Original Article

Feasibility and prognostic benefit of induction chemoradiotherapy followed by surgery in patients with locally advanced non-small cell lung cancer

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Background: The optimal treatment for patients with resectable non-small cell lung cancer (NSCLC) involving adjacent organs (T3 or T4) and/or cN2 remains unclear. We investigated whether or not induction chemoradiotherapy (ICRT) followed by surgery improves the survival.

Methods: We retrospectively analyzed 84 patients with NSCLC involving the adjacent organs and/or cN2 who underwent ICRT followed by surgery at our hospital from 2006 to 2018. Presurgical treatment consisted of 2 courses of platinum-doublet and concurrent radiotherapy (40–50 Gy) to the tumor and involved field.

Results: All 84 patients completed ICRT. One patient died after completion of ICRT due to bacterial pneumonia. Radiological responses to ICRT were a complete response (CR), n=1; partial response (PR), n=48; stable disease (SD), n=32; and progressive disease (PD), n=2 (overall response rate: 58.3%). Eighty-one patients underwent radical surgery. The procedures included lobectomy, n=66; bilobectomy, n=7; pneumonectomy, n=6; and segmentectomy, n=2 (including 49 extended resections). Seventy-three patients (90%) underwent complete resection. The postoperative morbidity rate was 30%. The 30- and 90-day mortality rates were 1.2% and 2.4%, respectively. A pathological CR (Ef3) and major response (Ef2) were achieved in 17 (21.0%) and 38 (46.9%) patients, respectively; a minor response (Ef1) was observed in 26 (32%). The 5-year overall survival (OS) and recurrence-free survival (RFS) rates were 58.0% and 45.6%, respectively. The median survival time was 73.2 months. Based on the response to ICRT, patients with radiological CR or PR showed better 5-year OS than those with SD (63.7% *vs.* 40.0%, P=0.020). Patients with Ef3 or Ef2 demonstrated a much better 5-year OS than those with Ef1 (65.0% *vs.* 24.4%, P=0.005).

Conclusions: ICRT followed by surgery for patients with NSCLC involving the adjacent organs and/or cN2 was feasible and improved the survival. A CR/PR or Ef2/Ef3 after ICRT led to a better prognosis.

Keywords: Lung cancer; induction chemoradiotherapy (ICRT); surgery

Introduction

Lung cancer remains the leading cause of cancer-related death in many countries, as many patients are diagnosed at an advanced stage (1). More than one third of all patients with non-small cell lung cancer (NSCLC) present with advanced disease at the time of the diagnosis (2). The standard treatment modality for patients with unresectable stage III NSCLC invading adjacent organs and/or cN2 is thought to be definitive chemoradiotherapy (3,4). However, the optimal treatment for patients with potentially "resectable" stage III NSCLC remains unclear. The standard therapy for patients with T3N0-1M0 NSCLC involving the chest wall is considered primary surgical resection. However, the prognosis of those patients has also been unsatisfactory (5,6).

Surgery alone results in a poor overall survival (OS) in patients with locally advanced NSCLC, such as lung cancer invading adjacent organs (invasive T3 or T4) and/or N2 lung cancer, as most such patients have microscopic distant metastases (7). Thus, the treatments for such advanced NSCLC should control both local and microscopic systemic disease. Multimodal treatment is therefore thought to be essential for improving the survival.

The administration of postoperative adjuvant chemotherapy is one approach to reduce the risk of recurrence. Adjuvant chemotherapy has been shown to significantly improve the survival in a meta-analysis and clinical trial (8,9); however, after undergoing major surgery, many patients are unable to receive adjuvant chemotherapy due to deterioration in their performance status (5). Another approach is to administer induction chemotherapy or chemoradiotherapy (ICRT) before the surgical procedure in order to control microscopic metastases and render the tumor completely resectable. Some analyses have demonstrated that ICRT improved the pathological complete response (CR) and local control rates in comparison to chemotherapy alone (10-14). ICRT has the potential to reduce the tumor size, achieve complete resection, eradicate micrometastases, and extract occult metastasis by performing a re-staging examination after ICRT (15).

The aim of this retrospective study was to analyze patients with resectable locally advanced NSCLC invading adjacent organs (invasive T3 or T4) and/or cN2 who underwent ICRT followed by surgery at our institute in order to evaluate the short- and long-term outcomes and investigate the relationship between the radiological/ pathological response and survival.

