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ORIGINAL ARTICLE

Pneumonectomy after induction chemoradiotherapy for locally advanced non-small cell lung cancer: should curative intent pulmonary resection be avoided?

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Abstract

Purpose We conducted a retrospective analysis to assess the practicality of pneumonectomy, especially after concurrent induction chemoradiotherapy (i-CRT), for locally advanced non-small cell lung cancer (LA-NSCLC). The operative risks vs. the survival benefit of this procedure for such patients is a subject of controversy.

Methods The subjects of this retrospective study were 71 consecutive LA-NSCLC patients with cStage IIIA-C NSCLC, who underwent i-CRT followed by curative intent pulmonary resection between February, 2001 and March, 2013.

Results Thirty-two patients underwent pneumonectomy (group P) and 39 patients underwent lobectomy (group L). In group P, 17 (54.8%) patients underwent right pneumonectomy. There was no 30-day postoperative mortality in either group and no significant difference in 90-day postoperative mortality between the groups (3.1% vs. 2.6% in groups P and L, respectively). The 5-year overall survival (OS) rate was 58.7% (95% CI: 41.5–75.9%) in group P and 57.3% (95% CI 41.2–73.4%) in group L, without a significant difference between the groups.

Conclusion Our findings suggest that i-CRT followed by pneumonectomy is feasible, with a similar survival benefit to lobectomy. Thus, pneumonectomy after i-CRT should not be avoided as it is a potentially curative intent strategy for carefully selected patients.

Keywords Locally advanced non-small cell lung cancer · Induction chemoradiotherapy · Pneumonectomy

Introduction

Based on the results of a phase III clinical trial that directly compared sublobar resection with lobar resection for patients with clinical Stage I NSCLC [1], the conventional treatment for non-small cell lung cancer (NSCLC) is lobar or more anatomical resection of the lung parenchyma with adequate mediastinal lymph node removal. Furthermore, most of the principle clinical practice guidelines for the management of NSCLC recommend this type of lobectomy or more pulmonary resection as a standard surgical procedure [2–5]. Lobectomy is generally preferred over pneumonectomy since greater postoperative pulmonary function can be preserved and patients may have a lower incidence of serious postoperative morbidities, such as bronchial fistula, empyema, or acute respiratory distress syndrome (ARDS), potentially resulting in lower postoperative mortality. However, those risks might be increased for patients with locally advanced non-small cell lung cancer (LA-NSCLC) receiving induction concurrent chemoradiotherapy (i-CRT) followed by pneumonectomy, even when performed as curative intent pulmonary resection [6, 7].

Given these concerns, bronchial and/or pulmonary artery sleeve resection is often recommended to avoid pneumonectomy if the tumor or regional metastatic lymph nodes invade the adjacent central bronchi or proximal segmental branch of the pulmonary artery. This approach has been reported to achieve an equivalent survival benefit in association with pneumonectomy [8–10] with similar or lower rates of postoperative morbidity and mortality [11, 12]. However, the clinical features of LA-NSCLC are heterogeneous,

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presenting as a broad tumor and/or extra-nodal invasion of metastatic lymph nodes to the proximal stem of the bronchi or bronchus concomitant to the segmental pulmonary artery, or as a larger tumor that invades via the fissure between the lobes. In such cases, pneumonectomy might be required for curative intent pulmonary resection.

We report the outcomes of i-CRT followed by pneumonectomy as curative intent treatment for LA-NSCLC patients in a single institution.

Methods

We reviewed the medical records of 71 consecutive patients with LA-NSCLC, who underwent both planned and unplanned i-CRT followed by curative intent pulmonary resection between February, 2001 and March, 2013 in the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan. All patients in this analysis had cytologically or histologically confirmed LA-NSCLC prior to induction treatment.

