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Clinical Research

Risk Factor Analysis of Morbidity and 90-Day Mortality of Curative Resection in Patients with Stage IIIA–N2 Non-Small Cell Lung Cancer after Induction Concurrent Chemoradiation Therapy

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Background: Major pulmonary resection after neoadjuvant concurrent chemoradiation therapy (nCCRT) is associated with a substantial risk of postoperative complications. This study investigated postoperative complications and associated risk factors to facilitate the selection of suitable surgical candidates following nCCRT in stage IIIA–N2 non-small cell lung cancer (NSCLC).
Methods: We conducted a retrospective analysis of patients diagnosed with clinical stage IIIA–N2 NSCLC who underwent surgical resection following nCCRT between 1997 and 2013. Perioperative characteristics and clinical factors associated with morbidity and mortality were analyzed using univariable and multivariable logistic regression.
Results: A total of 574 patients underwent major lung resection after induction CCRT. Thirty-day and 90-day postoperative mortality occurred in 8 patients (1.4%) and 41 patients (7.1%), respectively. Acute respiratory distress syndrome (n=6, 4.5%) was the primary cause of in-hospital mortality. Morbidity occurred in 199 patients (34.7%). Multivariable analysis identified significant predictors of morbidity, including patient age exceeding 70 years (odds ratio [OR], 1.8; p=0.04), low body mass index (OR, 2.6; p=0.02), and pneumonectomy (OR, 1.8; p=0.03). Patient age over 70 years (OR, 1.8; p=0.02) and pneumonectomy (OR, 3.26; p<0.01) were independent predictors of mortality in the multivariable analysis.
Conclusion: In conclusion, the surgical outcomes following nCCRT are less favorable for individuals aged over 70 years or those undergoing pneumonectomy. Special attention is warranted for these patients due to their heightened risks of respiratory complications. In high-risk patients, such as elderly patients with decreased lung function, alternative treatment options like definitive CCRT should be considered instead of surgical resection.

Keywords: Neoadjuvant concurrent chemoradiation therapy, Non-small cell lung carcinoma, Mortality, Risk factor

Introduction

Lung cancer remains the leading cause of death from malignancies worldwide [1]. Locally advanced non-small cell lung cancer (NSCLC) is a heterogeneous entity, and the optimal intervention for stage IIIA–N2 NSCLC remains a subject of debate. However, neoadjuvant therapy before surgery, including chemotherapy and chemoradiotherapy, has been increasingly used to improve locoregional control and eradicate lymph node metastasis in the mediastinum [2]. Clinical trials have explored effective approaches for combining radiation therapy and chemotherapy to improve treatment results. At Samsung Medical Center, we employ a tri-modality approach, involving preoperative concurrent chemoradiation therapy (CCRT) followed by surgical resection, aimed at curing stage IIIA NSCLC with

mediastinal lymph node metastases. Tri-modality therapy has been prospectively performed in medically fit patients with stage IIIA–N2 NSCLC at Samsung Medical Center, and it has subsequently shown acceptable oncologic treatment outcomes [3-6]. However, patients who undergo major pulmonary resection after induction therapy confront a considerably heightened risk of postoperative complications, which constitute the predominant source of operative morbidity and mortality. Furthermore, detailed reports on perioperative outcomes following lung resection in the neoadjuvant context are scarce, particularly those involving large-scale analyses.

In the present study, we retrospectively analyzed perioperative outcomes, including surgical morbidity and mortality, after neoadjuvant CCRT in patients with stage IIIA NSCLC. We present the clinical results and an analysis of risk factors associated with morbidity and mortality following tri-modality therapy.

Methods

Patients' demographics

We conducted a comprehensive review of cases that underwent pulmonary resection following induction therapy from August 1997 to December 2013. The inclusion criteria were as follows: (1) a confirmed diagnosis of NSCLC, (2) clinical stage IIIA disease, as determined by the presence of mediastinal lymph node metastasis, (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, (4) no significant medical conditions that could interfere with intensive treatment, and (5) exclusion of patients with a prior history of other solid malignancies. Additionally, patients with a second primary or recurrent NSCLC were excluded from the study. The study protocol received approval from the Institutional Review Board (IRB) of Samsung Medical Center (IRB approval no., 2023-11-087-001). The requirement for informed consent from individual patients was omitted because of the retrospective design of this study.

