Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer

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Objective: To improve the prognosis of cN2, N3 non-small cell lung cancer, we performed induction chemoradiotherapy (carboplatin-taxane chemotherapy and concurrent 50-Gy radiation) followed by surgery.

Methods: Patients with pathologically proven non-small cell lung cancer with bulky cN2, N3 disease were enrolled. Forty-one patients underwent an operation after chemoradiotherapy from January 2000 to April 2006. Either carboplatin-paclitaxel ($n = 19$) or carboplatin-docetaxel ($n = 22$) chemotherapy was randomly used. Two cycles of chemotherapy were performed with concurrent radiation (50 Gy). In all cases, conventional radiological reevaluations were performed; in the latest 21 cases, reevaluations with positron-emission tomography with fludeoxyglucose F 18 were also performed.

Results: In all 41 cases, complete resections were performed, with no operative mortality. The histologically complete response rate, major response rate, and minor response rate were 17.1% (7/41), 56.1% (23/41), and 26.8% (11/41), respectively. The 5-year overall survival was 52.7%. There were no differences in survival between taxane groups. Both the complete response and the major response groups revealed a significantly better 5-year survivals than the minor response group (85.7%, $P = .044$, 52.4%, $P = .01$). Even with persistent N2 disease, the 5-year survival in the major response group (66%) was promising. With the combination of conventional computed tomography and positron-emission tomography with fludeoxyglucose F 18 for reevaluation, eligible patients could be selected for this protocol.

Conclusion: Surgery after chemoradiotherapy (carboplatin-taxane and 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer can be safely performed with promising results. Even with persistent N2 disease, the survival in the major response group was promising.

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The treatment of patients with bulky cN2, N3 non-small cell lung cancer (NSCLC) remains controversial and challenging. At present, few patients with bulky N2, N3 disease undergo surgery before induction therapy. Several studies have suggested that preoperative chemotherapy^{1,2} or chemoradiotherapy³⁻⁶ can improve the survival of patients with such N2 NSCLC. The optimal protocol for chemotherapy or the recommended radiation dose, however, is still undefined. Cisplatin-etoposide (EP) therapy has commonly been used for the induction therapy

Abbreviations and Acronyms

CT	= computed tomography
CD	= carboplatin-docetaxel
CP	= carboplatin-paclitaxel
EP	= cisplatin-etoposide
FDG-PET	= positron emission tomography with fludeoxyglucose F 18
NSCLC	= non-small cell lung cancer
SUV	= standardized uptake value

of advanced NSCLC.^{3,4} A recent study reported that carboplatin-paclitaxel (CP) therapy demonstrated an equivalent survival to EP therapy but with an overall benefit in morbidity and quality of life.^{7,8} Regarding taxane, the selection of paclitaxel or docetaxel is still undetermined.⁹ Concerning the radiation dose, the most commonly used dose for induction therapy may be 40 to 45 Gy.³⁻⁶ Recent studies have reported that high-dose radiation promotes a high pathologically complete response rate with a favorable survival.¹⁰

The accurate selection of optimal candidates for surgery after induction chemoradiotherapy is therefore extremely important. Recently, a pathologically complete response and pN0 have been reported to be accurate predictors of a better outcome.^{3,11} In this study, we attempted to evaluate the efficacy of each taxane with a moderately high radiation

dose (50 Gy) in induction chemoradiotherapy for bulky-N2, N3 NSCLC to determine useful predictors of better survival.

Patients and Methods

This prospective, randomized trial was carried out on selected patients with bulky cN2, N3 NSCLC from January 2000 to April 2006. This study was approved by the institutional review board of the Kagawa University. The patient eligibility criteria were established as follows: (1) The patient had pathologically proven NSCLC. (2) There was no previous therapy. (3) Performance status was 0 to 2. (4) Patient was younger than 75 years. (5) Mediastinal lymph nodes were seen with a short-axis diameter more than 2 cm on chest computed tomography (CT), considered to be bulky cN2 metastasis. The CT findings of representative cases are shown in Figure 1. Although mediastinoscopy may be the standard criterion for an evaluation of N2 disease,^{12,13} we did not routinely perform it. Because most of our cases were suspected of having invasive and extranodal expansion, a safe biopsy without any complications appeared to be a debatable procedure. Furthermore, because the sensitivity of mediastinoscopy is reported to be around 80%,^{12,13} 20% of the patients with possible N2 disease can lose the chance to receive potentially valuable treatment. (6) No distant metastasis were revealed by chest CT, abdominal CT, brain CT or magnetic resonance imaging, and bone scan. Positron emission tomography with fludeoxyglucose F 18 (FDG-PET) was introduced in our institution in June 2004; since then, the assessment of distant metastasis has been done by FDG-PET. (7) The patient was able to tolerate chemoradiotherapy in terms of complete blood count, chemistry profile, and creatinine clearance. (8)

