision-making are more variable.

While oncologic response, such as tumor and nodal downstaging, remains a key objective of neoadjuvant therapy, it does not necessarily ensure surgical feasibility. In routine practice, factors unrelated to tumor biology—such as deterioration in performance status, decline in cardiopulmonary reserve, or treatment-related complications—frequently contribute to attrition. Many investigators have assumed that surgical attrition primarily results from disease progression; however, other mechanisms, including patient refusal, treatment-related toxicity, and physician-directed non-operative management after a near-complete clinical response, are also important and should not be overlooked.

Existing studies have largely focused on survival outcomes and pathological response rates, whereas predictors of surgical attrition after nCIT remain poorly defined. This gap in knowledge is clinically relevant because interruption of the intended multimodality sequence may compromise long-term oncologic outcomes. Accordingly, this study sought to determine the incidence and causes of surgical attrition following nCIT for stage II–III NSCLC and to identify pre-treatment clinical, functional, and radiologic factors associated with this outcome. By comparing patients who proceeded to surgery with

those who did not, we aimed to provide evidence to refine patient selection and optimize treatment planning at the time of therapy initiation.

Materials and Methods

Study Population

This single-institution cohort study used data from the Registry for Lung and Esophageal Cancer Center at Samsung Medical Center, which prospectively collects clinical, radiologic, pathologic, and treatment information for all patients undergoing neoadjuvant therapy for lung cancer. We included consecutive patients with histologically confirmed clinical stage II–III NSCLC who received nCIT between November 2022 and December 2023. Among 103 eligible patients, two were excluded due to loss to follow-up and one due to reclassification as NUT carcinoma, leaving 100 patients for analysis. The study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2023-09-086); the need for informed consent was waived. Patients were followed from the start of nCIT until death or last clinical contact (data cutoff: February 28, 2025).

Pre-treatment Workup and Treatment Protocol

Baseline staging included chest computed tomography (CT), ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, and brain magnetic resonance imaging. Invasive mediastinal staging (endobronchial ultrasound or thoracoscopy) was performed when imaging suggested nodal metastasis, such as enlarged (≥1 cm) or FDG-avid mediastinal nodes.[2,3] Tumor stage was assigned according to the 8th edition of the AJCC TNM classification.[4] Baseline pulmonary function tests included forced vital capacity, forced expiratory volume in 1 second (FEV_1), and diffusion capacity for carbon monoxide (DLCO), expressed as percent predicted by Korean reference equations.[5] Low FEV_1 and DLCO were

defined as less than 60% predicted.[6,7]

Indication for nCIT included clinical stage II-III NSCLC without EGFR or ALK alterations. Neoadjuvant therapy was determined through multidisciplinary discussion. Patients with EGFR or ALK alterations typically received neoadjuvant concurrent chemoradiotherapy (CCRT), whereas others received nivolumab or pembrolizumab plus platinum-based doublet chemotherapy every 3 weeks for three cycles (paclitaxel for squamous, pemetrexed for non-squamous histology). After nCIT, patients underwent restaging with chest CT, PET/CT, and repeat pulmonary function testing. Surgery was scheduled 4–6 weeks after the third cycle, if no disease progression or functional decline was observed. Resection consisted of anatomic pulmonary resection (preferably lobectomy) with systematic hilar and mediastinal lymph node dissection.

All resected specimens were reviewed by thoracic pathologists. Major pathologic response (MPR) was defined as less than 10% residual viable tumor in the primary lesion, and pathologic complete response (pCR) as the absence of viable tumor in both the primary tumor and lymph nodes.[8,9] Postoperative surveillance included clinical evaluation and CT and/or PET/CT every 3 months for 2 years, then every 6 months thereafter.

Imaging Evaluation

All CT and PET/CT studies were performed according to institutional protocols (see **Supplementary Methods)**. Two thoracic radiologists (19 and 8 years of experience) and one nuclear medicine physician (22 years of experience) independently reviewed all imaging, blinded to clinical and pathologic data. Primary tumor characteristics—size, location (central versus peripheral)[10] , contour, necrosis, cavitation, peri-tumoral ground-glass opacity[11], and invasion of adjacent structures—were recorded. Lymph nodes were evaluated for size, morphology, and radiologic extranodal extension, defined by indistinct margins, coalescence, invasion of adjacent structures, or central necrosis.[12] The maximum standardized uptake value (SUVmax) of the primary tumor was measured. Clinical stage was determined at baseline (cTNM)

and after nCIT (ycTNM).

Outcomes and Definitions

The primary outcome was surgical attrition, defined as failure to complete the planned resection after nCIT. Patients were categorized according to whether they underwent surgery or received a non-surgical treatment. Reasons for attrition—including disease progression, functional decline, or patient refusal—were documented. Secondary outcomes included clinical and nodal downstaging, pathologic response rates, and event-free survival (EFS) according to treatment strategy. Exploratory analyses evaluated baseline predictors of surgical attrition.

Statistical Analysis

Continuous variables were compared using Student's t-test or the Mann–Whitney U test, and categorical variables using the chi-square test. Missing data were handled using multiple imputation by chained equations (MICE) under a missing-at-random assumption, with predictive mean matching across 100 datasets and 10 iterations. Univariable logistic analyses identified candidate predictors ($p \leq 0.20$) for multivariable modeling. Predictors with variance inflation factor (VIF) >2 were excluded to minimize multicollinearity. Variables retained in ≥50% of imputed models were included in the pooled multivariable model. Regression coefficients were combined using Rubin's rules to obtain pooled odds ratios (ORs) and 95% confidence intervals (CIs). Sensitivity analyses were performed using complete-case and single-imputation approaches.[13–15] Analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

