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REVIEW ARTICLE

Keys to successful induction chemoradiotherapy followed by surgery for stage III/N2 non-small cell lung cancer

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Abstract
Surgical intervention after induction chemoradiation is designed as curative treatment for resectable stage III/N2 non-small cell lung cancer. However, there is no definitive evidence to support this approach, possibly because successful treatment requires certain "arts", such as proper patient selection, an appropriate induction regimen, and choice of the best surgical procedure. We review the previous reports and discuss our own experience to explore the appropriate strategy for patients with resectable stage III/N2 disease, and to identify the factors associated with successful surgical intervention. Among the studies reviewed, the complete resection rate among intention-to-treat cases was correlated well with the 5-year survival rate, whereas the pneumonectomy rate was correlated inversely with the 5-year survival rate. The clinical response rate and downstaging after induction treatment were not associated with survival. Based on these findings, we conclude that complete resection with the avoidance of pneumonectomy is important when selecting candidates for multimodal treatment including radical surgery.

Keywords Induction treatment · Stage III · N2 · Non-small cell lung cancer · Surgery

Introduction

The surgical strategies for stage III/N2 non-small cell lung cancer (NSCLC) with mediastinal nodal metastasis remain controversial, even when the disease is resectable. A pivotal-phase III study comparing definitive chemoradiation therapy (CRT) versus induction CRT followed by surgery showed no difference in overall survival, possibly because the rate of treatment-related mortality in patients who receive trimodal treatment is too high, especially in patients who undergo right pneumonectomy [1]. Another phase III study comparing surgery versus radiation in patients who had responded to chemotherapy also failed to demonstrate a benefit from surgery [2]. Conversely, a phase III trial conducted by Eberhardt et al. [3] demonstrated that induction CRT followed by surgery was associated with better OS and PFS than definitive CRT, but this trial was closed after the second scheduled interim analysis because of slow accrual and insufficient funding. The role of surgery in multimodal treatment for potentially resectable stage III/N2 NSCLC remains to be investigated. However, more than 80% of thoracic surgeons consider surgery after induction treatment [4], 62% would offer surgery after induction treatment if N2 disease was downstaged, and 19% would consider surgery after induction treatment even if N2 disease is persistent. Moreover, favorable outcomes have been reported in several studies. Thus, we review the previous reports, including retrospective studies, as well as our own experience to try and identify the optimal strategy for resectable stage III/N2.

Interpretation of two historic studies

The strongest evidence to support surgical intervention for resectable stage III/N2 NSCLC was from the North American Intergroup Trial 0139, reported by Albain et al. [1]. This phase III study reported that the 5-year overall survival rate of the induction CRT group was 27.2%; equivalent to that in the definitive CRT group (hazard ratio 0.87, $p = 0.24$); however, the 5-year disease-free survival rate of the induction CRT group was superior to that of the definitive CRT

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group (hazard ratio 0.77, $p = 9.017$). Although there were no treatment deaths during induction CRT with cisplatin/etoposide/45 Gy, there were 16 surgery-related deaths in the induction CRT group, and 14 of these 16 patients had undergone pneumonectomy. In the unplanned matching analysis, patients in the induction CRT group who underwent lobectomy had a significantly better prognosis than those in the definitive CRT group ($p = 0.020$), whereas patients in the induction CRT group who underwent pneumonectomy had a worse prognosis than those in the definitive CRT group, although the difference did not reach significance ($p > 0.05$). These results mean that the outcome of induction CRT is largely affected by the high mortality rate after pneumonectomy. In Toronto General Hospital, selected patients with resectable stage III/N2 were given the same induction regimen as the intergroup trial 0139 and better survival was observed, with a 5-year survival rate of > 40%, even though 27.5% of the patients underwent pneumonectomy [5], whereas that in the intergroup trial 0139 was 27.2%. These results suggest that surgical and management skills, as well as patient selection, contribute to the outcome after induction CRT. These results imply that the outcome of induction CRT followed by surgery for resectable stage III/N2 is affected significantly by patient selection.