Pretreatment staging work-up and treatment regimen

The preoperative work-up included pulmonary function tests, computed tomography (CT) scans of the chest and upper abdomen, 18F-fluorodeoxyglucose positron emission tomography (PET)/CT, and brain magnetic resonance imaging. Nodal staging involved fiberoptic bronchoscopy, mediastinoscopy, or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). For cases with nodes in challenging locations, video-assisted thoracoscopic surgery (VATS) or the Chamberlain procedure was employed for staging. Patients who did not have histological confirmation of nodal involvement were diagnosed with N2 disease based on radiological evidence.

Neoadjuvant CCRT consisted of chemotherapy and concurrent thoracic radiotherapy. From May 1997 to 2008, radiation therapy was administered at a total dose of 45 Gy over 5 weeks (1.8 Gy/fraction/day). Starting from 2009 and onwards, the radiation dose was 44 Gy over 4.5 weeks (2.0 Gy/fraction/day). The chemotherapy regimen included weekly paclitaxel or docetaxel plus carboplatin or cisplatin for 5 weeks.

After the completion of chemoradiotherapy, tumor response was assessed using CT or PET scans, following the Response Evaluation Criteria in Solid Tumors guidelines (version 1.0). A multidisciplinary committee determined patient eligibility for surgical resection and evaluated tumor response. Routine restaging with re-mediastinoscopy or EBUS was not conducted.

Surgery

Surgery was scheduled for 4–6 weeks after the completion of neoadjuvant CCRT. The choice between lobectomy, bilobectomy, or pneumonectomy was based on the size and extent of the primary tumor to ensure its complete removal. After excising the main tumor, all patients underwent comprehensive mediastinal lymph node dissection according to the American Joint Committee on Cancer (AJCC) lymph node map, which includes nodal stations 2R, 4R, 7, 8, and 9 for right-sided tumors, and 4L, 5, 6, 7, 8, and 9 for left-sided tumors. R0 resection and R1/R2 resection were defined in line with the AJCC/Union for International Cancer Control definition. Postoperative radiation therapy and/or chemotherapy were considered if histologically positive N2 lymph nodes were present or if a positive resection margin was detected during surgery.

Perioperative management

Patients who underwent major pulmonary resection, except for those receiving a pneumonectomy, were routinely extubated in the operating room. Those who underwent a pneumonectomy were transferred to the intensive care unit (ICU) and extubated thereafter. Postoperatively, all patients spent at least one day in the ICU. Upon discharge from the

ICU, patients were transferred to and managed in the thoracic surgical ward. Throughout the postoperative period, all patients participated in active chest physiotherapy, which included deep breathing exercises and incentive spirometry.

Postoperative complications

Postoperative complications were defined as those occurring within 30 days after surgery or before hospital discharge. To analyze any complications, we used the Clavien-Dindo classification: grade I: any deviation from the typical postoperative recovery that does not necessitate medication or medical procedures, including surgery, endoscopy, or radiology; grade II: needing medication for treatment, but not the same drugs used for grade I complications; grade III: requiring surgical, endoscopic, or radiological intervention; grade IIIa: intervention without the need for general anesthesia; grade IIIb: intervention that requires general anesthesia; grade IV: a complication that poses a life-threatening situation necessitating ICU management; and grade V: death. The identification of pneumonia was considered when patients presented with lung infiltration and purulent sputum, along with a significant presence of microorganisms in the sputum culture. Acute respiratory distress syndrome (ARDS) was characterized by the sudden onset of arterial hypoxemia resistant to oxygen therapy (with a partial pressure of oxygen/fraction of inspired oxygen [PaO_2/FiO_2] ratio of ≤200), diffuse infiltrates on chest radiographs, and no evidence of heart failure. Acute lung injury was defined similarly to ARDS, except with a PaO_2/FiO_2 ratio >200 and ≤300.