Although the eligibility for i-CRT followed by curative intent pulmonary resection in this series of patients was based on clinical practice, patients were generally considered eligible if they were aged between 20 and 80 years, had an Eastern Cooperative Oncology Group performance status of 0–1, and sufficient pulmonary function (postoperative pulmonary function of FEV1 > 600 ml/m^2 of the body surface area). Chest radiography, computed tomography of the chest and upper abdomen, computed tomography or magnetic resonance imaging of the brain, flexible optical bronchoscopy, and a bone scan or 18-fluorodeoxyglucose positron emission tomography (FDG-PET) were performed routinely for all patients. Patients with concomitant uncontrolled malignancy or serious comorbidities, such as clinically significant cardiac disease, active infection, or neurologic or psychiatric disorders, were excluded.

The institutional review board and ethics committee of our hospital reviewed and approved the protocol of this retrospective analysis. Written informed consent was obtained from all of the patients.

Induction concurrent chemoradiotherapy

The choice of preoperative treatment modality was decided on an individual basis in our hospital or in other regional hospitals that treated the patients preceding transfer to our institution. Briefly, the majority of chemotherapy regimens used for i-CRT in this analysis comprised cisplatin with a pro-drug of 5-FU, uracil-tegafur (UFT; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) [13] from 2001 until 2006, and thereafter, cisplatin with a second-generation oral anticancer agent based on uracil-tegafur S-1 (TS-1; Taiho Pharmaceutical Co., Ltd.) [14]. The selected radiation dose for planned i-CRT was 40 Gy at 2 Gy/fraction/day for the radiation field, which included the primary tumor, ipsilateral hilum, and mediastinum from the ipsilateral paratracheal to subcarinal lymph node area, as described previously [14]. The contralateral hilum was excluded, as were the supraclavicular areas, except when supraclavicular node involvement was detected at the time of treatment. In this series, four patients underwent unplanned surgical resection after i-CRT. Three of these patients received 60 Gy of radiation before surgery and one received 70 Gy.

Evaluation of the response and toxicity

The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [15]. A histological analysis of the tumor was conducted according to the WHO classification for cell types [16]. The clinical or pathologic stage of the disease was diagnosed according to the general rules for the TNM Classification of malignant tumors (8th edition) [17].

Surgical resection

Approximately 3–6 weeks after completion of the induction treatment, the patients were restaged and curative intent pulmonary resection was planned if appropriate. The principles of curative intent pulmonary resection were en bloc removal of the affected lobe or lung parenchyma or adjacent structure(s) if necessary, with systemic hilar and mediastinal lymph node dissection. In general, bronchial and/or vessel plasty was performed to avoid pneumonectomy when possible; however, if complete resection was inevitable, then pneumonectomy was performed.

Statistical analyses

Statistical analyses were performed using the Chi-square test and two-tailed Student's *t* test for comparison of the variables. The Kaplan–Meier method was used for the overall survival and disease-free survival curves. Disease-free survival (DFS) was defined as the time from the start date of i-CRT until disease progression or death. Overall survival (OS) was defined as the time from the start date of i-CRT until death from any cause. The median follow-up was 50.1 (4.5–163.0) months for all patients, 80.4 (35.7–162.9) months for living patients, and 18.3 (4.5–102.2) months for patients with disease at the time of analysis. All statistical analyses were performed with the IBM SPSS Statistics 18 software package (SPSS Japan, an IBM company, Tokyo, Japan).

Results

The 71 patients comprised 58 men and 13 women, with a median age of 59 years (range 34–77 years). Thirty-two patients underwent pneumonectomy (group P) and 39 underwent lobectomy (group L). Most of the patients had an acceptable general status, with 55 (77.5%), 15 (21.1%), and 1(1.4%) showing an ECOG performance status (PS) of 0, 1, and 2, respectively. Histologically, 36 (50.7%) patients had adenocarcinoma, 21 had squamous cell carcinoma (29.6%), 9 (12.7%) had not-otherwise-specified NSCLC, 4 had large cell carcinoma, and 1 had pleomorphic carcinoma. Of the 71 patients, 52 (73.2%) had cStage IIIA, including 9 with T3N1, 10 with T4N0–1, and 33 with T1–3N2; 14 (19.7%) had cStage IIIB, including 4 with T2aN3, one with T2bN3, and 11 with T4N2; and 5 (7.1%) had cStage IIIC, including 1 with T3N3 and 4 with T4N3. No significant difference was observed between the groups in these variables. Moreover, there were no significant differences between groups L and P in the pretreatment pulmonary function test in terms of %VC and FEV1.0% (Table 1).