Methods

The patient selection and evaluation

We retrospectively reviewed the clinical records of 84 patients with locally advanced NSCLC involving the adjacent structures or major vessels (invasive T3 or T4) and/or cN2 who underwent ICRT followed by surgery at Seirei Mikatahara General Hospital, Hamamatsu, Japan from December 2006 to May 2018. In order to avoid including false-positive cases, we only enrolled invasive T3/T4 patients in whom invasion of the surrounding structures invasion was pathologically confirmed after surgery. Patients with cN2 required radiological evidence of N2 disease, defined as both mediastinal nodal enlargement (short-axis diameter: >1 cm) on CT and an abnormal 18F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) as well as pathological confirmation of the presence of N2 disease.

ICRT was performed for patients ≤75 years of age and with an Eastern Cooperative Oncology Group performance status of 0–1 and adequate organ functional reserves. In all cases, the tumor was potentially resectable with regression after ICRT. Patients were assessed by a thoracic surgeon, radiation oncologist, and medical oncologist before treatment. The disease stage was evaluated using chest radiography, enhanced chest and abdominal CT, enhanced brain magnetic resonance imaging (MRI), PET/CT, and bronchoscopy. The international Association of the Study of Lung Cancer TNM staging system for NSCLC, eighth edition, was used to determine the disease stage and nodal location (16).

Therapeutic schedule

In all cases, the chemotherapy regimens consisted of two courses of platinum doublet therapy. All patients underwent concurrent radiotherapy with 40 or 50 Gy to the primary tumor and involved lymph nodes. After ICRT, the patients were re-staged by thoracic CT, PET/CT, and brain MRI, and those without progressive disease (PD) were scheduled to receive radical surgery within six weeks of the completion of ICRT.

The surgical procedure employed was determined based on the extent of the tumor. Resection and reconstruction of the adjacent structures or major vessels was performed as necessary. The bronchial stump or anastomosis was

basically covered with an intercostal muscle pedicle flap or pericardial fat tissue.

Postoperative adjuvant chemotherapy was administered to the greatest extent possible according to the pathological tumor response. If a pathological complete effect (Ef3) or major pathological effect (Ef2) was achieved by ICRT, the drugs that were administered for the induction regimen were administered for adjuvant chemotherapy. If no effect (Ef0), a minor effect (Ef1a), or mild effect (Ef1b) on pathological findings was observed, other platinum-based doublet agents were selected for adjuvant chemotherapy.

The patients were followed up every month until 12 weeks, every 3 months until 2 years after surgery, and every 6 months thereafter. Patients were scheduled to receive chest CT and brain MRI every 3 months and to receive abdominal CT, brain MRI, and a radionuclide bone scan or PET/CT every 12 months for at least 2 years. During the first 3–5 years after the completion of treatment, chest CT was repeated every 12 months.

The evaluation of the efficacy and toxicity

The pathologic tumor response (Ef) of induction therapy was assessed using resection specimens according to the General Rule for Clinical and Pathological Record of Lung Cancer (Eighth edition) by the Japan Lung Cancer Society (17): Ef0, no effect, no morphological changes including degeneration or necrosis caused by treatment; Ef1a, minor effect, viable cancer cells observed in two-thirds or more of cancer tissue; Ef.1b, mild effect, viable cancer cells observed in one-third or more but less than two-thirds of cancer tissue; Ef.2, moderate effect, viable cancer cells observed in less than one-third of cancer tissue; and Ef.3, marked effect, no viable cancer cells or residual cancer cells judged not to be viable. Complete resection (R0) was defined as resection with pathologic evidence of negative tumor margins.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 4.0).

Statistical analyses

Categorical variables were analyzed by a χ^2 test. The survival was estimated by the Kaplan-Meier method, and differences in the survival were determined by a log-rank analysis. Day zero was the date of pulmonary resection, and the final endpoint of the OS was death attributable to cancer, or due to a cause other than cancer. The final endpoint of the

recurrence-free survival (RFS) was the date of recurrence, the date of the last follow-up examination, or the date of death in the absence of recurrence. Not all recurrent cases were confirmed pathologically. P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the StatView software program (SAS Institute Inc., Cary, NC, USA).