EORTC8941 [2] also provided strong evidence of the futility of surgical intervention for patients with stage III/N2 disease that had become resectable after a response to systemic chemotherapy. The 5-year survival rate of the surgery arm was only 15.7% (radiation arm: 14.0%), whereas the complete resection rates in patients who underwent thoracotomy or pneumonectomy were 50.0% and 46.7%, respectively, which suggests that the tumor burden of the patients entered in the study was more extensive than "resectable".

Analysis of factors affecting survival

We analyzed, in detail, nine studies published between 2010 and 2018, as well as our experience of treating patients with induction therapy followed by surgery for stage III/N2 NSCLC. Among five studies of phase III trials (three of which were incomplete), four examined induction CRT followed by surgery and one examined chemotherapy followed by surgery. Four other studies were retrospective or single-arm studies, and two were phase II trials [1–3, 5–9, 12, 13]. Table 1 summarizes the data extracted from these studies and our data. The resection rate for patients managed on an intention-to-treat basis was calculated from these data. The reported resection rates, which were usually expressed as complete resection rates in patients treated with thoracotomy, were also extracted. In these studies, the 5-year survival rates were correlated positively with the calculated resection rates for patients managed on an intention-to-treat basis. A linear regression analysis revealed a positive correlation between the complete resection rates and the 5-year OS rates among these studies. When the complete resection rates for thoracotomy were examined, the correlation index (R^2) was 0.70 ($p = 0.002$) (data not shown), whereas the index was 0.58 ($p = 0.026$) when the complete resection rates for patients managed on an intention-to-treat basis were examined (Fig. 1a). On the other hand, the pneumonectomy rates were correlated inversely with the 5-year survival rates ($R^2 = 0.64$, $p = 0.005$) (Fig. 1b). Regarding pneumonectomy, a linear regression analysis of pneumonectomy rates and treatment-related mortality rates revealed a significant association and a positive correlation ($R^2 = 0.60$, $p = 0.01$) (Fig. 2). Downstaging and the response rate after induction treatment were not associated with survival (Fig. 1c, d).

Our experience at Chiba University Hospital

We report our experience and compare it with the previous reports.

Previously untreated patients with clinical stage III/N2 NSCLC (based on the seventh TNM classification system) [11] were considered for induction CRT followed by surgery at Chiba University Hospital. Surgical resectability was initially evaluated by board-certified thoracic surgeons and then by a multidisciplinary team of respirology, oncology, and radiology specialists. When trimodal therapy was indicated, the patient received induction CRT with S-1 and cisplatin, followed by surgery, and was enrolled in this retrospective review. The study was approved by the Institutional Review Board of Chiba University (approval number: 3181), and as it was retrospective, personal information was omitted and the need for individual consent was waived. The indications for induction CRT followed by surgery were as follows: age ≤ 75 years; an Eastern Cooperative Oncology Group (ECOG) PS of 0–1; and surgically resectable disease. The primary diagnosis of lung cancer was made by transbronchial biopsy via bronchoscopy in all the patients. The clinical stage of the disease was established by radiology, including chest contrast-enhanced computed tomography (CT), contrast-enhanced brain magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT). Nodal staging was initially based on the radiology findings of lymph nodes with a short-axis diameter of > 10 mm on chest CT or a standardized uptake value (SUV) of > 2.5 on PET-CT. Suspicious lymph nodes were sampled by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) when the lymph-node station was accessible by an EBUS scope. After the completion of induction CRT, re-staging was performed by chest contrast-enhanced CT, PET-CT, contrast-enhanced brain MRI, and EBUS-TBNA (as much as possible) prior to

