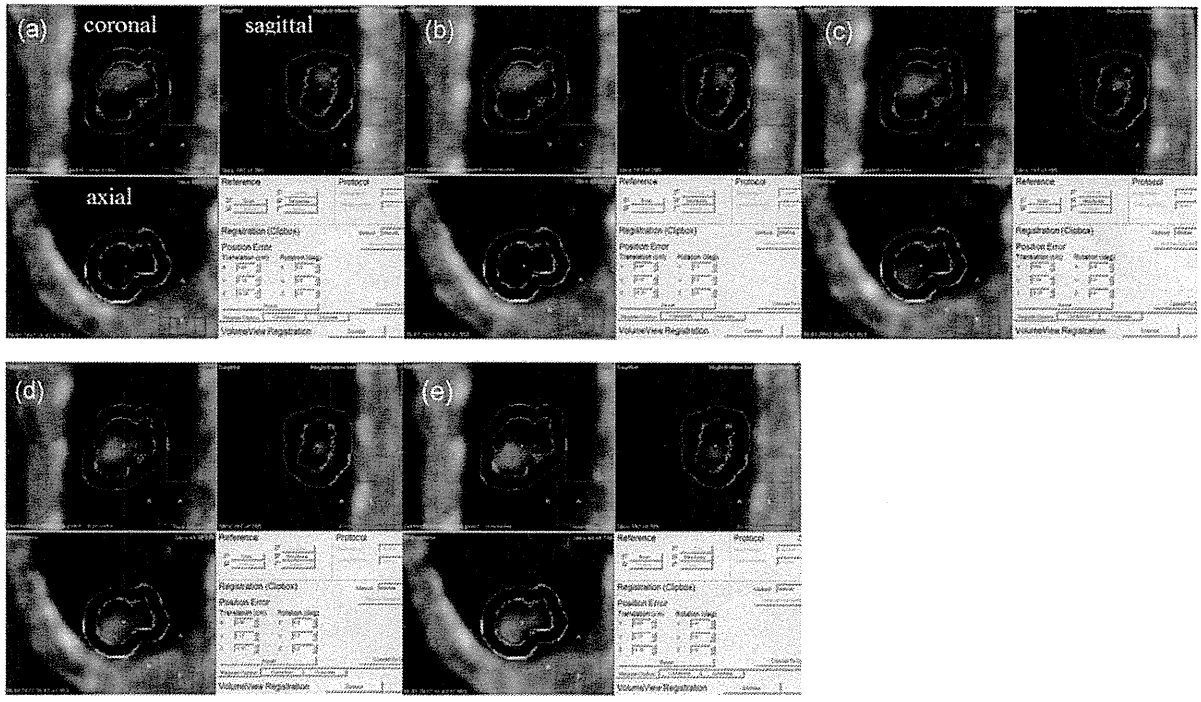

Fig. 1. 4D CBCT images on the first day overlaid with PTV (in sky blue) and ITV (in yellow) contours after lung tumor registration for five consecutive respiratory phases covering half a breathing cycle, where the tumor moves from cranial to caudal direction during the half cycle. After confirmation of the registration results on the display monitor, stereotactic VMAT is ready to run.

delivery time was 210 s. For the in-treatment CBCT, the number of phase bins was four, which covered an entire breathing cycle. It was confirmed that during the VMAT delivery on the first day the moving tumor was also located inside the PTV. Similar satisfactory results were obtained on the other three days.

DISCUSSION

It is assumed that the lung tumor has a periodic motion. This assumption is most likely valid if the beam delivery time is short. It is known that VMAT delivery is faster than any other intensity-modulated treatment. In addition, in-treatment CBCT can be acquired during VMAT delivery for 4D tumor position verification. Thus, VMAT may be a logical choice for lung tumor treatment. The CBCT images in Fig. 2 a–d show some blurring, possibly due to the smaller number of phase bins, which may be improved by providing 10-phase in-treatment 4D CBCT datasets. A limitation of this technique would be that the amplitude of tumor motion may not be sufficiently reduced by abdominal compression in the case of some tumors having a large breathing motion, possibly leading to a prohibitively large ITV volume. The measured respiratory movement in this study was relatively large and could have been reduced by increasing the compression of the plate to the abdominal surface. Whereas the dose calculation in this study was based on maximum exhalation phase CT images, the authors are currently updating their procedure using mid-ventilation CT data.