Results

Patient Characteristics and Treatment Completion

The mean age of the study population was 64.8 years (SD, 9.2); 86% were male and 87% were ever-smokers. Baseline clinical stages were IIB (10%), IIIA (63%) and IIIB (27%). Squamous cell carcinoma was the predominant histologic subtype (51%), followed by adenocarcinoma (46%). Although EGFR and ALK alterations were generally absent at baseline, six patients were later found to harbor EGFR mutations after the initiation of neoadjuvant therapy; four of them had high PD-L1 expression (tumor proportion score ≥ 50%), and two were PD-L1 negative (**Tables 1** and **2**).

nCIT was completed in 98% of patients (n = 98). Two patients discontinued treatment due to disease progression (n = 1) or drug-induced pneumonitis (n = 1). After nCIT, post-treatment clinical staging revealed yc-stage I disease in 26 patients (IA1–IB: 3/14/8/1), yc-stage II in 19 (IIA/IIB: 7/12), yc-stage III in 53 (IIIA/IIIB: 43/10), and yc-stage IVB in 2 patients. Overall, clinical downstaging occurred in 52 patients (52%), whereas upstaging was observed in 6 (6%) (**Figure 1**).

Tumor size decreased in 75 patients (75%) and increased in 4 (4%), with a shift from predominantly T3–T4 tumors at baseline to mainly T1b–T1c tumors after treatment. Among patients with baseline N2 disease (n = 73), nodal downstaging occurred in 26 (35.6%; to N0 in 15 and to N1 in 11). Among those with baseline N1 disease (n = 14), downstaging occurred in 8 (57.1%). Overall, nodal upstaging was observed in 9 patients (9.0%), including 7 of 13 (53.8%) with baseline N0 disease **(Figure S1**).

Final Treatment Pathways After Neoadjuvant Therapy

Among the 100 patients, 82 (82%) proceeded to surgery, while 18 (18%) received non-surgical management. Non-surgical approaches included close observation without treatment (COWT, n = 8), definitive CCRT (n = 3), definitive radiotherapy (n = 2), and palliative chemotherapy (n = 5) (**Figure 1**). Reasons for non-surgical management varied. Among those treated with radiotherapy or CCRT, three patients were deemed medically unfit for surgery due to poor cardiopulmonary function, one was considered unresectable after restaging, and one had insufficient pulmonary reserve. Of the five patients who received palliative chemotherapy, two showed radiologic response but could not undergo surgery

owing to impaired pulmonary function, while three experienced disease progression. Among the eight patients who underwent COWT, five had favorable radiologic response but inadequate functional reserve, and three declined surgery despite acceptable (**Figure S2** and **Supplementary Table S1**).

Predictors of Surgical Attrition

The median interval from baseline CT to treatment initiation was 29 days (interquartile range [IQR], 18–44), and from therapy completion to restaging was 14 days (IQR, 9–22). In univariable analyses, older age, smoking history, low DLCO, tumor cavitation, and abutment of the primary tumor to the main bronchus were associated with increased risk of surgical attrition (**Supplementary Table S2**). Baseline imaging characteristics were compared between patients who completed surgery and those who experienced surgical attrition; most radiologic features, including tumor solidity, central location, contour characteristics, air-bronchogram, peritumoral ground-glass opacity, satellite nodules, pleural effusion, and radiologic extranodal extension, did not differ significantly between the two groups (**Supplementary Table S3**).

In the multivariable logistic regression model using the multiply imputed datasets, four baseline variables remained independently associated with surgical attrition. Older age was associated with a gradual increase in the likelihood of surgical attrition (OR, 1.10; 95% CI, 1.01–1.20; P = 0.024). Patients with low DLCO had more than a fivefold higher risk of not proceeding to surgery (OR, 5.61; 95% CI, 1.41–22.35; P = 0.015). In addition, two radiologic tumor features—cavitation and abutment of the primary tumor to the main bronchus—were independently associated with surgical attrition. The presence of tumor cavitation increased the odds of non-surgical management approximately sixfold (OR, 6.01; 95% CI, 1.06–34.09; P = 0.043), and abutment of the tumor to the main bronchus carried a similarly elevated risk (OR, 6.82; 95% CI, 1.29–36.22; P = 0.025) (**Figure 2** and **Supplementary Table S2**).

Survival Outcomes According to Treatment Strategies

At data cutoff (February 28, 2025), the median follow-up duration was 18.7 months (IQR, 15.8–21.4). Among patients who underwent surgery (n = 82), 56.1% achieved clinical downstaging, 40.2% remained stable, and 3.7% were upstaged. MPR and pCR were observed in 48.8% (n = 40) and 31.7% (n = 26), respectively. The surgical group demonstrated 1-year and 2-year EFS rates of 77.7% and 64.5%, respectively, compared with 58.8% and 41.1% in the non-surgical group (P = 0.028; **Figure 3**). When patients were categorized into three treatment groups—surgery (n = 82), alternative treatment (n = 10), and COWT (n = 8)—the overall comparison showed a non-significant trend toward improved EFS in the surgical group (P = 0.082). When the analysis was restricted to the non-surgical subgroups, EFS did not differ between the alternative treatment and COWT groups (P = 0.78) (**Supplementary Figure S3**). To assess robustness to missing-data handling, we performed sensitivity analyses using complete-case and single-imputation methods. Detailed results are provided in the Supplementary Materials (**Supplementary Table S4**).

Discussion

This study examined how baseline clinical and radiologic factors before nCIT influence the likelihood of completing planned surgical resection. Although more than half of the cohort achieved clinical downstaging and 36.6% of those with N2 disease demonstrated nodal downstaging, 18% did not undergo surgery, most often due to cardiopulmonary deterioration during or after therapy. Multivariable analysis identified reduced DLCO and older age as functional risk factors for surgical attrition, while tumor cavitation and main-bronchus abutment were independent radiologic predictors. These findings emphasize that physiologic reserve and airway involvement—rather than oncologic response alone—are decisive determinants of surgical attrition after nCIT (**Figure 2**).