Table 1 Summary of data from several historical studies

Author	Induction regimen	Induction radiation dose	Complete CRT	CR + PR	Complete resection rate in intention-to-treat cases	Complete resection in thoracotomy	Bronchoplasty	Vascular plasty	Pneumonectomy	Operation-related mortality	Downstaging	Treatment-related mortality	OS	RFS
Phase III study														
Van Meerbeeck 2007 [2]	Platinum-doublet + RT	–	332/579 (57.3%)	NA	NA	77/154 (50.0%)	NA	NA	72/154 (46.7%)	6/154 (3.8%)	64/154 (41.5%)	NA	5y 15.7%	2y 27%
Albain 2009 [1]	CDDP + ETP + RT	45 Gy	193/202 (95.5%)	NA	144/202 (71.2%)	144/164 (87.8%)	NA	NA	54/164 (32.9%)	16/164 (9.7%)	153/202 (75.7%)	16/202 (7.9%)	5y 27%	5y 22%
Katakami 2012 [7][a]	CDDP + ETP + RT	40 Gy	29/29 (100%)	7/29 (44.3%)	24/29 (82.7%)	24/26 (92.3%)	NA	NA	0/26 (0%)	0/26 (0%)	10/29 (34.3%)	0/29 (0%)	3y 51.7%	3y 34.5%
Eberhardt [3][a]	CDDP + DTX + RT	45 Gy	227/237 (95.7%)	NA	NA	66/70 (94.2%)	NA	NA	23/70 (32.8%)	5/70 (7.1%)	NA	7/81 (8.6%)	5y 44%	5y 32%
Pless [9][b]	Platinum-doublet + RT	44 Gy	108/117 (92.3%)	71/117 (60.6%)	90/117 (76.9%)	90/99 (90.9%)	NA	NA	25/99 (25.2%)	0/99 (0%)	63/117 (53.8%)	1/117 (0.8%)	Median 37.1 m	Median 12.8 m
Phase II study														
Friedel [6]	CBDCA + PTX + RT	45 Gy	108/120 (90.0%)	NA	62/120 (51.6%)	62/78 (79.4%)	9/78 (11.5%)	4/78 (5.1%)	36/78 (46.1%)	7/78 (8.9%)	57/120 (47.5%)	8/120 (6.6%)	5y 24.5%	NA
Chen [8]	CBDCA + PTX + RT	42 Gy	19/22 (86.3%)	14/22 (63.6%)	19/22 (86.3%)	19/19 (100%)	3/19 (15.7%)	NA	1/19 (5.2%)	0/19 (0%)	10/22 (45.4%)	0/22 (0%)	5y 62%	2y 62.7%
Retrospective study														
Uy [5]	CDDP + ETP + RT	45 Gy	37/40 (92.5%)	27/40 (67.5%)	37/40 (92.5%)	37/40 (92.5%)	NA	NA	11/40 (27.5%)	3/40 (7.5%)	11/40 (27.5%)	3/40 (7.5%)	3y 51.7%	3y 52.3%
Kim [13]	Platinum-doublet + RT	4445 Gy	642/664 (96.6%)	NA	543/664 (81.7%)	543/574 (94.5%)	25/574 (4.3%)	NA	73/574 (12.7%)	36/574 (6.2%)	304/664 (45.7%)	39/664 (5.8%)	5y 48%	5y 29%
Chiba University	CDDP + S-1 + RT	45 Gy	25/25 (100%)	12/25 (48.0%)	25/25 (100%)	25/25 (100%)	2/25 (8%)	9/25 (36%)	0/25 (0%)	0/25 (0%)	11/25 (44.0%)	0/25 (0%)	5y 57.5%	5y 24.2%

Data are expressed as numbers (%)

NA Not available, *CDDP* cisplatin, *CBDCA* carboplatin, *ETP* etoposide, *DTX* docetaxel, *PTX* paclitaxel, *RT* radiation therapy, *CRT* chemoradiation therapy, *CR* complete response, *PR* partial response, *OS* overall survival, *RFS* recurrence-free survival

[a]These phase III studies were stopped because of the slow patient accrual

[b]The phase III trial study was stopped, because the futility boundary was crossed