Data collection and analysis

Descriptive statistics were used to examine patient demographic characteristics and outcomes. Continuous data that followed a normal distribution were expressed as the mean±standard deviation, and categorical data were presented as frequencies and percentages. To compare continuous variables, we used the Student t-test or the Wilcoxon rank-sum test, depending on whether the data were normally distributed. The chi-square test or Fisher exact test was used to compare categorical variables, as deemed appropriate. We analyzed risk factors for morbidity and perioperative mortality using both univariate and multivariate logistic regression. Variables that achieved a p-value of less than 0.1 in the univariate analysis were subsequently included in the multivariate analysis. All statistical tests were 2-tailed, with the significance threshold set at 0.05. The analyses were performed using JMP ver. 10.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics

From 1997 to 2013, 574 patients underwent major pulmonary resection at Samsung Medical Center after neoadjuvant CCRT due to stage IIIA–N2 NSCLC. Patients' demographic characteristics are summarized in Table 1. The median age was 60 years (range, 23–76 years), and majority of patients were men (77.4%). The median body mass index (BMI) was 23.5 kg/m^2 (range, 15.4–46.0 kg/m^2). The ECOG performance status was 0 in 566 patients (98.6%) and 1 in 8 patients (1.4%). There were 399 smokers (59.1%) and 235 never-smokers (40.9%).

Pretreatment staging work-up and treatment regimen

All patients enrolled in this study underwent neoadju-

Table 1. Patients' demographics

Characteristic	Value
Age (yr)	60 (23–76)
Male	444 (77.4)
Body mass index (kg/m^2)	23.5 (15.4–46.0)
ECOG performance status	
0	566 (98.6)
1	8 (1.4)
2	0
3	0
4	0
Chronic obstructive pulmonary disease	18 (3.1)
Smoking status	
Ever smoker	339 (59.1)
Never smoker	235(40.9)
Cerebrovascular accident	15 (2.6)
Coronary artery disease	3 (0.5)
Hypertension	163 (28.4)
Diabetes	67 (11.7)
FEV1 %	93.0±18.6
FEV1/FVC%	71.1±9.8
DLCO% (N=282)[a]	89.9±20.3

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.
[a]292 (50.9%) did not undergo a preoperative DLCO test.

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vant CCRT prior to surgery. Perioperative characteristics are summarized in Table 2. Of the patients, 322 (56.1%) had adenocarcinoma, followed by 210 with squamous cell carcinoma (36.6%), 12 with large cell carcinoma (2.3%), and 29 with NSCLC not otherwise specified (5.1%). The clinical T stage distribution was T1 in 128 patients (22.3%), T2 in 386 patients (67.2%), and T3 in 60 patients (10.4%). Histologic confirmation of N2 stage was obtained in 505 patients (88%). Among these, 341 underwent mediastinoscopy, 146 had EBUS-TBNA, 19 underwent VATS, and 10 were assessed using the Chamberlain approach. The median radiation therapy dose was 45 Gy (interquartile range, 44–45 Gy). The clinical response to CCRT was categorized as a complete radiographic response in 5 patients (0.8%), a partial response in 559 patients (97.4%), and stable disease in 10 patients (1.7%). The median interval between the completion of CCRT and surgery was 33 days (range, 5–79 days).

Table 2. Perioperative characteristics

Characteristic	Value
Tumor histologic type	
Adenocarcinoma	322 (56.1)
Squamous cell carcinoma	210 (36.6)
Large cell carcinoma	12 (2.3)
NSCLC, NOS	29 (5.1)
Time interval between CCRT and operation (day)	33 (5–79)
Histologic confirmation of N2	505 (88.0)
Mediastinoscopy	341
EBUS-TBNA	146
VATS	19
Chamberlain	10
Clinical T staging	
cT1	128 (22.3)
cT2	386 (67.2)
cT3	60 (10.4)
Type of resection	
Wedge resection	3 (0.5)
Segmentectomy	1 (0.2)
Lobectomy	440 (76.7)
Bilobectomy	57 (9.9)
Pneumonectomy	73 (12.7)
Surgical approach	
Thoracotomy	555 (96.7)
VATS	19 (3.3)
Completeness of resection	
R0 resection	543 (95)
R1/R2 resection	31 (5.4)

Values are presented as number (%) or median (interquartile range).
NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; CCRT, concurrent chemoradiotherapy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; VATS, video-assisted thoracoscopic surgery.