A key observation was the discordance between radiologic response and surgical completion. Although 52% of patients achieved downstaging, comparable to CheckMate-816 (31%)[1] and a Chinese real-world series (69%)[16] , this improvement did not ensure operability. Many patients who failed to proceed

to surgery had stable disease or partial responses but developed impaired pulmonary function or treatment-related toxicity that rendered them ineligible. Particularly, patients initially considered for pneumonectomy often became unsuitable after nCIT, underscoring that functional capacity—not tumor regression—is frequently the limiting factor. Early identification of individuals prone to functional decline is therefore essential to maintain surgical intent throughout multimodality therapy.

Reduced DLCO was a potent predictor of attrition, consistent with its established role in forecasting postoperative pulmonary complications and mortality.[17] Although ECOG performance status did not retain independent statistical significance in the multivariable model, all patients with ECOG performance status ≥2 in our cohort ultimately failed to proceed to surgery, suggesting that poor performance status may represent a practical clinical threshold beyond which surgical feasibility becomes unlikely in real-world practice. Such patients often have limited physiologic reserve and comorbidity burdens that are not fully captured by isolated pulmonary function measures. Similarly, older age likely reflects diminished physiologic reserve and increased burden of frailty, which could limit tolerance to multimodality therapy, thereby contributing to a higher risk of attrition.[18,19] These findings indicate that comprehensive pre-treatment functional assessment, including pulmonary diffusion capacity, performance status, and age, should guide patient selection and optimization before initiating nCIT.

Among radiologic parameters, tumor abutment to the main bronchus emerged as a strong independent predictor of surgical attrition. Such tumors typically require technically demanding procedures—sleeve lobectomy or pneumonectomy—to achieve R0 resection. Hilar fibrosis related to nCIT can complicate bronchial dissection, raising the risk of conversion or inoperability.[20] Many clinicians prefer definitive CCRT to avoid incomplete resection or postoperative bronchopleural fistula.[21] Thus, bronchial abutment represents an anatomical constraint that may override a radiologic response when determining operability.

Tumor cavitation was another significant predictor of surgical attrition. Cavitation has been linked to advanced stage, poor prognosis, and postoperative morbidity.[22–24] It may reflect necrosis, infection, or

vascular fragility, which complicate dissection, increase bleeding risk, and jeopardize bronchial or parenchymal closure. These factors likely discourage surgeons from proceeding with resection despite apparent response on imaging. In contrast, other features—tumor necrosis, endobronchial spread, peri-tumoral ground-glass opacity, or abutment to vessels or pleura—did not independently affect the decision to operate.

Survival analysis reinforced the clinical importance of surgical completion. Patients who underwent surgery achieved significantly superior one- and two-year EFS (77.7% and 64.5%) compared with those managed non-surgically (58.8% and 41.1%; P = 0.028). This aligns with the established curative role of complete resection in resectable NSCLC after effective systemic therapy. However, subgroup analysis within the non-surgical cohort—divided into definitive radiotherapy or CCRT, palliative chemotherapy, and observation—did not show significant EFS differences, likely due to small sample size and heterogeneity. Many patients who declined or were ineligible for surgery had poor functional reserve or progressive disease, which themselves predict inferior outcomes despite favorable radiologic responses.

This study has limitations. First, it was a single-center analysis with a relatively small sample, which may limit external validity. Nevertheless, it offers valuable real-world insight into nCIT implementation in an East Asian population. Second, because the registry combined prospectively collected and retrospectively reviewed data, and some PET/CT scans were obtained externally, SUVmax values were missing or heterogeneous across scanners. To mitigate this, we applied MICE, and sensitivity analyses confirmed the robustness of key predictors across imputation strategies (**Supplementary Tables S4**). Finally, surgical decision-making involves complex multidisciplinary judgment. With nine operating surgeons contributing to this cohort, unmeasured variability in practice patterns could not be fully accounted for.

In conclusion, our findings show that successful oncologic response after nCIT does not necessarily translate to surgical feasibility. Baseline functional capacity and specific anatomic constraints—particularly main-bronchus involvement and tumor cavitation—play critical roles in determining

whether patients ultimately proceed to resection. These results highlight the importance of comprehensive pre-treatment evaluation integrating physiologic assessment, detailed radiologic review, and multidisciplinary discussion. Future multicenter studies with longer follow-up are warranted to validate these predictors and develop refined selection algorithms to maximize surgical completion and survival benefit in the era of perioperative immunotherapy.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. Baseline Characteristics of Patients

Characteristics	**Planned surgery (N=82)**	**Non-surgical treatment group (N=18)**	**P value**
Age, yr	64.1 ± 9.1	68.1 ± 9.3	0.104
Male	70 (85.4)	16 (88.9)	0.988
Chemoimmunotherapy regimen			0.826
Nivolumab + TC	45 (54.9)	11 (61.1)	
Nivolumab + AC	37 (45.1)	7 (38.9)	
Completion of neoadjuvant chemoimmunotherapy	81 (98.8)	17 (94.4)	0.795
Smoking history			0.230
Current	37 (45.1)	12 (66.7)	
Former	33 (40.2)	5 (27.8)	
Never	12 (14.6)	1 (5.6)	
Smoking Pack-year	33.5 ± 22.7	32.6 ± 20.8	0.350
ECOG			0.028
0	74 (90.2)	16 (88.9)	
1	7 (8.5)	0 (0.0)	
≥2	0 (0.0)	2 (11.2)	
NA	1 (1.2)	0 (0.0)	
History of other malignancy	8 (9.8)	2 (11.1)	>.999
Hypertension	43 (52.4)	7 (38.9)	0.435
Diabetes mellitus	11 (13.4)	5 (27.8)	0.250
Cardiovascular disease	11 (13.4)	2 (11.1)	>.999
Cerebrovascular disease	3 (3.7)	2 (11.1)	0.474
Low DLCO < 60 %	9 (11.0)	7 (38.9)	0.008
Low $FEV1_{pred}$ < 60 %	8 (9.8)	3 (16.7)	0.412

Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. Low DLCO and low FEV1 predicted were defined as <60 of the predicted value. ECOG performance status was assessed at baseline before initiation of neoadjuvant therapy. Neoadjuvant chemoimmunotherapy consisted of nivolumab combined with platinum-based doublet chemotherapy.