This retrospective analysis was approved by the Institutional Review Board of Seirei Mikatahara General Hospital (approval number: 18-30). The requirement for informed consent from each patient was waived owing to the retrospective nature of the study, with patient information obtained from the database.

Results

Patients' characteristics

The characteristics of the patients are shown in *Table 1*. The median age was 59.7 years old (42–73 years old). There were 75 men and 9 women. The histological subtypes were as follows: adenocarcinoma (n=35), squamous cell carcinoma (n=29), non-small cell carcinoma (n=15), pleomorphic carcinoma (n=3), and adenosquamous cell carcinoma (n=2). Eighteen patients had stage IIB disease (T3N0), 47 patients had stage IIIA disease [T1N2 (n=11), T2N2 (n=9), T3N1 (n=6), T4N0 (n=10), and T4N1 (n=11)], and 19 patients had stage IIIB disease [T3N2 (n=10), T4N2 (n=9)]. In the clinical N2 patients, mediastinal nodal involvement was diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (n=21) or CT/PET (n=18).

ICRT

The chemotherapy regimens of ICRT included cisplatin plus docetaxel (n=36), cisplatin plus vinorelbine (n=36), carboplatin plus paclitaxel (n=10), cisplatin plus S-1 (n=1), and carboplatin plus docetaxel (n=1). The radiation doses were 50 Gy (n=50) and 40 Gy (n=34).

The radiological responses to ICRT included a CR in 1 patient, a PR in 48, SD in 32, PD in 2 (both patients developed brain metastasis), and not evaluated due to death in 1; the overall response rate (ORR) was 59%.

All 84 patients completed ICRT, which was generally well tolerated. Grade ≥3 adverse events are listed in *Table 2*. The most common grade 3 or 4 toxicity was neutropenia in 21 (25%) patients. One patient died after completing ICRT

Table 1 The characteristics of the 84 patients who underwent ICRT

Variable	Number (%)
Age, years; median [range]	59.7 [42–73]
Sex	
Male	75 (89.3)
Female	9 (10.7)
Histology	
Adenocarcinoma	35 (41.7)
Squamous cell carcinoma	29 (34.5)
Pleomorphic carcinoma	3 (3.6)
Adenosquamous cell carcinoma	2 (2.4)
Non-small cell carcinoma	15 (17.9)
Clinical stage	
IIB	18 (21.4)
IIIA	47 (56.0)
IIIB	19 (22.6)
cT-status	
cT1	11 (13.1)
cT2	9 (10.7)
cT3	34 (40.5)
cT4	30 (35.7)
cN-status	
cN0	28 (33.3)
cN1	17 (20.2)
cN2	39 (46.4)
Chemotherapy regimen	
Cisplatin/docetaxel	36 (42.9)
Cisplatin/vinorelbine	36 (42.9)
Carboplatin/paclitaxel	10 (11.9)
Cisplatin/S1	1 (1.2)
Carboplatin/docetaxel	1 (1.2)
Radiation dose	
40 Gy	34 (40.5)
50 Gy	50 (59.5)
Tumor response	
Complete response	1 (1.2)
Partial response	48 (57.1)
Stable disease	32 (38.1)
Progressive disease	2 (2.4)
Not evaluated	1 (1.2)

Table 2 Induction chemoradiotherapy-related toxicity

Adverse events	Grade			Frequency of
	3	4	5	Grade ≥3 (%)
Leucopenia	4	0	0	4.8
Neutropenia	12	9	0	25
Febrile neutropenia	3	0	0	3.6
Venous thromboembolism	2	0	0	2.4
Diarrhea	1	0	0	1.2
Bacterial pneumonia	0	0	1	1.2
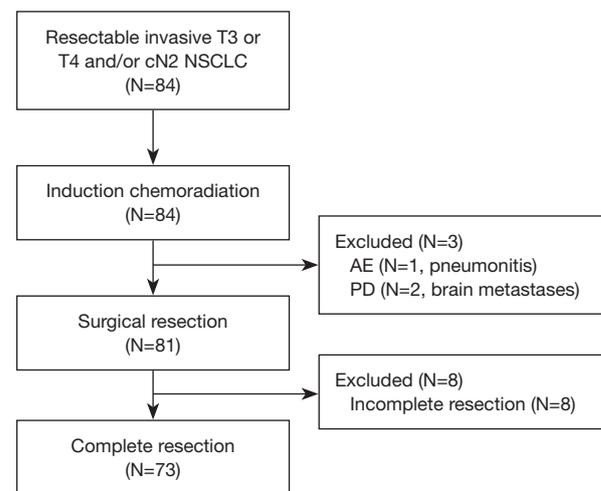
Figure 1 CONSORT diagram. NSCLC, non-small cell lung cancer; AE, adverse event; PD, progressive disease.

due to Nocardia pneumonia.