Surgical treatment and pathologic findings

Among these patients, 440 underwent a lobectomy, 57 had a bilobectomy, 73 underwent a pneumonectomy, and 4 received a limited resection (3 wedge resections and 1 segmentectomy). Fig. 1 illustrates the distribution of these procedures. The surgical approach involved thoracotomy in 555 patients (96.7%) and VATS in 19 patients (3.3%). Complete resection was achieved in 543 patients (95%), while the resection was incomplete in 31 patients (5.4%). Within the cohort, 57% of patients (n=327) underwent adjuvant treatment, which included radiation therapy alone in 30.3% (n=174), chemotherapy alone in 13.1% (n=75), and CCRT in 13.6% (n=78).

In terms of resection completeness, complete resection was achieved in 543 patients (95%), while R1 resection was observed in 31 patients. The average number of lymph nodes dissected was 17, with a range from 0 to 52. Notably, a pathologic complete response was exhibited by 72 patients (13%). Compared to the nodal status before treatment, mediastinal nodal downstaging was observed in 304 patients (53%), whereas 268 patients (47%) continued to exhibit persistent N2 disease.

Postoperative outcomes

Perioperative outcomes, including the length of hospital stay, morbidity, and mortality, are summarized in Table 3. The median hospital stay was 8 days. Early postoperative mortality (within 30 days) occurred in 1.4% of patients (n=8), while late postoperative mortality (within 90 days) occurred in 7.1% (n=41). The rates of morbidity and mortality were associated with the extent of the surgical resec-

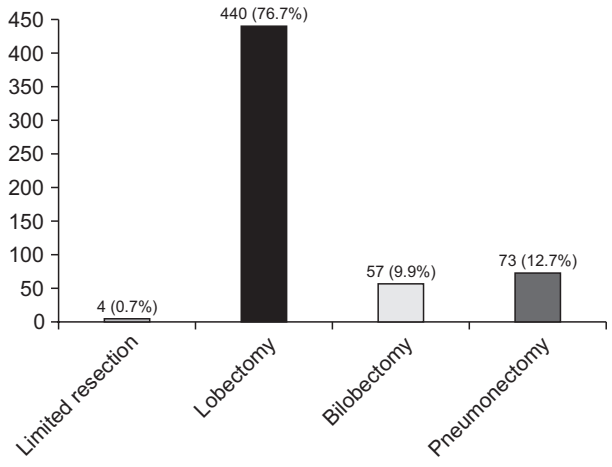

Fig. 1. The extent of surgery after neoadjuvant chemoradiotherapy.

Table 3. Perioperative outcomes

Outcomes	Total	The extent of surgical resection				p-value
		Limited resection	Lobectomy	Bilobectomy	Pneumonectomy	
30-Day mortality	8 (1.4)	0	3 (0.7)	1 (1.8)	4 (5.5)	0.014
60-Day mortality	25 (4.4)	0	15 (3.4)	2 (3.5)	8 (11.0)	0.031
90-Day mortality	41 (7.1)	0	23 (5.2)	5 (8.8)	13 (17.8)	0.006
Length of stay (day)	8 (7–11)	7 (4.5–15.5)	8 (7–11)	9 (8–15)	10 (8–12.5)	<0.001
Morbidity	199 (34.7)	0	137 (31.1)	26 (45.6)	36 (49.3)	0.002

Values are presented as number (%) or median (interquartile range).

Table 4. Postoperative complications

Morbidity	Total	The Clavien-Dindo classification of surgical complications[a]					
		I	II	IIIa	IIIb	IV	V
Arrhythmia	116 (20.2)		116				
Pneumonia	32 (5.6)		7	1	1	9	14
Acute lung injury	12 (2.1)		5	3		4	
Acute respiratory distress syndrome	18 (3.1)						18
Atelectasis[b]	10 (1.7)			10			
Bronchopleural fistula	11 (1.9)			1	1	7	2
Empyema	13 (2.3)			2		11	
Prolonged air leak	35 (6.1)	5		27	1	2	
Chylothorax	8 (1.4)		3	4	1		
Vocal cord paralysis	20 (3.5)		8	12			
Postop bleeding[c]	2 (0.3)				2		
Delirium	12(2.1)		12				
Acute kidney injury	3 (0.5)		3				
Pulmonary thromboembolism	3 (0.5)					1	2
Deep vein thrombosis	1 (0.2)		1				
Pleural effusion	4 (0.7)	1		3			
Hemoptysis	2 (0.3)				2		
Hemorrhagic gastritis	1 (0.2)			1			
Ileus	1 (0.2)		1				
Total	199 (34.7)						