Abbreviations: *AC*, platinum plus pemetrexed; *TC*, platinum plus taxane; *DLCO*, diffusing capacity of the lung for carbon monoxide; *ECOG*, Eastern Cooperative Oncology Group; *FEV1*, forced expiratory volume in 1 second.

Table 2. Clinical and Tumor Characteristics

Characteristics	**Planned Surgery (N = 82)**	**Non-Surgical Treatment (N = 18)**	**P value**
Pathology			0.512
Adenocarcinoma	39 (47.6)	7 (38.9)	
Squamous cell carcinoma	40 (48.8)	11 (61.1)	
Others[1]	3 (3.7)	0 (0.0)	
Clinical stage			0.525
IIB	8 (9.8)	2 (11.1)	
IIIA	54 (65.9)	9 (50.0)	
IIIB	20 (24.3)	7 (38.9)	
EGFR mutation status			0.331
Mutant	5 (6.1)	1 (5.6)	
Wild type	68 (82.9)	17 (94.4)	
NA	9 (11.0)	0 (0.0)	
ALK translocation			1
Yes	0 (0.0)	0 (0.0)	
No	76 (92.7)	17 (94.4)	
NA	6 (7.3)	1 (5.6)	
High PD-L1 expression (TPS ≥50)			0.71
Yes	35 (42.7)	9 (50.0)	
No	45 (54.9)	9 (50.0)	
NA	2 (2.4)	0 (0.0)	
Tumor size, mm	44.4 ± 21.6	52.6 ± 25.3	0.161
Tumor SUVmax	13.6 (10.6–17.7)	13.2 (12.5–17.5)	0.166

Data are presented as mean ± SD, median (interquartile range), or n (percentage), as appropriate.
1. Others include poorly differentiated carcinoma or mucoepidermoid carcinoma.
Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NA, not available; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; SUVmax, maximum standardized uptake value; TPS, tumor proportion score