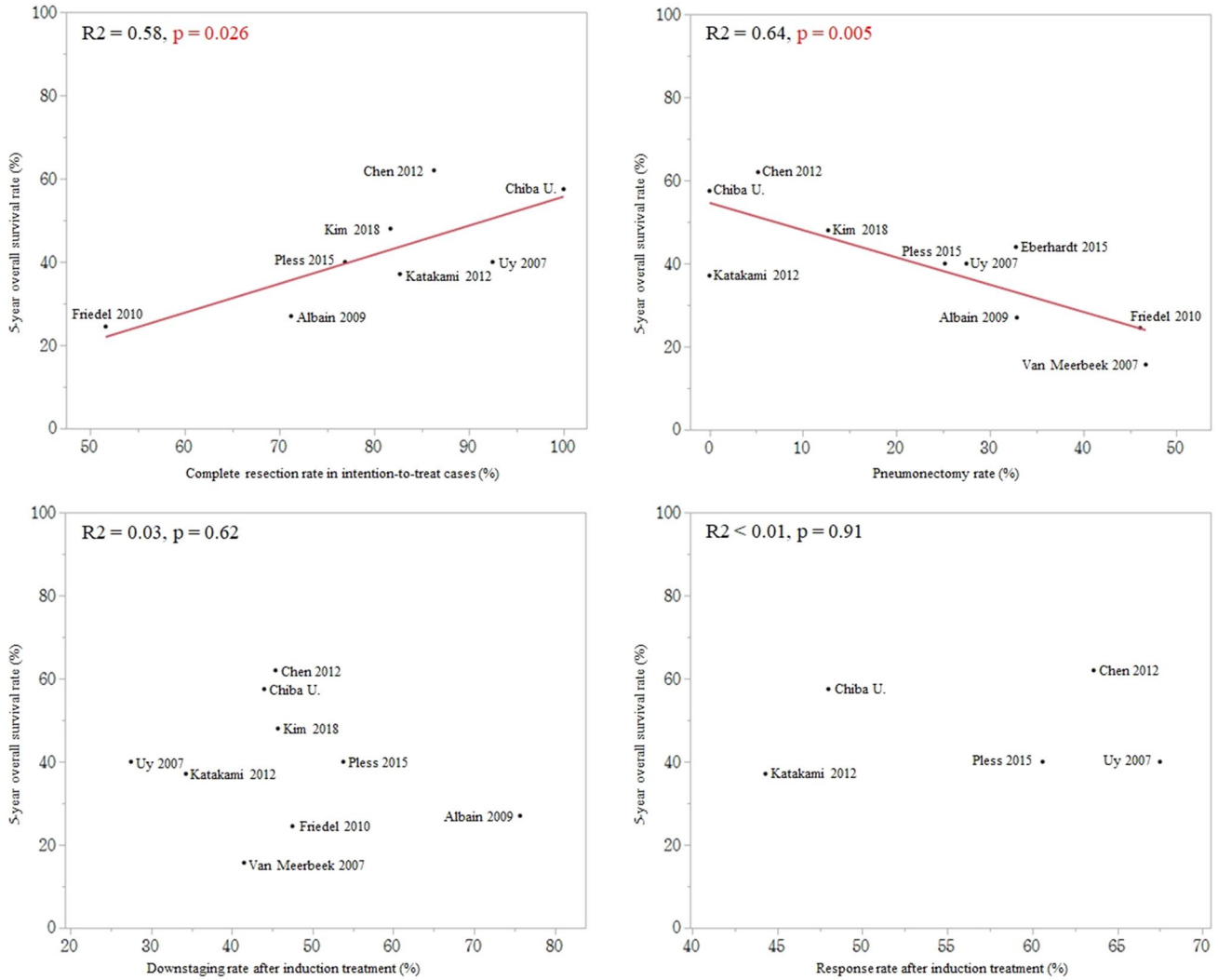

Fig. 1 Factors correlated with 5-year survival in the reported studies. **a** Relationship between the complete resection rates for patients managed on an intention-to-treat basis and the 5-year survival rates among the studies. The two factors exhibited strong positive correlation in the linear regression analysis ($R^2 = 0.61$, $p = 0.0015$). **b** Relationship between pneumonectomy rates and 5-year survival rates in the reported studies. The two factors exhibited a significant inverse correlation in the linear regression analysis ($R^2 = 0.51$, $p = 0.0058$). **c** Relationship between downstaging rates and 5-year survival rates in the reported studies. The two factors were not significantly correlated ($R^2 = 0.14$, $p = 0.25$). **d** Relationship between response rates (CR + PR) and 5-year survival rates in the reported studies. The two factors were not significantly correlated ($R^2 = 0.46$, $p = 0.09$)

thoracotomy. Radical thoracotomy was indicated when we judged that the patient did not have progressive disease and had maintained a reasonable performance status for surgery.