Values are presented as number (%) or number.
[a]Clavien-Dindo classification: grade I: any deviation from the typical postoperative recovery that does not necessitate medication or medical procedures, including surgery, endoscopy, or radiology; grade II: needing medication for treatment, but not the same drugs used for grade I complications; grade III: requiring surgical, endoscopic, or radiological intervention; grade IIIa: intervention without the need for general anesthesia; grade IIIb: intervention that requires general anesthesia; grade IV: a complication that poses a life-threatening situation necessitating intensive care unit management; and grade V: death. [b]Atelectasis requiring therapeutic bronchoscopy. [c]Postoperative bleeding requiring re-operation.

tion (Table 3). Postoperative complications according to the Clavien-Dindo classification are detailed in Table 4. The overall morbidity rate was 34.7% (199 patients). The most common complications included arrhythmia (20.2%), prolonged air leak (6.1%), and pneumonia (5.6%). Bronchopleural fistulas occurred in 11 patients (1.9%), and postoperative empyema was seen in 13 patients (2.3%).

In the univariate analysis using the predictors listed in Tables 1 and 2, several factors were identified as independent risk factors for postoperative morbidity. These factors included male sex, patient age over 70 years, non-adenocarcinoma histology, a history of smoking, a BMI below 18.5 kg/m^2, and undergoing a pneumonectomy (Table 5). The multivariable analysis further confirmed that being over 70 years of age (odds ratio [OR], 1.82; p=0.040), having a BMI below 18.5 kg/m^2 (OR, 2.62; p=0.022), and undergoing a pneumonectomy (OR, 1.8; p=0.026) were significant predictors of morbidity (Table 5).

Similarly, in the univariate analysis (Table 6), significant risk factors for postoperative mortality included male gender, patient age over 70 years, a history of smoking, an interval of more than 5 weeks between the completion of

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Table 5. Univariate and multivariate risk factor analyses for morbidity

Variable	No. of patients (%)	Univariate	Multivariate logistic regression analysis	
		p-value	Odds ratio (95% CI)	p-value
Sex		<0.001		0.056
Male	171 (38.5)		1.70 (0.98–2.98)	
Female	28 (21.5)		1	
Age (yr)		0.037		**0.040**
≥70	27 (47.4)		1.82 (1.03–3.20)	
<70	172 (33.3)		1	
Cell type		0.003		0.140
Non-ADC	104 (41.3)		1.33 (0.91–1.94)	
ADC	95 (29.5)		1	
Smoking		0.006		0.382
Ever smoker	133 (39.2)		1.21 (0.79–1.84)	
Never smoker	66 (28.1)		1	
Body mass index (kg/m^2)		0.026		**0.022**
<18.5	14 (56.0)		2.63 (1.15–6.15)	
≥18.5	185 (33.7)		1	
Extent of surgery		0.002		**0.026**
Pneumonectomy	36 (49.3)		1.8 (1.07–3.00)	
Non-pneumonectomy	163 (32.5)		1	

Statistically significant results are marked in bold.
CI, confidence interval; ADC, adenocarcinoma.

Table 6. Univariate and multivariate risk factor analyses for perioperative mortality(within 90 days)

Variable	No. of patients (%)	Univariate	Multivariate logistic regression analysis	
		p-value	Odds ratio (95% CI)	p-value
Sex		<0.001		
Male	41 (9.23)		-	
Female	0		-	
Age (yr)		0.037		**0.019**
≥70	9 (15.8)		1.82 (1.21–6.43)	
<70	32 (6.2)		1	
Smoking		0.006		0.100
Ever smoker	30 (8.9)		1.81 (0.90–3.91)	
Never smoker	11 (4.7)		1	
Time interval (wk)[a]		0.006		0.085
≥5	23 (10.6)		1.80 (0.92–3.56)	
<5	18 (5.2)		1	
Extent of surgery		0.002		**0.003**
Pneumonectomy	13 (17.8)		3.25 (1.50–6.78)	
Non-pneumonectomy	28 (5.6)		1	

Statistically significant results are marked in bold.
CI, confidence interval; ADC, adenocarcinoma.
[a]Time interval refers to the time period between the end of neoadjuvant chemoradiation therapy and surgery.