Induction treatment

The chemotherapy regimen used was as described previously. The median doses of radiation were 40 (38–63) Gy

Table 1 Clinical characteristics of the patients

	Group P	Group L	All	*p* value
Number	32	39	71	
Gender				
Male	28	30	58	NS
Female	4	9	13	
Age, years				
Median (range)	59 (34–72)	60 (34–77)	59 (34–77)	NS
ECOG PS				
0	27	28	55	
1	5	10	15	
2	0	1	1	
Histology				
Adenocarcinoma	14	22	36	NS
Squamous cell carcinoma	12	9	21	
Large cell carcinoma	1	3	4	
Pleomorphic carcinoma	0	1	1	
NSCLC, NOS	5	4	9	
cStage				NS
IIIA	22	30	52	
T3N1	2	7	9	
T4N0–1	2	8	10	
T1–3N2	18	15	33	
IIIB	8	6	14	
T2aN3	0	2	2	
T2bN3	1	0	1	
T4N2	7	4	11	
IIIC	2	3	5	
T3N3	0	1	1	
T4N3	2	2	4	
Pulmonary function test				
%VC	102.3	107.2	105.0	NS
(95% CI)	(95.8–108.9)	(102.8–11.7)	(101.2–108.8)	
FEV1.0%	75.2	78.1	76.8	NS
(95% CI)	(70.9–79.6)	(73.2–83.0)	(73.5–80.1)	

Group P pneumonectomy group, *Group L* lobectomy group, *NS* not significant, *NSCLC* non-small cell lung cancer, *NOS* not otherwise specified, *TNM* is described according to version 8

in group P and 40 (25–70) Gy in group L, with significant differences ($p = 0.0178$). Twelve patients (2 from group P and 10 from group L), received more than 60 Gy of radiation concurrent with chemotherapy before curative intent pulmonary resection. The direct tumor response after i-CRT was partial response (PR) in 50 (70.4%) patients and stable disease (SD) in 21 patients (29.6%). No progressive disease was observed and there was no significant difference between the groups in tumor response.

Surgical resection

In group P, 17 (53.1%) patients underwent right pneumonectomy and 15 (46.9%) underwent left pneumonectomy. Seven of these patients (24.1%) required carinal sleeve pneumonectomy. In group L, 26 (66.7%) patients underwent right lobectomy and 13 (32.3%) underwent left lobectomy. Twelve (30.8%) patients required bronchial sleeve lobectomy. Because of the locally advanced nature of the disease, 46 of the 71 (64.8%) patients required combined resection of an adjacent structure or organ. Table 2 summarizes the details of combined resection. The most common areas of combined resection were the pericardium and superior vena cava (SVC) in group P and the chest wall and parietal pleura in group L, but without a significant difference. The bronchial stump was not covered routinely, but it was covered in 13 patients from group P (40.6%; on the right side in 12 and the left side in 1) and in 17 patients from group L (43.6%; on the right side in 13 and the left side in 4). There was no significant difference between the groups in operative time or blood loss (Table 3).

Postoperative morbidity and mortality

Table 3 shows the postoperative morbidity and mortality. The 90-day postoperative morbidity was 53.1% (17/32 patients) in group P and 59.0% (23/39) in group L, without a significant difference. The major postoperative morbidity in group P was bronchopleural fistula (BPF) after right pneumonectomy in one patient, whereas in group L the major postoperative morbidities included empyema in one patient with BPF, postoperative bleeding that required reoperation in one patient, and blindness in one eye after SVC resection and reconstruction using a vascular prosthesis in one patient. Another three patients experienced atrial fibrillation. There was no case of postoperative acute respiratory distress syndrome (ARDS). The patient in group L with empyema without BPF recovered without open window thoracostomy. Two patients also suffered prolonged air-leakage for more than 7 days, and one suffered respiratory failure, but all recovered.