CONCLUSION

We have proposed a clinical workflow of stereotactic lung VMAT capable of 4D registration and 4D verification of the tumor position, and initial promising results have been obtained. The authors believe that the proposed 4D workflow for stereotactic lung VMAT is valid for respiratory motion management because the VMAT delivery is sufficiently fast to maintain respiratory periodicity, but much longer than the patient breathing cycle for obtaining 4D CBCT. Our lung VMAT delivery employs a sequence with a maximum leaf speed of 1 mm/degree [10], and therefore it is anticipated that doubling the dose rate using flattening filter free techniques [12], combined with doubled leaf speeds, may reduce the treatment time down to an order of 100 seconds for delivering a prescribed dose of 50 Gy in four fractions.

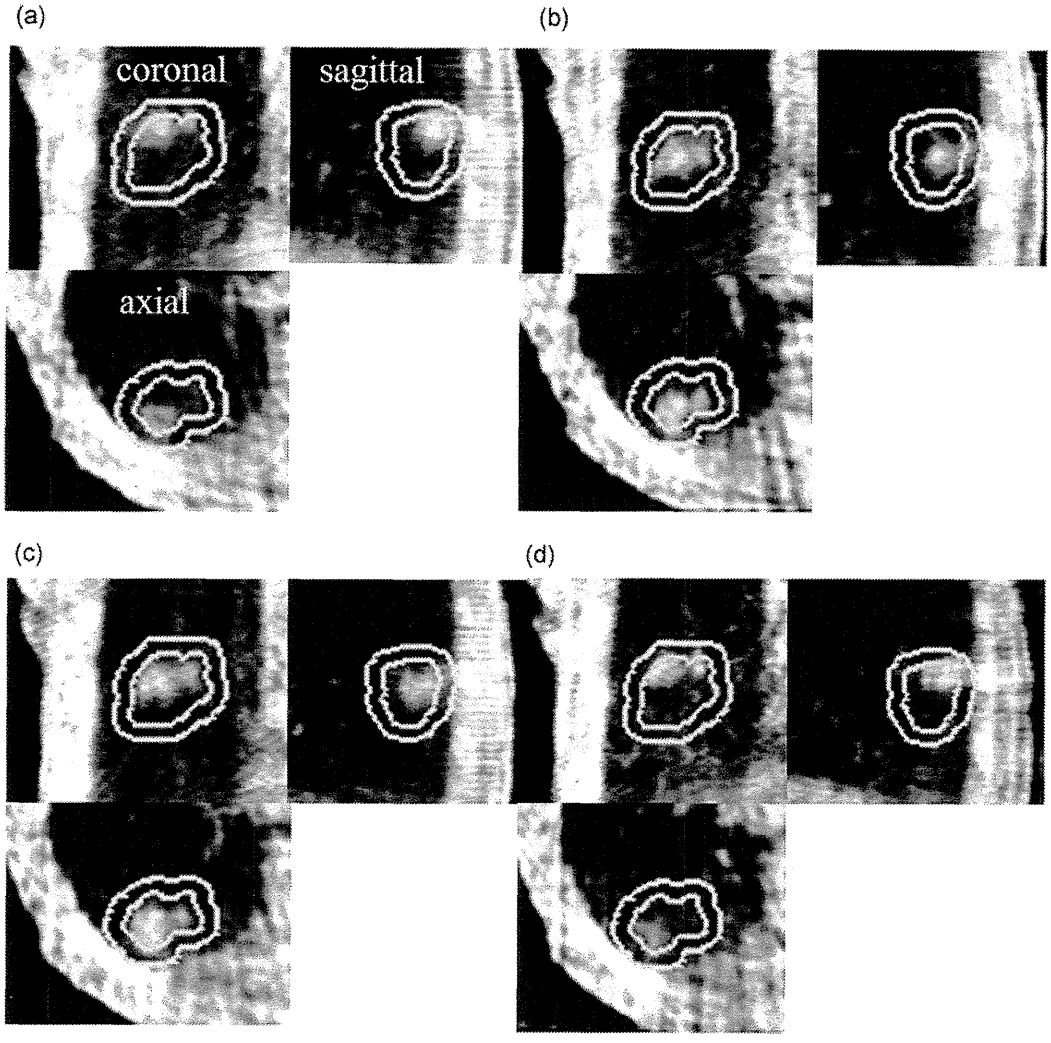

Fig. 2. 4D CBCT images acquired during VMAT delivery on the first day to verify the in-treatment moving tumor position in reference to the PTV and ITV contours. In this case, the number of phase bins was four, which covered an entire breathing cycle.