CCRT and surgery, and undergoing a pneumonectomy. The subsequent multivariate analysis revealed that being over the age of 70 (OR, 1.82; p=0.022) and undergoing a pneumonectomy (OR, 3.256; p=0.003) were independently associated with an increased risk of mortality within 90 days following surgery (Table 6).

Discussion

The impact of induction therapy on postoperative morbidity and mortality for patients with stage IIIa–N2 NSCLC undergoing major pulmonary resection has been a subject of debate. Some studies have suggested that induc-

tion therapy may increase the risk of morbidity and mortality following surgery [7,8]. It is logical to expect that neoadjuvant chemoradiation therapy could affect the likelihood of postoperative complications and death. Consequently, it is crucial to carefully select patients for surgery who are likely to achieve complete resection with minimal morbidity and mortality following induction chemoradiation therapy. Typically, the most significant risk factors for perioperative morbidity and mortality include age, pulmonary reserve, cardiovascular disease, respiratory infection, arrhythmia, renal failure, and diabetes [9-11]. However, there is scant literature on the risk factors associated with morbidity and mortality in surgical treatment for patients with stage IIIa–N2 NSCLC after induction therapy.

Herein, we have reported the morbidity and mortality rates of patients who underwent major pulmonary resection following induction therapy for stage IIIA–N2 NSCLC. Our study evaluated various predictors of postoperative morbidity and mortality in a uniform cohort of patients who had significant pulmonary resections after induction therapy. Notably, being over the age of 70 years was also identified as a risk factor for increased morbidity and mortality. Chronological age is widely recognized as a significant risk factor for elderly patients undergoing surgical procedures. The authors of this study believe that individuals aged 70 years or older have reduced cardiopulmonary reserve, which places them in the category of the elderly population undergoing lung resection. According to Birim et al. [12], advancing age was a significant prognostic factor for long-term outcomes, along with other indices such as the Charlson comorbidity index. It is suggested that patients aged 70 years or older be considered elderly in medical evaluations, as this age threshold typically marks the beginning of numerous age-related adverse changes [13]. The adoption of the Comprehensive Geriatric Assessment (CGA) for evaluating elderly cancer patients [14,15] aims to identify those who are robust and more likely to benefit from standard cancer treatment, as opposed to those who are vulnerable and require personalized surgery or chemotherapy regimens, or those who are frail and are suitable for supportive care only [16]. However, there is an ongoing debate about the actual impact of the CGA on treatment decision-making in clinical settings, due to its time-consuming, burdensome, and non-standardized nature [17].

Another risk factor identified for adverse outcomes following trimodal therapy is pneumonectomy. Among pulmonary resections, pneumonectomy is associated with the highest rates of morbidity and mortality of all elective thoracic surgical procedures. Furthermore, the mortality rate after pneumonectomy without neoadjuvant therapy has been reported to range from 1.6% to 13.4% [18,19]. Some authors have suggested that pneumonectomy should be considered a distinct disease entity due to its significant impact on cardiorespiratory physiology and consequent reduction in overall survival [20]. Therefore, pneumonectomy with neoadjuvant therapy is regarded as a major procedure with high mortality rates and should be only performed by experienced surgeons [21]. In the Intergroup Study (INT) 0139, 429 patients with stage IIIA–N2 disease were randomized after receiving 2 cycles of cisplatin/etoposide and concomitant radiotherapy (45 Gy), followed by either surgical resection or 2 additional cycles of chemotherapy [22]. A 30-day mortality rate of 25.9% was observed in patients who underwent pneumonectomy in the INT 0139 trial. Our data indicate that the 30-day and 90-day mortality rates for pneumonectomy after neoadjuvant therapy were 5.5% and 17.8%, respectively. Clearly, the operative mortality is significantly high. Consequently, we advocate for every effort to be made to avoid pneumonectomy, such as opting for sleeve lobectomy whenever feasible.