Induction CRT consisted of S-1 and cisplatin chemotherapy with concurrent thoracic radiation of the primary tumor and mediastinum. The effectiveness of cisplatin and S-1 plus radiotherapy has been reported previously. S-1 is known to increase radiation sensitivity and was expected to increase the antitumor effect [12–15]. Enrolled patients received oral S-1 (40 mg/m^2, twice per day) on days 1–14 and 29–42, plus cisplatin (60 mg/m^2) on days 1 and 29. Radiotherapy was started on day 1 of chemotherapy and delivered at a daily dose of 1.8 Gy each weekday (total dose: 45 Gy). The radiologist determined the radiation field, which did not exceed 40% of the lung field (radiation exposure of the lung field was limited to < 20Gy). In general, the radiation field included the primary tumor site and the regional node regions (hilar, ipsilateral mediastinal, and bilateral supraclavicular regions). Patients were scheduled to undergo surgery approximately 6–8 weeks after the completion of induction CRT. The surgical procedure was decided based on the extent of the disease. Lobectomy with mediastinal lymph dissection was the first choice, but when appropriate, bilobectomy, sleeve resection, or resection with reconstruction of the major vessels was performed to avoid pneumonectomy. In general, lobar or interlobar nodal metastasis was

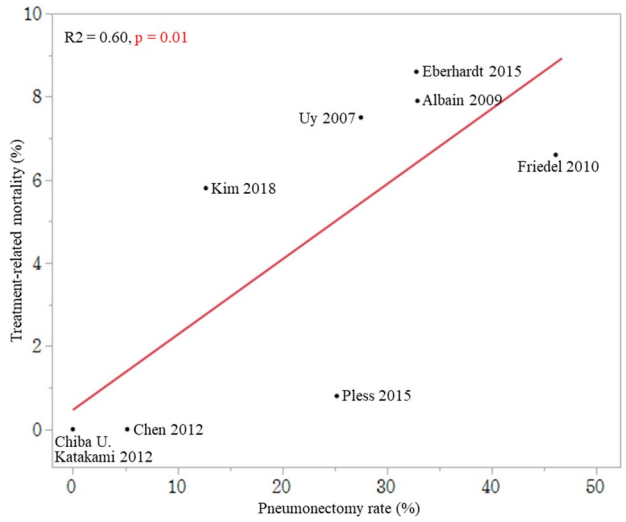

Fig. 2 Relationship between pneumonectomy rates and treatment-related mortality in the reported studies. The two factors showed a significant positive correlation ($R^2 = 0.52$, $p = 0.0052$)

Table 2 Patient characteristics in the Chiba University study

Characteristics	
Age (years): median (range)	63.8 (49–75)
Sex	
Male	20
Female	5
Histological type	
Squamous cell carcinoma	8
Adenocarcinoma	17
Method of mediastinal staging	
EBUS-TBNA	21
PET-CT	4
Clinical stage	
IIIA	25
T1bN2M0	9
T2aN2M0	10
T2bN2M0	5
T3N2M0	1
Tumor size (cm)	3.82 (1.9–7.3)
Number of metastatic mediastinal lymph nodes	2.0 (1–4)

EBUS-TBNA Endobronchial ultrasonography-guided transbronchial needle aspiration, *PET-CT* positron emission tomography

not exposed, to avoid implantation during the operation. The bronchial stump was reinforced by stitching with absorbable sutures and covered with freed or pedicled pericardial fat tissue. Postoperative chemotherapy was considered, depending on the patient's condition.