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1

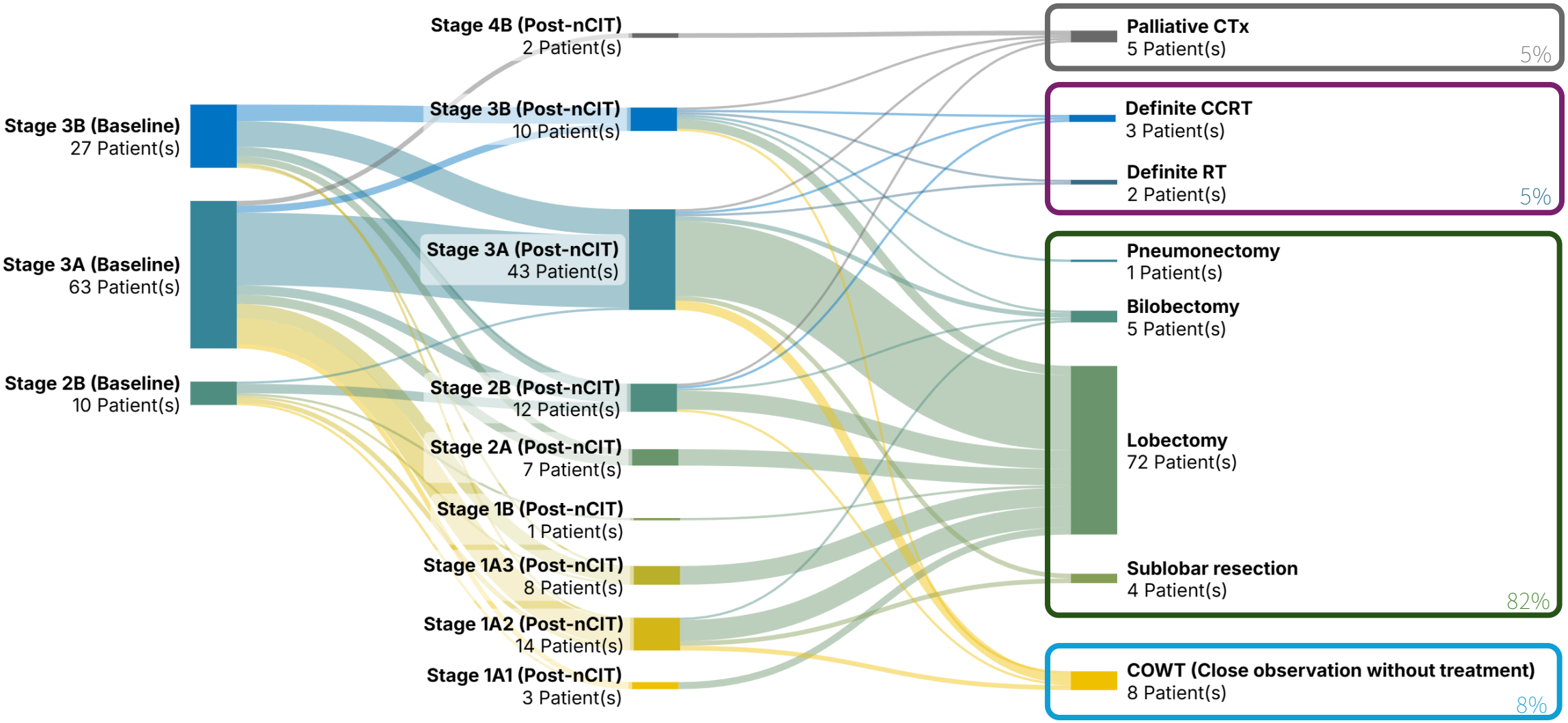

Figure 2

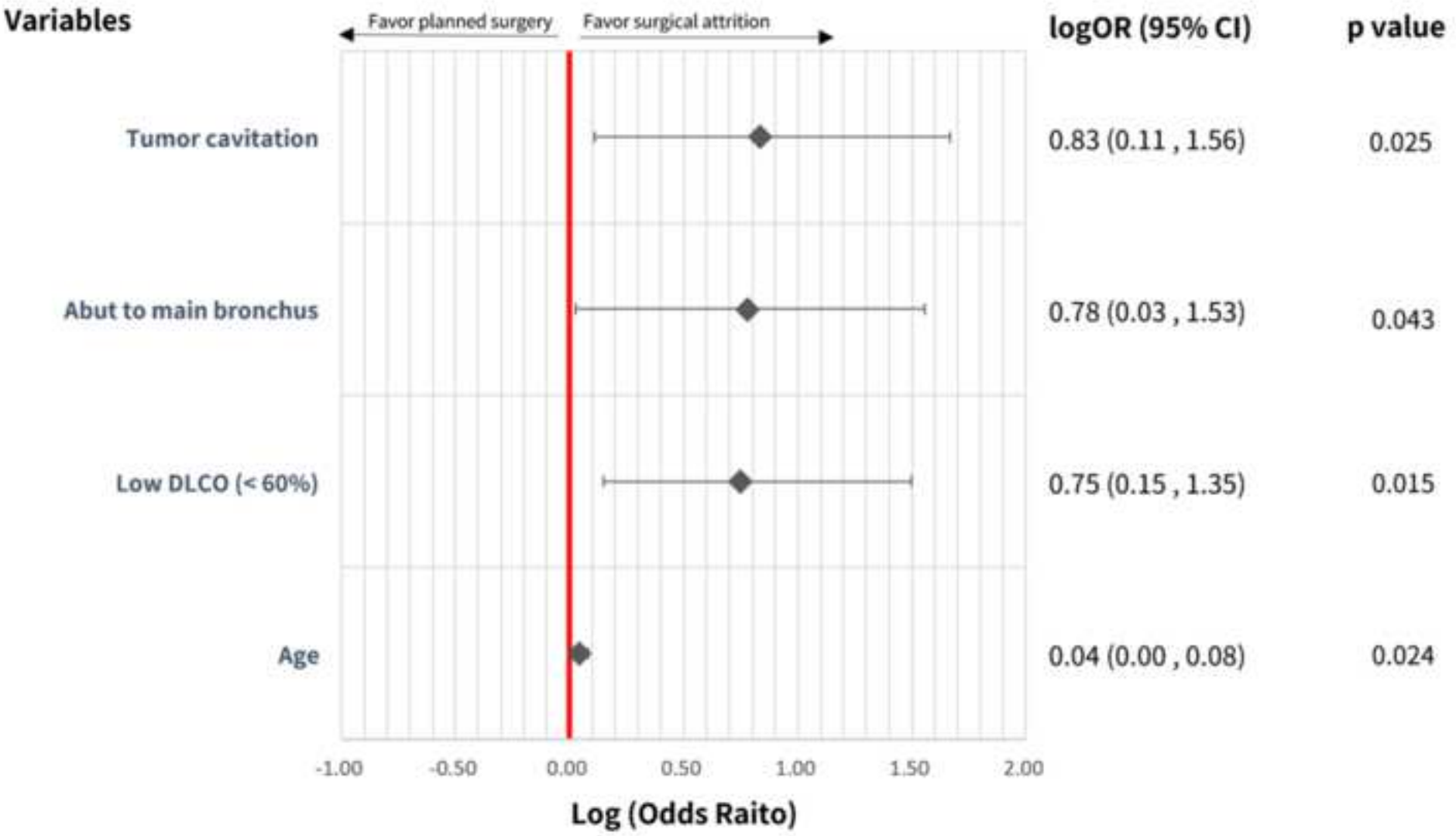

Figure 3

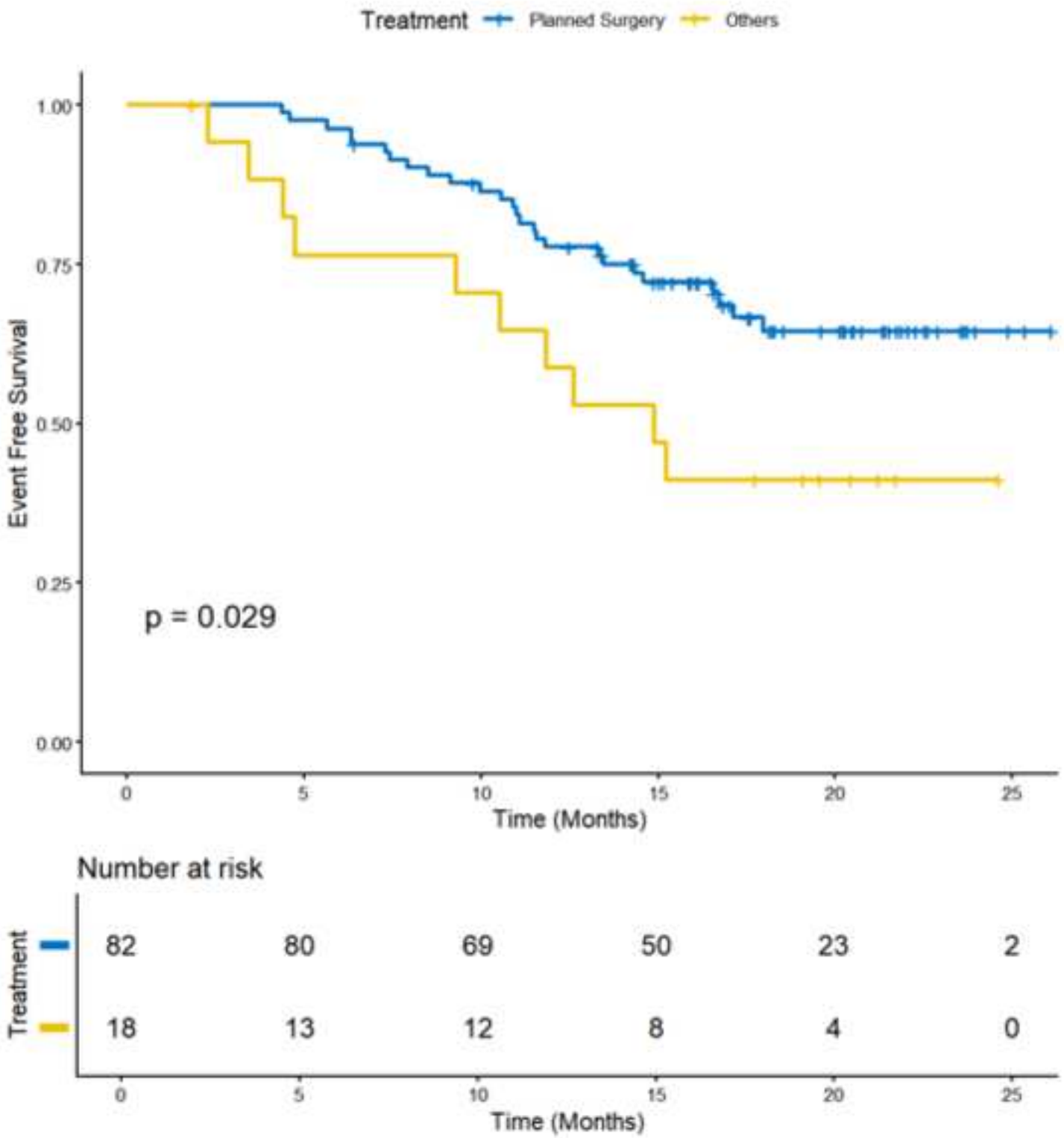

Figure 1. Sankey diagram for the study cohort.

Figure 2. Figure 2. Forest plots of factors associated with surgical attrition, excluding patients managed with close observation without treatment (COWT). (A) Univariable screening analysis including variables with $p < 0.20$. (B) Multivariable analysis including variables with a selection frequency ≥ 0.50 during the selection procedure.

Figure 3. Kaplan–Meier Analysis of Event-Free Survival (EFS): Comparison between patients who underwent planned surgery and those who did not

Supplementary Figure S2

Supplementary Table S1. Reasons for changes in the patient's therapeutic strategy.

	COWT	Definitive RT/CCRT	Palliative chemotherapy
Patient's refusal	3 (37.5%)	0	0
Poor cardiopulmonary function	5 (62.5%)	2 (40.0%)	2 (40.0%)
Pneumonectomy candidate	0	2 (40.0%)	0
Unresectable	0	1 (20.0%)	0
Disease progression	0	0	3 (60.0%)
Total	8	5	5

COWT (Close observation without treatment), CCRT (Concurrent chemoradiotherapy), RT (Radiotherapy)

Supplementary Table S2. Uni- and multi-variable analysis of factors associated with surgical attrition using multiple imputation by chained equations (MICE)

	Univariable analysis*			**Multivariable analysis**	
	OR (95% CI)	P value	Freq. (%)	OR (95% CI)	P value
Clinical characteristics					
Age	1.06 (0.99 – 1.13)	0.106	**100%**	**1.10 (1.01 – 1.20)**	**0.024**
Sex | Female	1.37 (0.28 – 6.74)	0.697			
Hypertension	0.58 (0.20 – 1.64)	0.301			