The role of nutrition in predicting the outcome of operations for lung cancer is also of growing interest. We identified the underweight BMI category as a potential risk factor for postoperative morbidity. The detrimental impact of malnutrition has been recently emphasized, especially for pneumonectomy [23]. Furthermore, research by Thomas et al. [24] has shown that underweight patients are significantly more likely to suffer from pulmonary, surgical, and infectious complications. In this study, prolonged air leaks and bronchial stump dehiscence were significantly more frequent in underweight patients than in patients with a normal BMI, but obesity was not associated with an increased incidence of postoperative complications.

Regarding morbidity, studies have reported postoperative complication rates of approximately 30%, irrespective of whether patients received induction therapy [11,25,26]. Arrhythmia is the most frequently reported complication in these studies. Our morbidity rate was 34.7%, aligning with the rates found in prior research.

The primary focus after surgery is to prevent morbidity and mortality. Careful patient selection, informed by comprehensive preoperative assessments, can reduce the risk of postoperative complications. In thoracic oncology, it is important to create personalized treatment plans based on detailed risk analysis to prevent postoperative issues. However, despite meticulous patient selection, postoperative

complications can still occur. Experienced thoracic surgeons and intensive care specialists should manage these complications. Over the past 2 decades, our group has developed a multidisciplinary approach for patients with stage IIIA–N2 NSCLC, addressing preoperative and postoperative management, including complications. This approach is based on our experience with nearly 600 patients who underwent surgery following induction therapy. Consequently, our group continues to endorse trimodal therapy as the most effective treatment for stage IIIA–N2 NSCLC, except when preoperative radiologic findings indicate that complete tumor resection is unlikely.

This study had several limitations. First, it utilized a retrospective design. Additionally, the research included a diverse patient cohort, with variability in histologic subtypes and the prevalence of bulky N2 disease. This diversity could have affected the outcomes of surgical interventions following induction therapy. Moreover, the study covered a period of nearly 16 years, potentially leading to inconsistencies in outcomes due to changes in chemotherapy and radiotherapy practices over this time. Specifically, the extended duration of the study may have introduced unmeasured bias into our results.

In conclusion, the surgical outcomes following neoadjuvant CCRT are less favorable for individuals over the age of 70 years or for those undergoing pneumonectomy. These patients require special attention due to an increased risk of respiratory complications. For high-risk patients, particularly older individuals with diminished lung function, alternative treatment options such as definitive CCRT may be preferable to surgical resection.

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Conflict of interest

Seong Yong Park is an associate editor, Junghee Lee is an editorial board member, and Hong Kwan Kim was an associate editor of the journal during the submission of this article. They were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11-30. https://doi.org/10.3322/caac.21166
2. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330:153-8. https://doi.org/10.1056/NEJM199401203300301
3. Ahn YC, Park K, Kim DY, et al. Preoperative concurrent chemoradiotherapy for stage IIIA non-small cell lung cancer. Acta Oncol 2001;40:588-92. https://doi.org/10.1080/028418601750444123
4. Kang MK, Ahn YC, Lim DH, et al. Preoperative concurrent radiochemotherapy and surgery for stage IIIA non-small cell lung cancer. J Korean Med Sci 2006;21:229-35. https://doi.org/10.3346/jkms.2006.21.2.229
5. Kim KJ, Ahn YC, Lim DH, et al. Analyses on prognostic factors following tri-modality therapy for stage IIIa non-small cell lung cancer. Lung Cancer 2007;55:329-36. https://doi.org/10.1016/j.lungcan.2006.10.024
6. Lee H, Ahn YC, Pyo H, et al. Pretreatment clinical mediastinal nodal bulk and extent do not influence survival in N2-positive stage IIIA non-small cell lung cancer patients treated with trimodality therapy. Ann Surg Oncol 2014;21:2083-90. https://doi.org/10.1245/s10434-014-3540-x
7. Doddoli C, Thomas P, Thirion X, Seree Y, Giudicelli R, Fuentes P. Postoperative complications in relation with induction therapy for lung cancer. Eur J Cardiothorac Surg 2001;20:385-90. https://doi.