The clinical response was classified into one of the following four categories according to the radiological findings and the RECIST criteria: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [16]. The grade of histologic tumor regression was determined according to the histologic tumor regression grading system established by The Japan Lung Cancer Society [17] as: Ef.0, no tumor regression; Ef.1, incomplete tumor regression, more than one-third of vital tumor tissue; Ef.2, less than one-third of vital tumor tissue; Ef.3, complete tumor regression.

Overall survival (OS) and recurrence-free survival (RFS) were calculated from the date of the initiation of induction CRT until confirmed death of any cause or recurrence at a local or distant site (for RFS). Kaplan–Meier survival curves were calculated and differences between groups were compared by the log-rank test. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. All data were analyzed using the JMP® Pro 13.0.0 for Windows software program (SAS Institute, Inc., Cary, NC). In each of the analyses, p values of < 0.05 were considered to indicate significance.

Between January, 2009 and December, 2017, 25 patients underwent induction CRT followed by radical surgery at Chiba University Hospital. Table 2 summarizes the patients' clinical characteristics. The mean maximum tumor diameter was 3.74 cm (range 1.9–7.3 cm), and the mean size and number of lymph nodes were 2.28 cm (range 0.8–4.3 cm) and 2.0 (range 1–4), respectively. Twenty-one (84%) patients underwent EBUS-TBNA for the initial nodal staging prior to the initiation of CRT. Four patients were considered to have N2 disease based on radiology alone, and three of these patients had a suspicious lymph node that could not be accessed by EBUS-TBNA (such as station 5 or station 9).

The chemotherapy regimens and radiotherapy were completed in all 25 patients. Fifteen patients suffered grade 3 complications related to CRT, but none suffered grade 4 side effects and there was no treatment-related mortality (Table 3). A reduction in the tumor size was observed in 23 patients (92%) and downstaging was achieved in 11 (40%). Surgery was performed for all the patients, as lobectomy in 20 [80%] and bilobectomy in 5 [20%]. No patients underwent pneumonectomy. Plasty procedures were performed in nine patients (36%), as vascular plasty in seven, bronchoplasty in one, and double plasty in one. Complete tumor resection with a microscopically negative pathological margin was achieved in all patients. Two patients suffered lung injury and one suffered pulmonary venous thrombosis, but all postoperative complications were managed successfully.

Histological examinations revealed complete response (Ef.3) in four patients (16%) and a partial response (more than Ef.2) in 14 patients (56%). Postoperative adjuvant chemotherapy was given to 21 patients (84%). Recurrence developed in 14 of the 25 patients who underwent resection. Distant metastasis (including brain and bone

Table 3 Toxicity of induction chemoradiation therapy in the Chiba University study

Toxicity	Grade of toxicity (number of patient)				Percentage of grade ≥ 3 toxicities
	1	2	3	4	
Neutropenia	4	6	9	0	34.6
Febrile neutropenia	0	0	1	0	3.8
Anemia	22	2	0	0	0
Thrombocytopenia	12	2	0	0	0
Nausea/vomiting	5	7	1	0	3.8
Diarrhea	3	0	0	0	0
Constipation	5	2	0	0	0
Hepatic dysfunction	1	0	0	0	0
Renal dysfunction	3	0	0	0	0
Esophagitis	0	19	1	0	3.8
Dermatitis	6	5	2	0	7.6

CRT Chemoradiation therapy

metastasis) was found as the first site of recurrence in nine patients and regional recurrence was found in five patients, including pleural dissemination and mediastinal lymph-node recurrence. Figure 3 shows the overall and disease-free survival curves for the entire population. The 3- and 5-year OS rates after the initiation of induction treatment were 71.2% and 56.8%, respectively, and the 3- and 5- RFS rates were 50.4% and 25.2%, respectively. Subset analyses were conducted to identify factors that were related to a favorable prognosis, in terms of OS and RFS. Table 4 shows these results. There were no preoperative factors significantly associated with OS and RFS in our study.

Discussion

Resectable stage III/N2 NSCLC is often treated by induction therapy followed by surgery; however, the indications for this trimodal treatment are determined by individual departments, since there is no definitive evidence to show that it improves the survival of these patients. Thus, candidates for trimodal treatment must be selected carefully.