The 30-day postoperative mortality rate was 0% in both groups. Regarding 90-day postoperative mortality, one

Table 2 Summary of the surgical procedures

	Group P	Group L	*p* value
Number	32	39	
Side of procedure			
Right/left	17/15	26/13	NS
Sleeve carinal/ bronchial resection	7 (21.9%)	12 (30.8%)	NS
Combined resection (n)	23 (71.9%)	23 (59.0%)	NS
Resected part (redundant)			
Pericardium	12	4	
Superior vena cava	6	2	
Chest wall	2	12	
Parietal pleura	1	5	
Left atrium	1	1	
Esophagus	1	0	
Vertebra	0	1	
Aorta	1	0	
Others	2	6	
Coverage of bronchial stump	13 (40.6%)	17 (43.6%)	NS
Right/left	12/1	13/4	
Pedicled pericardial fad pad	12	15	
Intercostal muscle	1	1	
Others	0	1	
Surgical time (median (range), min)	295 (190–855)	345 (178–860)	NS
Amount of bleeding (median (range), g)	305 (70–2470)	350 (trace-4200)	NS

Group L lobectomy group, *Group P* pneumonectomy group, *NS* not significant

Table 3 Postoperative morbidity and mortality

Subjects	Group P	Group L	All	*p* value
	32	39	71	
Morbidity < 90 days	17 (53.1%)	23 (59.0%)	40 (56.3%)	NS
Subjects (redundant)				
Atrial fibrillation	3	0	3	
Ventricle paroxysmal constriction	1	0	1	
Pleural effusion increase	1	2	3	
Pneumatocele	1	0	1	
Liver dysfunction	1	0	1	
BPF	2	0	1	
Air leak > 7 days	0	2	2	
Empyema (open window thoracostomy)	4 (1)	1 (0)	5 (1)	
Bleeding (re-thoracotomy)	1 (1)	2 (0)	2 (0)	
Anemia (transfusion)	1 (1)	1 (1)	2 (2)	
Chylothorax	1	1	2	
Fever > 38 degrees C	1	2	3	
Blindness	1	0	1	
TIA	0	1	1	
Ileus	0	1	1	
Anorexia	0	1	1	
Delirium	0	2	2	
Wound infection	0	1	1	
Ulnar nerve palsy	0	1	2	
Recurrent nerve palsy	0	1	1	
Atelectasis	0	1	1	
Respiratory failure	0	1	1	
Mortality < 30 days	0	0	0	NS
Mortality < 90 days	1 (3.1%)	1 (2.6%)	2 (2.8%)	NS
Interstitial pneumonia	1	0	1	
Empyema	0	1	1	

Group L lobectomy group, *Group P* pneumonectomy group, *NS* not significant, *BPF* bronchopleural fistula, *TIA* transient ischemic attack

patient (3.1%) in group P died subsequent to deterioration of interstitial pneumonia, and one patient (2.6%) in group L died of empyema with massive intrathoracic bleeding on postoperative day 65 after left upper lobectomy.

Postoperative chemotherapy

Pathological down-staging was confirmed in 17 patients (53.1%) from group P and 25 patients (64.1%) from group L. A pathological CR was observed in seven patients (21.9%) from group P and four (10.3%) from group L, although without a significant difference between the groups. Of the 32 group P patients, 17 (53.1%) received postoperative chemotherapy; as cisplatin and UFT in 5, and as cisplatin and S-1 in 8, both at the same dose, as induction treatment. Another three patients received docetaxel and one received cisplatin and gemcitabine. Of the 39 patients in group L, 18 (46.2%) received postoperative chemotherapy; as cisplatin and UFT in 2 and as cisplatin and S-1 in 12, both also at the same dose as induction treatment. Another three patients received docetaxel and one received cisplatin and vinorelbine. There was no significant difference between the groups.