org/10.1016/s1010-7940(01)00764-3
8. Roberts JR, Eustis C, Devore R, Carbone D, Choy H, Johnson D. Induction chemotherapy increases perioperative complications in patients undergoing resection for non-small cell lung cancer. Ann Thorac Surg 2001;72:885-8. https://doi.org/10.1016/s0003-4975(01)02836-3
9. Patel RL, Townsend ER, Fountain SW. Elective pneumonectomy: factors associated with morbidity and operative mortality. Ann Thorac Surg 1992;54:84-8. https://doi.org/10.1016/0003-4975(92)91145-y
10. Wada H, Nakamura T, Nakamoto K, Maeda M, Watanabe Y. Thirty-day operative mortality for thoracotomy in lung cancer. J Thorac Cardiovasc Surg 1998;115:70-3. https://doi.org/10.1016/s0022-5223(98)70444-1
11. Duque JL, Ramos G, Castrodeza J, et al. Early complications in surgical treatment of lung cancer: a prospective, multicenter study. Grupo Cooperativo de Carcinoma Broncogenico de la Sociedad Espanola de Neumología y Cirugia Toracica. Ann Thorac Surg 1997;63:944-50. https://doi.org/10.1016/s0003-4975(97)00051-9
12. Birim O, Kappetein AP, Bogers AJ. Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer. Eur J Cardiothorac Surg 2005;28:759-62. https://doi.org/10.1016/j.ejcts.2005.06.046
13. Balducci L. ESH-SIOG International Conference on Haematological Malignancies in the Elderly. Expert Rev Hematol 2010;3:675-7. https://doi.org/10.1586/ehm.10.72
14. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25:1824-31. https://doi.org/10.1200/JCO.2007.10.6559
15. Extermann M. Integrating a geriatric evaluation in the clinical setting. Semin Radiat Oncol 2012;22:272-6. https://doi.org/10.1016/j.semradonc.2012.05.003
16. Wedding U, Kodding D, Pientka L, Steinmetz HT, Schmitz S. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. Crit Rev Oncol Hematol 2007;64:1-9. https://doi.org/10.1016/j.critrevonc.2007.05.001
17. Puts MT, Hardt J, Monette J, Girre V, Springall E, Alibhai SM. Use of geriatric assessment for older adults in the oncology setting: a systematic review. J Natl Cancer Inst 2012;104:1133-63. https://doi.org/10.1093/jnci/djs285
18. Licker M, Spiliopoulos A, Frey JG, et al. Risk factors for early mortality and major complications following pneumonectomy for non-small cell carcinoma of the lung. Chest 2002;121:1890-7. https://doi.org/10.1378/chest.121.6.1890
19. Van Raemdonck DE, Schneider A, Ginsberg RJ. Surgical treatment for higher stage non-small cell lung cancer. Ann Thorac Surg 1992;54:999-1013. https://doi.org/10.1016/0003-4975(92)90677-v
20. Mansour Z, Kochetkova EA, Santelmo N, et al. Risk factors for early mortality and morbidity after pneumonectomy: a reappraisal. Ann Thorac Surg 2009;88:1737-43. https://doi.org/10.1016/j.athoracsur.2009.07.016
21. Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. Chest 1992;101:1332-7. https://doi.org/10.1378/chest.101.5.1332
22. 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;374:379-86. https://doi.org/10.1016/S0140-6736(09)60737-6
23. Bagan P, Berna P, De Dominicis F, et al. Nutritional status and postoperative outcome after pneumonectomy for lung cancer. Ann Thorac Surg 2013;95:392-6. https://doi.org/10.1016/j.athoracsur.2012.06.023
24. Thomas PA, Berbis J, Falcoz PE, et al. National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. Eur J Cardiothorac Surg 2014;45:652-9. https://doi.org/10.1093/ejcts/ezt452
25. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995;13:1880-92. https://doi.org/10.1200/JCO.1995.13.8.1880
26. Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. Chest 1994;106(6 Suppl):329S-330S. https://doi.org/10.1378/chest.106.6_supplement.329s