Surgery, pathological response, and postoperative adjuvant therapy

Surgery was performed in 81 (96%) patients, excluding 1 case of grade 5 pneumonia and 2 cases of PD (*Figure 1*).

The surgical outcomes are shown in *Table 3*. The surgical procedure included lobectomy in 66 patients (81.5%), bilobectomy in 7 (8.6%), pneumonectomy in 6 (7.4%), and segmentectomy in 2 (2.5%). Tracheobronchoplasty was performed in 18 patients (22.2%); this included carinal resection in 4 and pulmonary arterioplasty in 8 (9.9%). Among the 6 pneumonectomies, 3 were right-sided (50%), and 2 involved carinal resections (33%). Combined resection was performed in 49 patients, involving the chest wall

Table 3 The surgical outcomes

Variable	Number (%)
Type of surgical resection	
Lobectomy	66 (81.5)
Bilobectomy	7 (8.6)
Pneumonectomy	6 (7.4)
Segmentectomy	2 (2.5)
Combined resected organs	
Chest wall	38 (46.9)
Vertebrae	8 (9.9)
Carina	4 (4.9)
Left atrium	3 (3.7)
Brachiocephalic/subclavian artery	3 (3.7)
Superior vena cava	2 (2.5)
Aorta	1 (1.2)
Plasty	
Bronchoplasty	18 (22.2)
Pulmonary artery plasty	8 (9.9)
Complete resection	73 (90.1)
Pathologic response[a]	
Complete response (Ef3)	17 (21.0)
Major response (Ef2)	38 (46.9)
Mild response (Ef1b)	11 (14.0)
Minor response (Ef1a)	15 (19.0)

[a]Pathologic response: Ef3, no microscopic residual tumor; Ef2, less than one third of tumor cells viable; Ef1b, one-third or more but less than two-thirds of tumor cells viable; Ef1a, two-thirds or more of tumor cells viable.

(n=38), vertebrae (n=8), left atrium (n=3), brachiocephalic/subclavian artery (n=3), superior vena cava (n=2), and aorta (n=1) (include duplicate patients). A total of 73 patients (90%) achieved complete resection (R0) (*Figure 1*).

Grade ≥3 complications after surgery are listed in *Table 4*. The most common grade 3 or 4 toxicity was pneumonia in 7 (8.6%) patients. No intraoperative mortality was observed. Complication-related death within 30 postoperative days occurred in 1 patient (1.2%). The patient underwent left upper lobectomy combined with resection of the left subclavian artery and died eight days after surgery due to postoperative bleeding. Death after 30 postoperative days

Table 4 Postoperative complications

Adverse events	Grade			Frequency of
	3	4	5	Grade ≥3 (%)
Pneumonitis	6	1	0	8.6
Empyema	4	2	0	7.4
Prolonged air leakage	4	0	0	4.9
Tracheal dehiscence	0	1	0	1.2
Chylothorax	1	0	0	1.2
Arrhythmia	1	0	0	1.2
Wound infection	0	1	0	1.2
Postoperative bleeding	0	0	1	1.2
Interstitial pneumonia	0	0	1	1.2

but within 90 days occurred in 1 patient (1.2%). The patient underwent right upper lobectomy combined with resection of carina and died 64 days after surgery due to interstitial pneumonia. One patient developed tracheal dehiscence after right wedge pneumonectomy combined with resection of the SVC, although the tracheal stump was buttressed using an intercostal muscle flap, and the patient was rescued by omentopexy. There were no significant differences in the mortality or morbidity rates of the patients who underwent lobectomy and pneumonectomy.

The therapeutic effect on the pathology was as follows: Ef3 (n=17; 21%), Ef2 (n=38; 47%), Ef1b (n=11; 14%), and Ef1a (n=15; 19%) (*Table 3*). Forty-three patients (51%) received adjuvant chemotherapy.