Survival

The median duration and 3- and 5-year DFS rates of all 71 patients were 33.9 (95% confidence interval [CI]: 22.3–45.5) months, 49.3 (95% CI 37.7–60.9)% and 46.0 (95% CI 34.2–57.7)%, respectively (Fig. 1a). The median duration and 3- and 5-year OS rates were not reached, 67.4 (95% CI 56.0–76.9)% and 58.3% (95% CI 46.7%-69.9%), respectively (Fig. 1B).

When patients were stratified by surgical procedure (pneumonectomy or lobectomy), the median duration and 3- and 5-year DFS rates were 30.8 (95% CI 13.5–48), 46.9 (95% CI 29.7–64.1)%, and 43.5 (95% CI 26.2–6.07)%

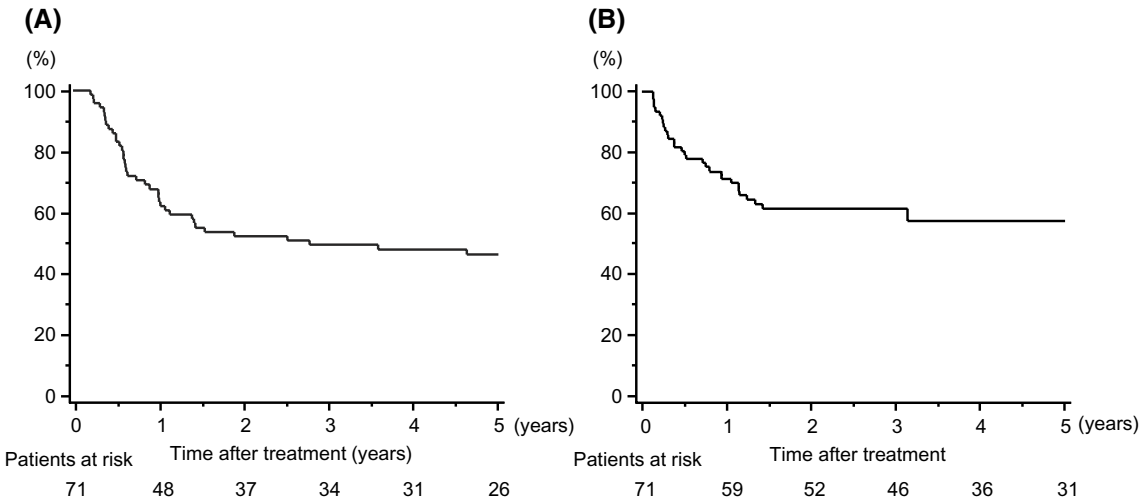

Fig. 1 Survival analyses of the 71 patients. **a** Disease-free survival. **b** Overall survival

months, respectively in group P; and 43.8 (95% CI 27.9–59.8), 51.3 (95% CI 35.6–67.0)%, and 48.3% (95% CI 32.4–64.2)% months, respectively, in group L, without significant differences between the groups ($p = 0.4490$, Fig. 2a). The median duration and 3- and 5-year OS rates were not reached, 62.0% (95% CI 44.9–79.1)% and 58.7% (95% CI 41.5–75.9)%, respectively, in group P; and not reached, 71.8% (95% CI 57.7–85.9)% and 57.3% (95% CI 41.2–73.4)%, respectively, in group L, also without significant differences between the groups ($p = 0.8101$, Fig. 2b).

Discussion

The safety and survival benefits of parenchymal-sparing procedures, such as bronchial and/or pulmonary artery sleeve lobectomy, for patients with LA-NSCLC are well known. Thus, pneumonectomy can be avoided in some cases. Indeed, Okada et al. reported no 30-day postoperative mortality and significantly better OS in 151 patients who underwent bronchial sleeve lobectomy than in patients who underwent pneumonectomy [18]. Although it might be difficult to compare both procedures directly, because of the heterogeneity of LA-NSCLC, several subsequent retrospective