DM	2.48 (0.74 – 8.34)	0.141	15%		
History of tuberculosis	2.32 (0.63 – 8.58)	0.208			
Cardiovascular disease	0.81 (0.16 – 4.00)	0.793			
Cerebrovascular disease	3.29 (0.51 –21.31)	0.211			
Previous history of cancer	1.16 (0.22 – 5.97)	0.862			
Smoking	2.05 (0.87 – 4.83)	0.101			
ECOG	**2.13 (0.80 – 5.68)**	**0.129**			
Low $FEV1_{pred}$ | < 60%	1.85 (0.44 – 7.79)	0.402			
Low DLCO | < 60%	**5.16 (1.60 – 16.69)**	**0.006**	**100%**	**5.61 (1.41 – 22.35)**	**0.015**
Clinical stage at baseline*	1.48 (0.61 – 3.58)	0.389			
Cycle of nCIT	1.19 (0.41 – 3.54)	0.750			
Tumor and imaging characteristics					
Pathology | SqCC	1.65 (0.58 –4.68)	0.346			
EGFR mutant	0.80 (0.09 – 7.32)	0.843			
PD-L1 (TPS ≥50%)	1.29 (0.46 – 3.59)	0.625			
Tumor size	1.02 (0.99 – 1.04)	0.177			
SUVmax of tumor	1.04 (0.95 – 1.13)	0.451	15%		
Tumor necrosis	0.99 (0.35 – 2.83)	0.991			
Tumor cavitation	3.90 (0.79 – 19.23)	0.095	**97%**	**6.01 (1.06 – 34.09)**	**0.043**
Tumor spread via adjacent bronchus	1.45 (0.52 – 4.04)	0.480			
Peripheral GGO	0.75 (0.08 – 6.6)	0.791			
Satellite nodule	1.58 (0.29 – 8.57)	0.594			
Obstructive pneumonia	1.48 (0.53 – 4.13)	0.449			
Pleural effusion	1.16 (0.22 – 5.97)	0.862			
Abut to major vessel	1.18 (0.34 – 4.07)	0.795			
Abut to main bronchus	4.12 (1.13 – 14.97)	0.031	**100%**	**6.82 (1.29 – 36.22)**	**0.025**
Abut to pleura	1.39 (0.4 – 4.85)	0.608			
Abut to fissure	1.22 (0.44 – 3.38)	0.707			
N1 node involvement	0.8 (0.29 – 2.24)	0.671			
rENE of N1 node	1.65 (0.59 – 4.59)	0.342			
N2 node involvement	1.35 (0.44 – 4.16)	0.604			
rENE of N2 node	1.23 (0.43 – 3.49)	0.698			