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ORIGINAL ARTICLE

Pathological response and prognosis of stage III non-small cell lung cancer patients treated with induction chemoradiation

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Abstract

Aim: The aim of this study was to clarify the relationship between pathological effects and the prognosis of patients with stage III non-small cell lung cancer (NSCLC) treated with induction chemoradiation.

Methods: Patients who were untreated and potentially resectable with stage III NSCLC were enrolled. They received carboplatin and docetaxel with concurrent radiotherapy (5 × 2 Gy/week with a total dose of 40 Gy) followed by surgery. We assessed the relationship between the pathological effect (Ef) (Ef 1: slight pathological response, Ef 2: moderate pathological response, Ef 3: complete pathological response) and prognosis.

Results: In all, 30 patients with stage III NSCLC (24 men and 6 women, mean age 60.7 years, 17 with adenocarcinomas and 13 with squamous cell carcinomas, 21 with clinical stage IIIA and nine with stage IIIB) participated in the trial and underwent induction chemoradiation. A total of 27 patients (90%) with complete response, partial response and stable disease had surgical resection. The pathological effect was Ef 1 and Ef 2 in 10 patients each, and Ef 3 in seven patients. Median survival was 10.9 months in patients with Ef 1 and 49.6 months in patients with Ef 2. Six out of seven Ef 3 patients are alive at the time of writing with a mean survival of 77.1 months (14–104 months). There was a significant difference in overall survival based on pathological effect rating ($P = 0.0036$).

Conclusion: The Ef rating was well correlated with prognosis after induction chemoradiation.

Key words: carboplatin, chemoradiotherapy, docetaxel, induction chemoradiation, non-small cell lung cancer, pathological effect.

INTRODUCTION

Stage III non-small cell lung cancer (NSCLC) is associated with poor long-term survival; the 5-year survival rates being less than 25%.[1] Category T4 and N2-3 NSCLC encompass a heterogeneous subgroup. A single modality treatment resulted in low resectability and poor long-term survival.[1,2] According to National Comprehensive Cancer Network guidelines for NSCLC, definitive concurrent chemoradiation is recommended for stage III NSCLC disease (category 1). Although classified as category 2B, induction chemoradiation has demonstrated high resectability and better long-term survival.[3–6] Recently, induction chemotherapy with third generation regimens has shown response rates of over

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60% and 5-year survival rates of more than 30%.[7,8] The response rate and 3-year survival rate after induction chemoradiation with platinum-based chemotherapy regimen in stage III containing T4 and N2-3 were 59–73 and 22–24%, respectively.[4–6] Stupp *et al.* reported that 3 and 5-year survival rates were 67 and 40%, respectively, in a phase II trial with cisplatin (CDDP) plus docetaxel (DOC) and concurrent radiotherapy in stage IIIB (T4 or N3) NSCLC.[3] One of the important prognostic factors associated with prolonged survival time was a pathological response in the mediastinal lymph node and in the tumor.[7,9–15]

The present study was undertaken in order to assess the relationship between survival and pathological effect (Ef) 1–3 in stage III NSCLC.

METHODS

Prior to their participation in the study, patients were examined to ensure that they met the following criteria. The criteria for selecting induction chemoradiation were histologically or cytologically confirmed NSCLC with clinical stage IIIA or IIIB (without bulky mediastinal lymph node or pleural effusion, or pulmonary metastasis in same lobe), age (≤75), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, measurable and evaluable lesions, and adequate cardiac, pulmonary, hepatic, renal and bone marrow functions. They had not received chemotherapy and radiotherapy previously. Informed consent was obtained from all patients. Patients who had interstitial lung disease, severe infections, uncontrollable comorbidities and concurrent malignancies were excluded. Based on above criteria patients were selected by more than two thoracic radiotherapists, two thoracic oncologists or two pulmosurgeons on our institution's cancer board. Eligible patients received two cycles of carboplatin (CBDCA) (area under the curve 6) and 60 mg/m^2 DOC i.v. during one month, and concurrent radiotherapy (5 × 2 Gy/week with total dose of 40 Gy).