Figure 1. Representative computed tomographic findings of bulky cN2 mediastinal lymph nodes.

Cardiac function was normal. Normal cardiac function includes normal single and master-double electrocardiograms and ejection fraction greater than 50%. (9) The predicted postoperative forced expiratory volume in 1 second was more than 800 mL. (10) The patient's informed consent had been obtained.

Therapeutic Schedule

Chemotherapy was conducted during week 1, and concurrent radiotherapy with 30 Gy (2 Gy/d, 5 d/wk) was conducted during weeks 1, 2, and 3. After a 1-week withdrawal period, chemotherapy was carried out during week 5, and concurrent radiotherapy with 20 Gy was carried out during weeks 5 and 6. The therapies were discontinued for 1 to 4 weeks, depending on patient condition, and a reevaluation was carried out on the basis of chest CT, abdominal CT, brain CT or magnetic resonance imaging, and bone scan 2 to 3 weeks after the end of radiation therapy. The latest 21 patients were also evaluated preoperatively by FDG-PET and then reevaluated after induction therapy. A routine reevaluation was done according to the criteria of response evaluation criteria in solid tumors.^{14,15} A complete resolution of all targets was defined as complete response, and at least a 30% reduction (quantified as the longest diameter) in the tumor size was defined as partial response. A reevaluation by FDG-PET was done under the recently recommended criteria.^{16,17} The images were evaluated both qualitatively and quantitatively. The qualitative evaluations before and after induction therapy were done by a visual inspection. The intensity of FDG accumulation after induction therapy lower than mediastinal structures was classified as a better response and a greater accumulation was classified as a poor response. A quantitative evaluation was done according to the standardized uptake value (SUV) decreasing rate. A SUV decreasing rate of more than 70% after induction therapy was classified as a better response and less than 70% as a poor response. Both the visual inspection and SUV decreasing rate were used as a reevaluation index, and double-positive cases were defined as good responses in the FDG-PET study. A reference SUV may be variable even in the same patient, especially in different patients. We therefore performed a qualitative evaluation by visual inspection to compensate for the weakness of a reference SUV. Regarding the SUV decreasing rate, our radiologists report that the average of the decreasing rate in responders after induction therapy (74.1 ± 10.1) is significantly higher than in nonresponders (55.5 ± 14.8 , $P = .003$).¹⁷ As a result, we used the 70% threshold.

After reevaluation, operations were performed on all patients except those with progressive disease. In all cases, bronchial stumps were covered with intercostal muscle after a pneumonectomy or with a pericardial fat pad after a lobectomy. One thoracic surgeon (Yokomise H) performed all the operations.

Chemotherapy

The patients were randomly assigned to a CP arm or a carboplatin-docetaxel (CD) arm. The patients in the CP arm received carboplatin (area under the curve 6 mg/[mL · min], 30-minute intravenous infusion) on day 1 and paclitaxel (180 mg/m², 3-hour intravenous infusion) on day 1. Premedication for the prevention of hypersensitivity reactions included dexamethasone, diphenhydramine, and cimetidine. Patients in the CD arm received carboplatin (area under the curve 6 mg/[mL · min], 30-minute intra-

venous infusion) on day 1 and docetaxel (60 mg/m², 3-hour intravenous infusion) on day 1.

Radiotherapy

An area including the hilum of the lung and mediastinum with a 1.5-cm margin from the periphery of the primary lesion was irradiated with 2 Gy/d. In the patients with cervical N3 disease, the supraclavicular area was also irradiated. The patients received irradiation 5 times weekly, with 2 nonirradiation days set up.

Statistical Analysis

Statistical analysis of the data was carried out with the StatView 4.5J program (SAS Institute, Inc, Cary, NC). The survival curves were estimated by the method of Kaplan and Meier.¹⁸ The differences in the groups were evaluated with the log-rank test.