All t-tests and chi-square tests were conducted by excluding any NA values to avoid potential distortion of the results; *ORs, 95% CIs, and p values were obtained from logistic regression models fitted separately in each of the 100 imputed datasets and combined using Rubin's rules; Freq (Selection Frequency %): The percentage of imputed datasets (out of 100) in which the variable was selected via the AIC-based backward stepwise elimination process. Variables with a selection frequency ≥ 50% were included in the final multivariable model candidate set; A dash (-) indicates variables that were not retained in the final multivariable model after backward elimination.; **Abbreviation:** nCIT (neoadjuvant chemoimmunotherapy), Diabetes mellitus (DM), Eastern Cooperative Oncology Group (ECOG), Epidermal Growth Factor Receptor (EGFR), Programmed Death-Ligand 1 (PD-L1), SqCC (Squamous cell caricinoma), Tumor Proportion Score (TPS), $FEV1_{pred}$ (Forced Expiratory Volume in 1 second predicted), DLCO (Diffusing Capacity of the Lung for Carbon Monoxide), PFT

(Pulmonary Function Test), rENE(radiological extranodal extension)

Supplementary Table S3. Baseline imaging characteristics which evaluated in the study.

Characteristics	Planned surgery	Non-surgical treatment group	Total	P value
Solid vs non-solid	65 (79.3%)	15 (83.3%)	80 (80.0%)	0.921
Central location	33 (40.2%)	11 (61.1%)	44 (44.0%)	0.163
Shape | Spiculation	24 (29.3%)	6 (33.3%)	30 (30.0%)	0.955
Shape | Lobulated contour	70 (85.4%)	14 (77.8%)	84 (84.0%)	0.660
Air-bronchogram sign	30 (36.6%)	4 (22.2%)	34 (34.0%)	0.373
Tumor Necrosis	32 (39.0%)	7 (38.9%)	39 (39.0%)	1.000
Cavitation of Tumor	4 (4.9%)	3 (16.7%)	7 (7.0%)	0.206
Endobronchial spread to proximal bronchus	38 (46.3%)	10 (55.6%)	48 (48.0%)	0.654
	31 (37.8%)	10 (55.6%)	41 (41.0%)	0.262
Lymphangitic metastasis	2 (2.4%)	1 (5.6%)	3 (3.0%)	1.000
Peritumoral ground glass opacity	6 (7.3%)	1 (5.6%)	7 (7.0%)	1.000
Satellite nodule	6 (7.3%)	2 (11.1%)	8 (8.0%)	0.954
Obstructive pneumonia	33 (40.2%)	9 (50.0%)	42 (42.0%)	0.620
Pleural effusion	8 (9.8%)	2 (11.1%)	10 (10.0%)	1.000
Tumor abutment | Major vessel	16 (19.5%)	4 (22.2%)	20 (20.0%)	1.000
Tumor abutment | Main bronchus	7 (8.5%)	5 (27.8%)	12 (12.0%)	0.061
Tumor abutment | Pleura	37 (45.1%)	9 (50.0%)	46 (46.0%)	0.909
Tumor abutment | Fissure	14 (17.1%)	4 (22.2%)	18 (18.0%)	0.860
Number of involved LN station	1.8 ± 1.3	1.8 ± 0.9	1.8 ± 1.2	0.896
Involvement of N1 lymph node	50 (61.0%)	10 (55.6%)	60 (60.0%)	0.873
rENE of N1 lymph node	31 (37.8%)	9 (50.0%)	40 (40.0%)	0.490
Involvement of N2 lymph node	54 (65.9%)	13 (72.2%)	67 (67.0%)	0.808
rENE of N2 lymph node	46 (56.1%)	11 (61.1%)	57 (57.0%)	0.900
Skip N2 involvement	21 (25.6%)	8 (44.4%)	29 (29.0%)	0.191

Abbreviation: rENE; radiologic extracapsular extension

Supplementary Table S4-1. Uni- and multi-variate analysis of factors associated with surgical attrition using single imputation (median/mode) for missing predictors

	Univariate analysis**			**Multivariate analysis**	
	OR (95% CI)	P value	VIF	OR (95% CI)	P value
Clinical characteristics					
Age	**1.06 (0.99-1.13)**	**0.106**	**1.56**	**1.10 (1.01 – 1.20)**	**0.021**
Sex | Female	1.37 (0.33 – 9.37)	0.697			
Hypertension	0.58 (0.20-1.61)	0.301			
DM	**2.48 (0.69-8.13)**	**0.141**	**1.44**	-	-
History of tuberculosis	2.32 (0.57-8.26)	0.208			
Cardiovascular disease	0.81 (0.12-3.40)	0.793			
Cerebrovascular disease	3.29 (0.41-21.45)	0.211			
Previous history of cancer	1.16 (0.16-5.17)	0.862			
Smoking	**2.05 (0.92-5.26)**	**0.101**	**1.17**	-	-
ECOG	**2.16 (0.78-6.35)**	**0.125**	**1.06**	-	-
Low $FEV1_{pred}$ | < 60%	1.85 (0.37-7.28)	0.402			
Low DLCO | < 60%	**5.16 (1.57-16.92)**	**0.006**	**1.26**	**5.61 (1.43 – 21.96)**	**0.013**
Clinical stage at baseline*	1.48 (0.61-3.66)	0.389			
Cycle of nCIT	0.87 (0.38-2.06)	0.750			
Tumor and imaging characteristics					
Pathology | SqCC	1.65 (0.59-4.88)	0.346			
EGFR mutant	0.91 (0.05-6.11)	0.930			
PD-L1 (TPS ≥50%)	1.34 (0.48-3.78)	0.572			
Tumor size	**1.02 (0.99-1.04)**	**0.177**	**1.31**	-	-
SUVmax of tumor	1.06 (0.97-1.16)	0.206			
Tumor necrosis	0.99 (0.34-2.80)	0.991			
Tumor cavitation	**3.90 (0.71-19.51)**	**0.095**	**1.20**	**6.01 (1.08 – 33.33)**	**0.040**
Tumor spread via adjacent bronchus	1.45 (0.52-4.15)	0.480			
Peripheral GGO	0.75 (0.04-4.77)	0.791			
Satellite nodule	1.58 (0.22-7.63)	0.594			
Obstructive pneumonia	1.48 (0.53-4.19)	0.449			
Pleural effusion	1.16 (0.16-5.17)	0.862			
Abut to major vessel	1.18 (0.30-3.82)	0.795			
Abut to main bronchus	**4.12 (1.08-15.00)**	**0.031**	**1.35**	**6.82 (1.31 – 35.44)**	**0.022**
Abut to pleura	1.39 (0.35-4.58)	0.608			
Abut to fissure	1.22 (0.43-3.42)	0.707			
N1 node involvement	0.80 (0.29-2.30)	0.671			
rENE of N1 node	1.65 (0.58-4.65)	0.342			
N2 node involvement	1.35 (0.46-4.55)	0.604			
rENE of N2 node	1.23 (0.44-3.64)	0.698			