We assessed the relationship between the clinicopathological effect after induction chemotherapy and prognosis. Initial staging and re-staging after induction chemoradiation were based on the 6th edition TNM classification.[16] Down-staging and clinical response were defined by response evaluation criteria solid tumor (RECIST, version 1.1).

We categorized the pathological response according to the criterion of the 6th edition of the "General Rules of Clinical and Pathological Records of Lung Cancer" in Japan, as follows;[17] Ef 0: no pathological response (no pathological changes in the cancer cells in the resected specimen); Ef 1: slight pathological response (viable cancer cells remained in over one-third in the resected specimen); Ef 2: moderate pathological response (viable cancer cells remained in one-third in the resected specimen) and Ef 3: complete pathological response (there were no viable cancer cells in the resected specimen). The pathological response of induction therapy was reviewed by more than two surgical pathologists who made the final diagnostic decisions in consultation with each other.

We analyzed overall survival (OS) and recurrence-free survival (RFS) using a log–rank test, including age (<65 years *vs* ≥65 years), gender (male *vs* female), ECOG PS (0 *vs* 1), histopathological classification (adenocarcinoma *vs* squamous cell carcinoma), number of positive nodal stations (cN2-3 *vs* cN0-1), T stage (cT4 *vs* non-cT4), clinical response (CR *vs* PR *vs* SD), down-staging (positive *vs* negative), resectability (complete *vs* incomplete resection), Ef in the lymph node (pN0 *vs* pN1-2) and primary site (Ef 1 *vs* Ef 2 *vs* Ef 3). Analyses were done with SPSS (SPSS for Windows, version 12.0, SPSS, Tokyo, Japan). The primary endpoint of this prospective study was feasibility. The secondary end-points were to evaluate resectability, response rate, Ef 1–3, RFS, OS and treatment-related toxicity. The aim was to obtain a resectability 55% with this regimen and a resectability of 30% was set as the lowest level of interest. A sample size of 30 eligible patients was calculated to be necessary with an α-value of 5% and a power of 80% using Simon's minimax design. This study was approved by the Ethics Committee of Toho University Omori Medical Center (No. 17–91).

RESULTS

Between April 2001 and March 2010, 30 patients participated in this trial. The patient characteristics are shown in Table 1. There were 24 men and 6 women with a mean age of 60.7 years (range, 56–75). All 30 patients had ECOG PS 0–1. The histopathological classification of lung cancer was an adenocarcinoma in 17 patients (56.6%) and squamous cell carcinoma in 13 (43.4%). At the initial staging, 21 patients (70%) were in stage IIIA and nine patients (30%) were in stage IIIB. N2-3 locations were at multiple stations in nine and at a single station in 14. For N2-3 staging, 13 histological diagnoses were made by mediastinoscope (n = 8), thoracoscope (n = 2), computed tomography guided needle biopsy (n = 1) and transbronchial needle aspiration

Table 1 Patients' characteristics ($n = 30$)

Age (year) range	56–75
Mean	60.7
Gender	
Male	24
Female	6
ECOG performance status	
0	20
1	10
Histological classification	
Adenocarcinoma	17
Squamous cell carcinoma	13
Clinical stage	
IIIA	21
T1N2M0	5
T2N2M0	12
T3N2M0	4
IIIB	
T4 (spinal invasion) N0M0	5
T4 (aortic invasion) N0M0	1
T4 (tracheal invasion) N0M0	1
T4N2M0	2

ECOG, Eastern Cooperative Oncology Group.

($n = 2$). In another 11 patients N2-3 diagnoses were clinically made using 18-fluorodeoxyglucose positron emission tomography (FDG-PET). T4 staging was diagnosed with findings of invasion of the vertebral body in five patients, the main bronchus in one, and the aorta in one.