The median observation time was 37.2 months. The 5-year OS and RFS rates in all 81 surgically resected patients were 58.0% and 45.6%, respectively (*Figures 2,3*). The median survival time was 73.2 months. Among the 73 R0 patients, 26 developed recurrent disease during the follow-up period, and 21 of these 26 (81%) developed distant metastasis without loco-regional recurrence. Fourteen of the 17 patients with Ef3 were alive without recurrence, and 2 were alive with brain metastasis. The remaining patient was dead due to pneumonia at 9 months after surgery. Fifteen patients survived for more than 60 months after surgery.

In terms of the prognosis of clinical stage, cStage IIB (cT3N0) disease showed a better 5-year OS than cStage IIIA and IIIB disease (62.7% *vs.* 54.9% *vs.* 50.3%), but there were no significant differences (P=0.33). However, based
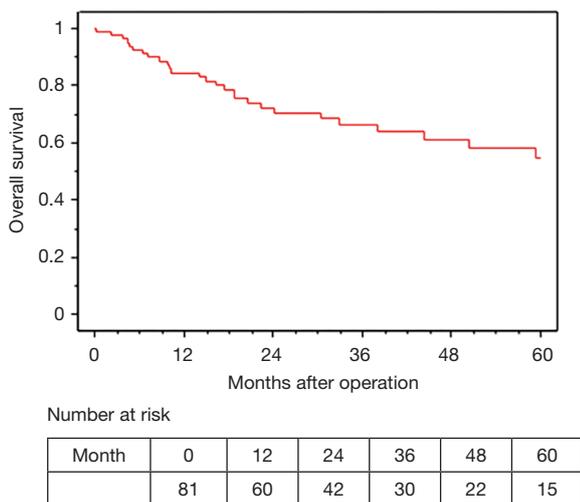
Figure 2 The overall survival of patients who underwent induction chemoradiotherapy followed by surgery.
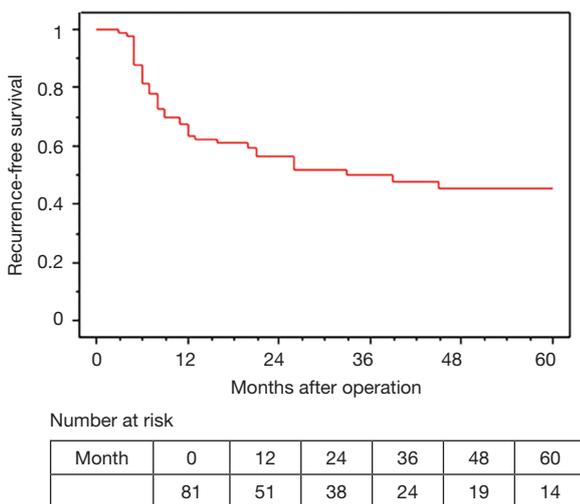
Month	0	12	24	36	48	60
	81	60	42	30	22	15

Figure 3 The recurrence-free survival of patients who underwent induction chemoradiotherapy followed by surgery.

Month	0	12	24	36	48	60
	81	51	38	24	19	14

Figure 4 The overall survival according to the response to induction chemoradiotherapy.

Month	0	12	24	36	48	60
CR + PR	47	37	29	23	18	11
SD	34	23	13	7	4	4
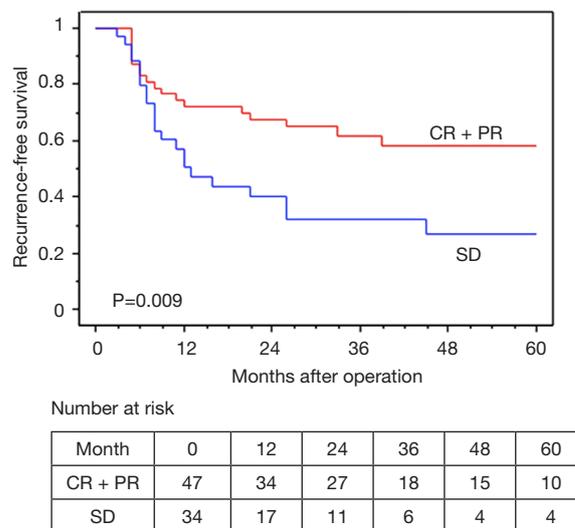
Figure 5 The recurrence-free survival according to the response to induction chemoradiotherapy.