A dash (-) indicates variables that were not retained in the final multivariable model after backward elimination.
Abbreviation: nCIT (neoadjuvant chemoimmunotherapy), Diabetes mellitus (DM), Eastern Cooperative Oncology Group (ECOG), Epidermal Growth Factor Receptor (EGFR), Programmed Death-Ligand 1 (PD-L1), SqCC (Squamous cell caricinoma), Tumor Proportion Score (TPS), FEV1pred (Forced Expiratory Volume in 1 second predicted), DLCO (Diffusing Capacity of the Lung for Carbon Monoxide), PFT (Pulmonary Function Test), rENE(radiological extranodal extension)

Supplementary Table S4-2. Uni- and multi-variate analysis of factors associated with surgical attrition using complete-case data

	Univariate analysis**			**Multivariate analysis**	
	OR (95% CI)	P value	VIF	OR (95% CI)	P value
Clinical characteristics					
Age	**1.05 (0.99-1.14)**	**0.161**	**1.96**	**1.12 (1.01 – 1.25)**	**0.028**
Sex | Female	1.23 (0.28-8.61)	0.807			
Hypertension	0.48 (0.14-1.53)	0.229			
DM	1.72 (0.42-6.16)	0.420			
History of tuberculosis	**5.36 (1.12-26.01)**	**0.031**	**1.48**	5.94 (1.00 – 35.27)	0.050
Cardiovascular disease	1.06 (0.15-4.87)	0.947			
Cerebrovascular disease	**4.69 (0.52-42.15)**	**0.139**	**1.38**		
Previous history of cancer	0.57 (0.03-3.60)	0.614			
Smoking	**3.00 (1.21-9.26)**	**0.031**	**1.52**	2.96 (0.83 – 10.55)	0.095
ECOG	**2.69 (0.93-10.29)**	**0.086**	**1.21**		
Low $FEV1_{pred}$ | < 60%	1.05 (0.05-7.84)	0.964			
Low DLCO | < 60%	**7.38 (1.69-34.68)**	**0.008**	**1.43**	**7.85 (1.16 – 53.37)**	**0.035**
Clinical stage at baseline*	1.93 (0.71-5.57)	0.207			
Cycle of nCIT	**0.46 (0.16-1.24)**	**0.129**	**1.38**		
Tumor and imaging characteristics					
Pathology | SqCC	**2.20 (0.70-7.75)**	**0.191**	**1.99**	-	**-**
EGFR mutant	Not estimated*	0.993			
PD-L1 (TPS ≥50%)	1.52 (0.49-4.85)	0.465			
Tumor size	1.02 (0.99-1.04)	0.271			
SUVmax of tumor	1.05 (0.96-1.15)	0.278			
Tumor necrosis	0.71 (0.20-2.25)	0.573			
Tumor cavitation	3.08 (0.38-20.44)	0.243			
Tumor spread via adjacent bronchus	1.34 (0.43-4.25)	0.611			
Peripheral GGO	Not estimated*	0.993			
Satellite nodule	1.78 (0.24-9.35)	0.516			
Obstructive pneumonia	1.33 (0.42-4.16)	0.622			
Pleural effusion	0.68 (0.03-4.43)	0.729			
Abut to major vessel	1.18 (0.24-4.52)	0.818			
Abut to main bronchus	**5.80 (1.39-24.72)**	**0.015**	**1.63**	**8.49 (1.15 – 62.58)**	**0.036**
Abut to pleura	1.72 (0.42-6.16)	0.420			
Abut to fissure	1.09 (0.34-3.41)	0.876			
N1 node involvement	0.80 (0.26-2.67)	0.713			
rENE of N1 node	**2.44 (0.78-8.10)**	**0.129**	**1.41**	-	**-**
N2 node involvement	1.28 (0.38-5.06)	0.702			
rENE of N2 node	1.20 (0.39-3.96)	0.755			

All t-tests and chi-square tests were conducted by excluding any NA values to avoid potential distortion of the results. *The OR could not be reliably estimated due to a wide confidence interval.

Abbreviations:nCIT (neoadjuvant chemoimmunotherapy), Diabetes mellitus (DM), Eastern Cooperative Oncology Group (ECOG), Epidermal Growth Factor Receptor (EGFR), Programmed Death-Ligand 1 (PD-L1), SqCC (Squamous cell caricinoma), Tumor Proportion Score (TPS), FEV1pred (Forced Expiratory Volume in 1 second predicted), DLCO (Diffusing Capacity of the Lung for Carbon Monoxide), PFT (Pulmonary Function Test), rENE(radiological extranodal extension)