Avoiding pneumonectomy is thought conventionally to be integral to the success of induction treatment, as the previous studies have reported mortality rates of as high as 37.5% associated with pneumonectomy following induction CRT [18]. Our review also demonstrates that the pneumonectomy rate was positively correlated with treatment-related mortality among independent studies (Fig. 2). In contrast, the mortality rates associated with pneumonectomy after induction therapy reported in recent studies have been as low as 8% [19, 20]. Nevertheless, pneumonectomy is still likely to be associated with a higher degree of risk than lobectomy [21]. Weder et al. [22] reported their experience and concluded that pneumonectomy is safe, with a mortality rate of 3%, even for patients treated with induction therapy; however, the 5-year survival rate of patients with stage III-N2 disease was still 38%. Kim et al. [10] reported that pneumonectomy was an adverse prognostic factor for OS and RFS. The present review also demonstrates an inverse correlation between pneumonectomy rates and 5-year survival rates among studies (Fig. 1b). In general, the post-pneumonectomy status is disadvantageous when systemic treatments such as cytotoxic agents, molecular-targeted therapy, or immunotherapy are required for the treatment of recurrent disease. Our experience and several studies have shown that RFS remains unfavorable (Table 1). Thus, avoiding pneumonectomy whenever possible is very important for post-recurrence management.

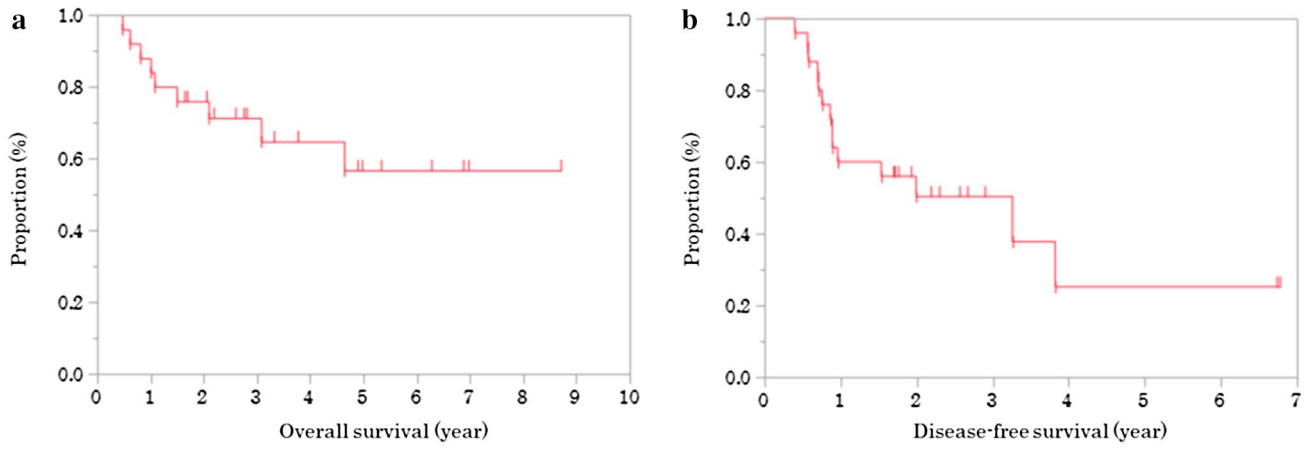

Fig. 3 Overall and disease-free survival curves for 25 patients who received induction therapy. The 3- and 5-years OS rates after the initiation of induction treatment were 71.2% and 56.8% (**a**), respectively. The 3-year and 5-year RFS rates were 50.4% and 25.2% (**b**), respectively

Table 4 Clinicopathological factors affecting the overall survival and recurrence-free survival rates in the Chiba University study