Results

From January 2000 to April 2006, a total of 41 patients were enrolled: 19 patients in the CP arm and 22 patients in the CD arm. The characteristics of the patients are shown in Table 1. The median age was 61.9 years (37-75 years). The group comprised 35 men and 6 women. Thirty-one patients had stage IIIA disease, and 10 had stage IIIB disease. Four had right ipsilateral cervical N3, and all N3 cases were diagnosed by aspiration cytologic examination. The cN2 statuses are shown in Table 1. Thirty patients had single-station N2 disease and 11 had multistation N2 disease. In addition, 21 had squamous cell carcinoma, 19 had adenocarcinoma, and 1 had large cell carcinoma.

All 41 patients completed the protocol. Induction therapy was generally well tolerated, and no serious complications or deaths related to induction therapy occurred. The grade 4 side effects observed were limited to granulocytopenia in 11 patients (26.8%); thrombocytopenia was seen in 0, renal dysfunction in 0, and abdominal symptoms in 0. Six patients had radiation pneumonitis (Radiation Therapy Oncology Group grade 3-4),¹⁹ and all recovered from it with the administration of corticosteroids. The details of morbidity during induction therapy and after operation are shown in Table 2.

The overall response rate of conventional reevaluation was 78% (4 cases of complete response and 28 cases of partial response), and stable disease was identified in 9 cases. A good response on FDG-PET was observed in 75% of cases. Because there was no progressive disease, surgery was performed in all 41 patients according to the protocol. In all cases, a complete resection could be done. Lobectomies or bilobectomies were performed in 28 patients; pneumonectomies were performed in 13 patients. In 4 patients with N3 disease (ipsilateral cervical node involvement), an additional cervical lymph node dissection was performed. The pathologic effect of induction therapy was evaluated according to *General Rule for Clinical and Pathological Record of Lung Cancer*, 6th edition.²⁰ A pathologically

TABLE 1. Patient characteristics

No. of patients	41
Age (y, median and range)	61.9 (37–75)
Sex (No.)	
Male	35
Female	6
Histologic type (No.)	
Squamous cell carcinoma	21
Adenocarcinoma	19
Large cell carcinoma	1
TNM staging (No.)	
IIIB	
T4 N3 M0	1 (T4: vertebra; N3: ipsilateral cervical)
T4 N2 M0	6 (T4: vertebra, 2; PA: 2; carina: 1; PM1: 1)
T2 N3 M0	3 (ipsilateral cervical N3: 3)
IIIA	
T3 N2 M0	4
T2 N2 M0	15
T1 N2 M0	12
Origin (No.)	
Right upper lobe	16
Left upper lobe	9
Right lower lobe	9
Left lower lobe	5
Right middle lobe	2
cN2 status (No.)	
Single nodal station	
#4	17
#7	7
#5	5
#3	1
Multiple nodal stations	
#4 and #7	5
#4 and #5	2
#2 and #7, #5 and #7, #3 and #5, #1-#4	1
Operation performed (No.)	
Lobectomy, bilobectomy	28
Pneumonectomy	13
Right	9
Left	4
Complex operation (No.)	
Combined resection of azygos vein	3
Vertebral body and rib resection	2
Combined resection of superior vena cava	1

PA, Pulmonary artery; PM1, metastasis to the same lobe as the primary tumor.

complete response (complete cancer cell death) was achieved in 7 cases (17.1%). A major response (fewer than one third of cancer cells viable) was achieved in 23 cases (56.1%). A minor response (more than two thirds cancer cells viable)

was observed in 11 cases (26.8%). All patients with N3 had right side cases, and 3 of 4 cases of cervical N3 achieved downstaging (2 to N2 and 1 to N0). There was no mortality or major morbidity after surgery. No bronchial fistula was seen after either lobectomy or pneumonectomy.