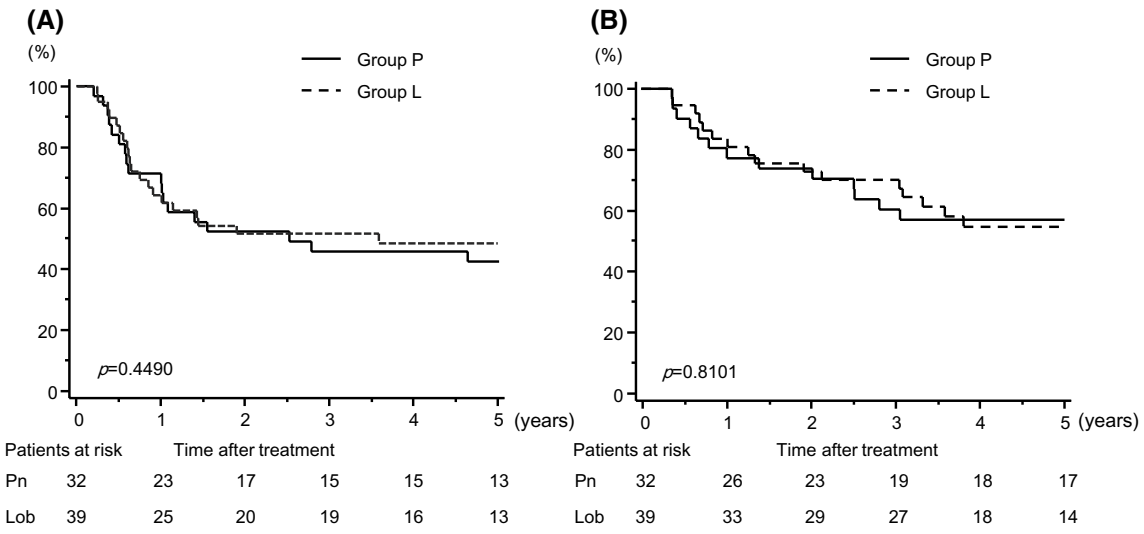

Fig. 2 Survival analyses stratified by the surgical procedure. The solid line represents pneumonectomy (group P), and the dashed line represents lobectomy (group L). **a** Disease-free survival. **b** Overall survival

analyses have shown that bronchial sleeve lobectomy is safer and provides better or at least equivalent outcomes to pneumonectomy [11, 19–21]. Bronchial sleeve lobectomy is also expected to preserve more pulmonary function then pneumonectomy, thereby maintaining the patient's quality of life (QOL) and activity of daily living (ADL) [22].

A major disadvantage of LA-NSCLC is that a primary tumor or metastatic infiltration of the lymph nodes can invade a more central part of the bronchus or pulmonary vessels, making bronchial and/or pulmonary artery sleeve lobectomy impossible or resulting in the primary tumor spreading to another lobe(s), thereby precluding any resection of sufficient pulmonary parenchyma. Such a lesion inevitably requires pneumonectomy for curative intent resection. In such cases, the relatively high postoperative mortality of pneumonectomy, especially in patients who have undergone i-CRT, has been a subject of discussion when considering the surgical treatment of NSCLC. The data derived from a prospective randomized phase III trial that compared i-CRT using cisplatin plus etoposide concurrently with 45 Gy of radiotherapy, followed by curative intent pulmonary resection, vs. definitive concurrent CRT with a total 61 Gy of radiotherapy, showed that the postoperative mortality after pneumonectomy was surprisingly high, at 25.9%. Furthermore, a subset cohort-matching analysis in this trial revealed a significantly poorer OS for patients who underwent pneumonectomy than for patients who underwent lobectomy [6]. In their analysis of 100 consecutive pneumonectomy patients, including 30 i-CRT patients, Doddoli et al. reported overall 30- and 90-day postoperative mortality rates of 12% and 21%, respectively, with a higher risk in i-CRT patients and concluded that pneumonectomy was a high-risk surgical procedure [7]. Similarly, d'Amato et al. reported significantly higher 30-day postoperative mortality in pneumonectomy patients who received chemo- or chemoradio-induction therapy than in those who did not receive any induction therapy (21% vs. 6.1%, respectively) [23].