	RFS (%) 3 years	*p* value	OS (%) 5 years	*p* value
Tumor size				
≤3 cm	55.5	0.89	29.1	0.55
>3 cm	48.2		67.5	
Number of metastatic mediastinal lymph nodes				
1	57.1	0.90	22.8	0.30
≥2	48.6		72.2	
Mediastinal downstaging[a]				
Downstaged	72.7	0.06	72.7	0.63
Not downstaged	32.1		48.8	
Type of enlarged mediastinal lymph node				
Discrete N2	47.6	0.89	57.4	0.62
Infiltrative N2	57.1		42.8	
Plastic surgery performed				
No	52.0	0.50	42.1	0.28
Yes	44.4		77.7	

RFS recurrence-free survival, *OS* overall survival

[a]The mediastinal downstaging was the comparison between clinical staging and pathological staging

To achieve complete resection while avoiding pneumonectomy, a certain level of surgical skill is essential, because plastic procedures are frequently required.

Downstaging has also been reported as an important factor for induction CRT. For a long time, mediastinoscopy was considered the gold standard for mediastinal nodal staging. The third ACCP guideline [23] considers less-invasive sonography-based needle biopsy procedures as the best first test for mediastinal staging [24, 25]. We initially used EBUS-TBNA as a nodal staging procedure. There have been several discussions on re-staging by the endosonographic procedures; however, the recent reports noted that endosonographic procedures had an acceptable diagnostic yield and were a less-invasive modality for re-staging after induction therapy [26]. Several studies found that the pathological status of the mediastinum and downstaging were associated with good OS and long RFS [7, 8, 10, 27–29], and re-staging the mediastinal nodes is useful for excluding patients with persistent N2 positivity from thoracotomy. However, a linear regression analysis showed no significant relationship between downstaging and OS (Fig. 1c). In other words, downstaging did not influence survival if complete resection was achieved in patients with persistent N2 disease.

Definitive CRT for unresectable stage III NSCLC is associated with a 5-year survival rate of approximately 20–40%, which has remained unchanged for 20 years [30–34]. However, a recent study on immune checkpoint inhibitor treatment after a response to definite CRT showed a dramatic improvement in survival [35]. In the PACIFIC trial, the 18-month progression-free survival rate of the durvalumab group was 44.2%, while that of the placebo group was only 27% (stratified hazard ratio, 0.52). Buyse et al. reported that the correlation coefficient between log HR_{PFS} and log HR_{OS} over the entire time range was 0.99 (95% CI 0.94–1.04), and the regression equation was log $HR_{OS} = 0.003 + 0.81 \times \log HR_{PFS}$ [36]. Based on calculations using these criteria, the estimated stratified hazard ratio for OS achieved by durvalumab versus a placebo (definitive CRT) would be 0.59. Thus, considering that definitive CRT for unresectable stage III NSCLC is associated with a 5-year survival rate of approximately 20–40%, the estimated 5-year survival rate of unresectable stage III NSCLC patients treated with definitive CRT followed by durvalumab would be at least 40–50%. In the era of immunotherapy, trimodal treatment with induction CRT followed by surgery should not be considered, even for selected patients, unless the 5-year survival rate is >50%.

In conclusion, induction CRT followed by surgery is a feasible therapeutic option for stage III/N2. To aim for a 5-year survival rate of >50%, it is important to select patients with 'resectable' stage III/N2, and perform complete resection, while avoiding pneumonectomy. If the indications are expanded to include patients with infiltrative N2, with bronchial or vascular invasion, plastic reconstruction of the affected sites would be needed to achieve the complete resection of infiltrative mediastinal lymph-node metastasis. In our experience, none of the factors associated with the nodal status affected OS or RFS (Table 4) for appropriately selected patients with "resectable" stage III/N2 NSCLC.

The indication for CRT followed by surgery should be decided by a multidisciplinary conference with thoracic surgeons, oncologists, respirologists, and radiation oncologists, to select the best treatment strategy for each patient. Complete resection with the avoidance of pneumonectomy is important to select the candidates for multimodal treatment including radical surgery.

Compliance with ethical standards

Conflict of interest Ichiro Yoshino received honorarium from Pfizer Inc., Shionogi & Co., Ltd., Astellas Pharma Inc., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Company, Limited, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Teijin Pharma Limited; Takahiro Nakajima received honorarium from Olympus Co. as lecture fees.

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