The median observation time was 2.63 years. The 5-year overall survival was 52.7% (Figure 2). No significant difference in survival was observed between the CP group and the CD group ($P = .92$; Figure 3). Six of the 7 patients with pathologically complete response are still alive. One died of a stroke 3 months after the operation. Fourteen of 23 patients with a major response are alive. Six of 11 patients with a minor response died early, and there were no cases of long-term survival (Figure 4). The 5-year survivals for pathologically complete response, major effect, and minor effect were 85.7%, 52.4%, and 0%, respectively. Both the complete response group and the major response group revealed significantly better 5-year survivals than the minor response group ($P = .044$ and $P = .01$). Twenty-four of 41 patients had persistent pN2 diseases (58.5%) after surgery. Seven had residual pN1 diseases, and 10 had pN0. The pathologic response after induction therapy was identical to that reported previously.^{3,21} We did not perform mediastinoscopy to evaluate N2 disease for the reasons mentioned previously, and our cases thus may have included some false-positive N2 (actually N0 or N1) disease. We identified 24 definitive pN2 cases after surgery. The overall 5-year survival of these 24 cases was 48%. Among them, the 14 in the major pathologic response group had a 5-year survival of 66%. On the other hand, the 10 in the minor response group showed an extremely poor survival. A significant difference was seen between these two groups ($P = .0003$; Figure 5). Among the pN2 cases, good responses for both conventional and FDG-PET reevaluation were seen in 8 patients, all with a major response. The impact of multistation cN2 was evaluated. The survival of patients with multistation cN2 (2-year survival 15%) was significantly poorer than that of patients with single-station cN2 (5-year survival 64%, $P = .0001$). Two of 4 patients with ipsilateral right N3 have been alive for more than 5 years. There was no difference in overall survival between patients with lobectomies and pneumonectomies. For both operative modalities, no major morbidity or mortality was observed.

Discussion

As chemoradiotherapy became the standard treatment for advanced nonresectable stage IIIA and IIIB NSCLC,²²⁻²⁴ several multidisciplinary treatments were tried for potentially resectable diseases.³⁻⁵ Recently, a large clinical trial (Intergroup protocol 0139) finished, and both the short-term and long-term results have been reported.^{11,25} Albain and colleagues^{11,25} reported the 5-year survival for patients un-

TABLE 2. Morbidity during induction therapy and operation with maximum toxicities during concurrent chemoradiation

	Grade of toxicity					Affected
	0	1	2	3	4	
Toxicity						
Leukopenia	1 (2%)	1 (2%)	7 (17%)	26 (63%)	6 (15%)	
Granulocytopenia	1 (2%)	1 (2%)	9 (22%)	19 (46%)	11 (27%)	
Thrombocytopenia	30 (73%)	5 (12%)	4 (10%)	2 (5%)	0 (0%)	
Anemia	16 (39%)	16 (39%)	7 (17%)	2 (5%)	0 (0%)	
Gastrointestinal tract	19 (46%)	11 (27%)	9 (22%)	2 (5%)	0 (0%)	
Vomiting	31 (76%)	5 (12%)	5 (12%)	0 (0%)	0 (0%)	
Renal dysfunction	34 (83%)	3 (7%)	2 (5%)	2 (5%)	0 (0%)	
Radiation pneumonitis RTOG grade 3-4						6 (15%)
Sepsis						1 (2%)
Bronchial fistula						0 (0%)

All data represent numbers and percentages of patients. *RTOG*, Radiation Therapy Oncology Group.

dergoing surgery after EP chemotherapy and 45-Gy radiation to be 27%, with pN0 predicting better survival.

Our study reveals that induction chemoradiotherapy followed by a complete surgical resection for advanced bulky cN2, N3 NSCLC can be performed with an acceptable morbidity and a promising survival. Our multidisciplinary treatments consist of taxane (paclitaxel or docetaxel) and carboplatin chemotherapy, concurrent 50-Gy radiation, and surgery. Recent studies report that the effect of taxane-carboplatin chemotherapy is equivalent to that of the EP regimen, which has been the criterion standard for chemoradiotherapy for advanced NSCLC.^{7,8} Furthermore, lower toxicity has been reported for taxane-carboplatin therapy relative to EP therapy.⁷ In our study, grade 4 toxicities occurred at a relatively low rate. Other grade 3 toxicities were commonly seen, but no particular treatments were required. As a result, the quality of life of the patients was maintained during our treatment. No severe perioperative

adverse events were documented. The side effects were equivalent for paclitaxel and docetaxel.