Clinicopathological response and surgical method are summarized in Table 2. The total response rate for the induction therapy was 73.3%. Clinical response was complete response (CR) in three (10%) patients, partial response (PR) in 19 (63.3%), stable disease (SD) in five (16.7%) and progressive disease (PD) in three (10%). The down-staging rate was 40% (12 of 30 patients) and 27 patients (90%) with CR, PR and SD received surgical resection. Three patients with a PD clinical response underwent additional chemotherapy and boost radiotherapy. Of these 27 surgical cases, 21 patients (77.8%) were resected completely. A lobectomy was performed in 26 of 27 patients (96.2%) and a pneumonectomy in one. Except for the one case of radiation pneumonitis, surgical mortality was 0% and morbidity was 7.4% with one empyema and one bronchial fistula. One patient died of radiation pneumonitis after the lobectomy. The pathological stage was as follows: stage IIIB in five patients, IIIA in seven, IIB in one, IIA in one, IB in two, IA in three and pT0N0M0 in seven. The Ef was Ef 1 in 10 patients, Ef 2 in 10 and Ef 3 in seven. In total

Table 2 Clinicopathological response and surgical method

Clinical response	
CR	3
PR	19
SD	5
PD	3
Response rate (%)	73.3
Down-staging *n* (%)	12 (40.0)
Pathological effect†	
Ef 1	10
Ef 2	10
Ef 3	7
Surgical method *n* (%)	27 (90.0)
Lobectomy‡ *n* (%)	26 (96.3)
Pneumonectomy	1
Complete resection *n* (%)	21 (77.8)

†Ef 1: slight pathological response, Ef 2: moderate pathological response, Ef 3: complete pathological response. ‡Including sleeve lobectomy: 1, hemivertebrectomy: 1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

14 patients underwent postoperative therapy, as follows: additional irradiation to the rest of tumor ($n = 6$); two cycles of the adjuvant chemotherapy with CBDCA and DOC for the prevention of recurrence ($n = 8$). Postoperative adjuvant chemotherapy was performed based on decisions by each thoracic oncologist or pulmosurgeon. Epidermal growth factor receptor *(EGFR)* mutations were found three of 30 patients (10%), and epidermal growth factor receptor-tyrosine kinase inhibitor therapy was performed in five patients after second-line chemotherapy for recurrent disease.

Treatment toxicities are summarized in Table 3. The most frequent toxicities were grade 3–4 neutropenia in 10 (33.3%) patients. The other toxicities were grade 3 anemia in two, grade 3–4 thrombocytopenia in four, grade 3 anorexia in four, and grade 3–5 radiation pneumonitis in two, respectively. One died of radiation pneumonitis after lobectomy.

Survival was estimated by the Kaplan–Meier method (Fig. 1). The mean follow-up period was 59.7 months (8–104 months) for the 27 patients who underwent surgery. Median RFS and median survival were 13.0 months and 66.0 months, respectively. 1-year, 3-year and 5-year survival rates were 75.4, 55.8 and 55.8%, respectively. A total of 16 patients (53.3%) were still alive at the evaluation time. Survival curves by pathological effect (Ef 1 *vs* Ef 2 *vs* Ef 3) are shown in Figure 2. Median survival was 10.9 months in Ef 1 and 49.6 months in Ef 2. Six out of seven Ef 3 patients are still alive at the time of writing, with a mean survival of 77.1 months (14–104 months).

Table 3 Treatment toxicities according to the National Cancer Institute Common Toxicity Criteria version 3.0

	Grade	1	2	3	4	5	≥3 (%)
Hematological							
Neutropenia		2	12	8	2	0	10 (33.3)
Anemia		8	9	2	0	0	2 (6.7)
Thrombocytopenia		2	2	2	0	0	4 (13.3)
Non-hematological							
Nausea/vomiting		17	4	0	–	–	0
Anorexia		8	1	2	0	0	2 (6.7)
Diarrhea		1	0	0	0	0	0
Constipation		6	1	0	0	0	0
Radiation esophagitis		9	0	0	0	0	0
Radiation pneumonitis		1	0	1	0	1	2 (6.7)