Month	0	12	24	36	48	60
CR + PR	47	34	27	18	15	10
SD	34	17	11	6	4	4

on the response to the ICRT, patients with a CR or PR showed a better 5-year OS and RFS than those with SD (OS: 63.7% *vs.* 40.0%, P=0.020, RFS: 58.4% *vs.* 26.7%, P=0.009) (*Figures 4,5*). Furthermore, patients with Ef3 or Ef2 exhibited a much better 5-year OS and RFS than those with Ef1b or Ef1a (OS: 65.0% *vs.* 24.4%, P=0.005, RFS: 60.1% *vs.* 17.9%, P<0.001) (*Figures 6,7*). There was no marked difference in the survival between patients who underwent lobectomy and those who underwent pneumonectomy

(P=0.82). Patients who received adjuvant chemotherapy had a significantly better survival than those who did not receive adjuvant chemotherapy (72.2% *vs.* 36.7%, P=0.024).

Discussion

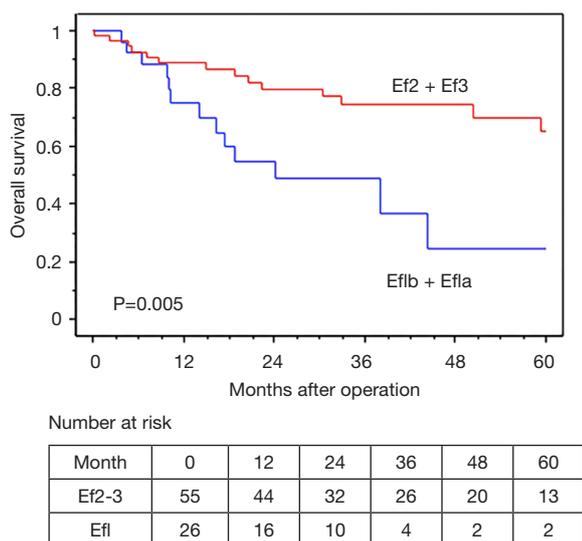The data presented in the present study suggested that

Month	0	12	24	36	48	60
Ef2-3	55	44	32	26	20	13
Efl	26	16	10	4	2	2

Figure 6 The overall survival according to the pathological response to induction chemoradiotherapy.

Month	0	12	24	36	48	60
Ef2-3	55	39	32	22	17	12
Efl	26	12	6	2	2	2
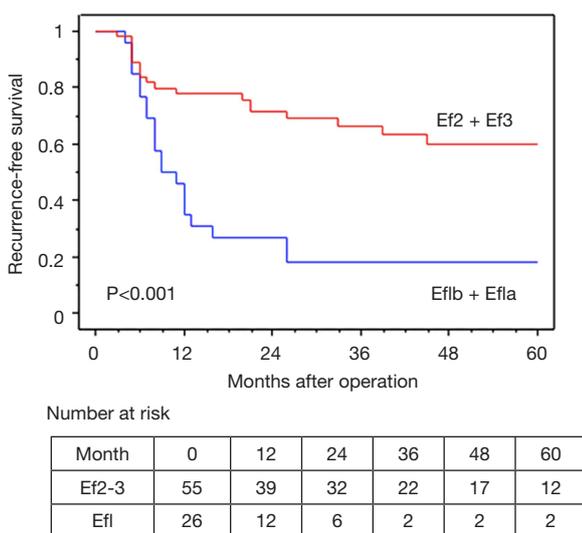
Figure 7 The recurrence-free survival according to the pathological response to induction chemoradiotherapy.

treatment with concurrent chemoradiotherapy followed by surgery might provide better local disease control and survival in patients with potentially resectable locally advanced NSCLC. Approximately half of the patients with resectable stage III (N2) NSCLC who received definitive chemoradiotherapy developed recurrence at a loco-regional site (18); thus, treatments that provide stronger local control, such as surgery, are necessary.