Contrary to those reports, other groups have documented a lower mortality rate after pneumonectomy, although there were no specific differences in treatment modality [24–29]. Right pneumonectomy is also generally considered to be associated with a higher frequency of major postoperative morbidities than left pneumonectomy [7], particularly BPF, which can provoke empyema. However, the postoperative mortality rate associated with the laterality of pneumonectomy varies [26]. Some published reports show no marked difference in the outcomes between operated sides. For example, Daly [30] noted a slightly higher postoperative mortality rate after left pneumonectomy than after right pneumonectomy, with no reasonable explanation. Although some of the patients in the present series experienced severe postoperative morbidities, such as empyema necessitating open window thoracostomy, the 90-day postoperative mortality rate for the those who underwent i-CRT followed by pneumonectomy was 3.1%, a non-significant difference vs. those treated with lobectomy. Moreover, the postoperative mortality rate in the current analysis was equivalent to or lower than that described in previously published reports on i-CRT followed by pneumonectomy. The only death was of a patient who underwent right pneumonectomy; however, the cause of death was deterioration of interstitial pneumonia. The relatively low median dose of radiotherapy of 40 Gy used in this series might have contributed to the lower incidence of morbidity and mortality, as we reported previously. In our previous study, 42 consecutive patients with potentially resectable cStage III non-small cell lung cancer (NSCLC) treated with S-1 and CDDP concurrent with 40 Gy of radiotherapy, followed by curative intent resection were analyzed retrospectively. In that study, the 5-year overall survival (OS) was 61.7% for all patients, with complete pathological response achieved in 23.1% [14]. Moreover, UFT or S-1 is generally used only for NSCLC in Japan; however, the results from a multicenter phase II trial with S-1 and CDDP and concurrent radiotherapy of 60 Gy for unresectable NSCLC achieved a 2-year OS of 70% (95% CI 55–81%) [31].

The survival benefit must be considered when assessing the validity of pneumonectomy as a potential treatment modality for LA-NSCLC. The reported 5-year OS rate achieved by i-CRT followed by pneumonectomy varies from approximately 22–38% [6, 29, 30]. In the current analysis, there was no significant difference in the DFS or OS rates when stratified by procedure (pneumonectomy or lobectomy), and the results were comparable to those of previously published reports: the 5-year DFS rate was 53.0% (95% CI 39.5%–66.5%), and the 5-year OS rate was 54.6% (95% CI 38.5%–70.7%) in the P group.

One potential limitation of the current study was its retrospective nature and relatively small patient population. For this reason, the patients in the current analysis who tolerated induction treatment followed by pneumonectomy may have represented a selected subgroup of the total patients with LA-NSCLC, although a quality assessment could not be performed.

In conclusion, every effort should be made to avoid pneumonectomy if bronchial and/or pulmonary artery sleeve lobectomy can be performed. However, if complete resection is technically impossible, except by pneumonectomy, because of the disease, induction treatment followed by pneumonectomy is not necessarily a contraindication, provided this strategy has the potential to cure LA-NSCLC. A multidisciplinary team should assess the indications of i-CRT followed by pneumonectomy for curative intent as a multimodality treatment.

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Compliance with ethical standards

Conflict of interest Masafumi Yamaguchi: No conflict of interest. Shinichiro Shimamatsu: No conflict of interest. Makoto Edagawa: No conflict of interest. Fumihiko Hirai: No conflict of interest. Ryo Toyozawa: No conflict of interest. Kaname Nosaki: No conflict of interest. Takashi Seto: Received honoraria (lecture fees) from AstraZeneca, Eli Lilly Japan and Ono Pharmaceutical. Received research grants from Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Merck Serono, Nippon Boehringer Ingelheim, Novartis Pharma and Pfizer Japan. Mitsuhiro Takenoyama: Received research grants from Eli Lilly Japan and Ono Pharmaceutical. Yukito Ichinose: No conflict of interest.

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