The most commonly used dose of radiation for induction therapy may be 40 to 45 Gy.³⁻⁶ Recent studies report that high-dose radiation may result in a high pathologically complete response rate with a favorable survival.¹⁰ Some of our patients seemed to require radiation before surgery, and high morbidity and mortality rates after pneumonectomy have been reported for chemoradiotherapy with 60-Gy concurrent radiation.²⁶ For these reasons, we selected 50 Gy as the concurrent radiation dose. In all 41 cases, definitive surgery (lobectomy and pneumonectomy) could be performed after concurrent 50-Gy chemoradiation with acceptable morbidity and no mortality. No bronchial stump fistulas occurred after surgery. The reinforcement of the bronchial stump with a muscular flap or pericardial fat pad may have contributed to these positive results.

Figure 2. Overall survival for all 41 cases.

Figure 3. Overall survival according to chemotherapy protocol. TXL, Paclitaxel; TXT, docetaxel.

Figure 4. Overall survival according to pathologic response.

The overall survival of the patients remains promising. The pathologically complete response rate is identical to those previously reported for studies in which pN2 was proved by mediastinoscopy.^{3,6} The survival for the complete response group is also encouraging. In most studies of induction therapy for cN2 NSCLC, mediastinoscopy has been applied for the confirmation of mediastinal nodes as a criterion standard.^{4,6,25} For commonly accepted cN2 with a short-axis diameter of 1 to 2 cm on chest CT, we usually perform mediastinoscopy. For previously mentioned reasons, however, we do not perform mediastinoscopy on candidates for this multidisciplinary therapy. Our bulky N2 disease was far advanced, and it appeared to be invasive with extranodal expansion. The morbidity and mortality of mediastinoscopy are low and acceptable.^{12,13} Our policy stresses that preoperative screening must be safe, without any morbidity or mortality. Furthermore, possible candidates for this therapy may also lose the chance to receive potentially valuable alternative treatments for these highly morbid diseases.

Indeed, N0 or N1 disease could have been included in our study because of the omission of mediastinoscopy; however, 24 patients (58.5%) had residual N2 disease after induction therapy. For such a small number of patients, the overall survival of this category is encouraging. In the major response group with residual N2 disease, the survival was superior to that reported before for those with N1 disease.²⁷ On the other hand, the survival of the minor response group was extremely poor.

In the Intergroup 0139 study,^{11,25} the treatment-related death rate after pneumonectomy was extremely high (25.9%, 14/52). Albain and colleagues^{11,25} concluded that their approach might not be optimal if a pneumonectomy was needed. A pneumonectomy may, however, be inevitable for those with advanced N2 disease. In our study, survivals were identical for patients who underwent lobectomy and those who underwent pneumonectomy.

Figure 5. Overall survival of patients with persistent pN2 disease according to pathologic response.

The selection of optimal candidates for surgery after induction chemoradiotherapy is considered to be extremely important. Recently, a pathologically complete response and pN0 have been reported to be accurate predictors of better outcome.^{3,11} Tremendous efforts, including remediastinoscopy, have been tried.¹² The pathologically complete response group, however, may comprise only 10% to 20% of all patients who receive induction therapy. Grunewald and Albain suggest that surgery is an efficient salvage treatment for patients with N3 NSCLC with viable residual disease after chemoradiotherapy.^{9,28} Our series may be akin to N3 disease. We showed that the status of the mediastinal nodes as major pathologic response versus minor response might be good a predictor of a better survival. The experience of our N3 series is limited, but 2 of 4 patients have been alive more than 5 years. Considering the surgical procedure, the patient with right ipsilateral N3 disease may be a good candidate for our induction therapy. In our study, the patients with pN2 disease who showed major pathologic response had a promising 5-year survival (66%). In addition, with the combination of a conventional CT study and FDG-PET study, we may have selected optimal surgical candidates after induction therapy without invasive procedures. Both the visual and the functional reevaluations may therefore be effective. It may be difficult to demonstrate the grade of the pathologic response of mediastinal nodes by remediastinoscopy. The survival of patients with multistation cN2 was extremely poor. That subset may thus not be candidates for this induction therapy.

In conclusion, surgery after induction therapy (taxane and carboplatin with 50-Gy radiation) for bulky cN2, N3 NSCLC could be performed with both an acceptable morbidity and promising results. Even with residual N2 disease, the survival was favorable in the major response group. To

predict better survival after induction therapy, the combination of conventional CT and FDG-PET reevaluations is useful.

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