Invasive T3 or T4 locally advanced disease is associated with a risk of incomplete resection, especially when there is extensive invasion of important structures. Furthermore, many of these invasive T3 and T4 lung cancers have associated lymph node involvement. In this regard, the optimal treatment strategy for patients with potentially resectable locally advanced NSCLC is considered to be concurrent chemoradiotherapy followed by surgery. Some phase I and II studies demonstrated promising results for ICRT followed by surgery (18-24). However, some large-scale multi-institutional clinical trials comparing definitive chemoradiotherapy to ICRT followed by surgery for Stage III patients showed that adding surgery had no benefit (25,26). Albain *et al.* reported that the OS of patients who received ICRT with or without surgery did not differ to a statistically significant extent (INT0139) (25). However, the subset of patients who underwent lobectomy without pneumonectomy showed a significantly better survival in that trial. Furthermore, in their resected pT0N0 patients, an excellent median survival of 39.8 months was observed. Eberhardt *et al.* reported that patients who received ICRT followed by surgery tended to have a better survival than those who received definitive chemoradiotherapy (44% *vs.* 40%) (ESPATURE study) (26).

In terms of resectable invasive T3 NSCLC involving the chest wall, most thoracic surgeons recommend primary surgery followed by adjuvant therapy. However, the 5-year OS of those patients, even with N0 disease, has remained at 40–50% in the few previous studies (5,6). Therefore, induction therapy may be needed in order to improve their survival as well as that of stage III NSCLC. In their prospective study, Kawaguchi *et al.* showed that ICRT followed by surgery for patients with T3N0-1 NSCLC involving the chest wall was safe and effective, with a 5-year OS of 62.6% (27). In our study, the 5-year OS of the patients with T3N0-1 NSCLC involving the chest wall (n=23) reached 64.2%, which was better than the values reported in previous studies (5,6).

Our results demonstrated that a pathological response to ICRT was an important prognostic factor in the management of locally advanced NSCLC. When a good pathological response (Ef2 or Ef3) was achieved, a good prognosis could be expected. In various studies, a good pathological response determined a favorable survival and was associated with lower rates of local and distant recurrence as well as a favorable progression-free survival (28,29). Local tumor control and downstaging resulting in a tumor response and mediastinal lymph node clearance are

potential surrogate endpoints for better patient outcomes. Achieving a good pathological response with ICRT is very important for improving the prognosis of patients with locally advanced NSCLC. In the present study, 17 (21%) patients achieved Ef3, which seems like a higher rate than in previous studies (25,30). The Ef3 rate of the patients receiving 50 Gy of radiation was higher than in those receiving 40 Gy of radiation (24.0% *vs.* 17.6%). Therefore, higher-dose radiotherapy with concurrent chemotherapy may provide a greater pathologic effect. In terms of tumor histology, a significantly higher percentage of patients with squamous cell carcinoma had Ef2 or Ef3 than those with non-squamous cell carcinoma (85.1% *vs.* 59.3%, P=0.018). Similar results have been reported previously (12). The mechanism underlying this result is unclear, however, and further investigation is required.

The surgical treatment of patients with locally advanced lung cancer remains a challenge. Chemoradiotherapy before surgery has been associated with a higher risk of intraoperative and postoperative complications. In a previous study, the incidence of surgical mortality after ICRT was reported to be high (15,18-20). However, the mortality rate in our study (1.2%) was lower than in previous studies. Recent studies have also reported low mortality rates; therefore, ICRT followed by surgery is thought to be feasible (13,14,30-32). In the INT0139 study, the patients who underwent pneumonectomy showed higher rates of surgical mortality (26%) and a worse prognosis than those who underwent lobectomy. However, Weder *et al.* reported that the 90-day mortality rate of 176 patients who underwent induction chemotherapy or chemoradiotherapy followed by pneumonectomy was only 3% in a retrospective evaluation of medical records at two specialized centers (33). Similarly, the mortality/morbidity and survival rates of the patients who underwent pneumonectomy and lobectomy in our study did not differ to a statistically significant extent. While pneumonectomy should be avoided by performing tracheobronchoplasty and/or arterioplasty whenever possible, pneumonectomy after ICRT is thought to be a valuable treatment option for achieving complete resection.

The present study was associated with several limitations. First, this study was retrospective in nature and lacked randomization. Second, the study population was relatively small. The fact that this was performed in a single institution may limit the generalizability of the findings. Finally, the study period was long, and various chemotherapy regimens were administered. We are currently performing a single-institutional phase II study of ICRT followed by surgery for

patients with stage III NSCLC.

In conclusion, our results suggested that a favorable prognosis can be expected when CR/PR or Ef2/Ef3 is achieved by ICRT. ICRT significantly improved the survival of patients with locally advanced lung cancer. In experienced centers, surgery after ICRT can be safely performed without significant mortality.

Acknowledgments

Footnote

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