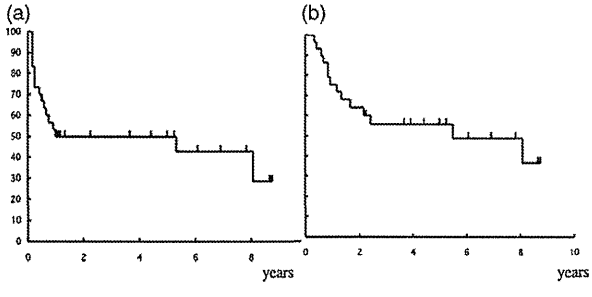

Figure 1 (a) Recurrence-free survival (RFS) curve and (b) overall survival (OS) curve after initial therapy (assessed by the Kaplan–Meier method). Median RFS curve and median OS were 13.0 and 66.0 months, respectively. Both OS and RFS curves include patients who progressed after chemoradiation.

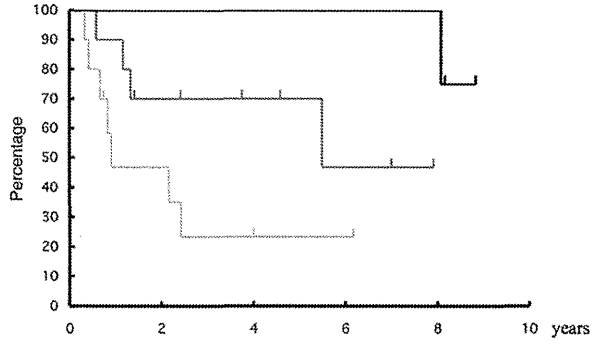

Figure 2 Survival curves according to pathological effect; (···) Ef 1 *vs* (—) Ef 2 *vs* (—) Ef 3. Median survival was 10.9 months in Ef 1 (slight pathological response: $n = 10$) and 49.6 months in Ef 2 (moderate pathological response: $n = 10$), respectively. Six of seven Ef 3 (complete pathological response) patients were still alive with a mean survival time of 77.1 months (14 –104 months).

The analysis of prognostic factors is summarized in Table 4. There was a significant difference in the RFS by pathological effect (Ef 1–3) ($P = 0.005$), age ($P = 0.028$) and gender ($P = 0.023$). There was a significant difference in OS by pathological effect (Ef 1–3) ($P = 0.0036$).

DISCUSSION

According to the International Association for the Study of Lung Cancer's international staging committee, stage IIIA and IIIB NSCLC have poor long-term survival and their 5-year survival rates are only 24 and 9%, respectively.[18] It is important to discuss how multimodality therapy or prognostic factors could be used to improve this dismal prognosis. One of the theoretical advantages of induction chemoradiation in stage III NSCLC is treating minute metastases before surgical resection. On the other hand, the disadvantages of induction chemoradiation were toxicity and complication. The first to consider is induction chemotherapy regimens: mitomycin C + vindesine + CDDP (MVP), CDDP + VP-16 (etoposide), CBDCA + paclitaxel, CDDP + DOC have been used in previous studies.[4,9,17–23]

CBDCA plus DOC has been shown to be better tolerated than other regimens. For example, the Tax 326 study showed that nausea and vomiting appeared to be less frequent among patients assigned to DOC + CBDCA than among those assigned to CDDP-based regimens.[24] In addition, DOC has been shown to have enhanced radiation sensitivity in preclinical studies.[25–27] The combination of CBDCA plus DOC led to encouraging results in terms of response rate in stage III locally advanced NSCLC. Sakai *et al.*[28] reported phase II studies in which chemotherapy with CBDCA + DOC and concurrent radiation therapy were administered in

Table 4 Prognostic factors analysis by log–rank test

Prognostic factors	PFS (*P*-value)	OS (*P*-value)
Age (≥65 years *vs* <65 years)	0.028	0.056
Gender (male *vs* female)	0.023	0.36
PS (0 *vs* 1)	0.68	0.35
Histological classification (ad *vs* S\sq)	0.18	0.16
Clinical stage (IIIA *vs* IIIB)	0.43	0.55
cT4 versus non-cT4	0.99	0.77
cN2-3 versus cN0-1	0.32	0.41
Clinical response (CR *vs* PR *vs* SD)	0.20	0.077
Down-staging (positive *vs* negative)	0.87	0.29
Resectability (completely *vs* incompletely)	0.48	0.46
pN0 versus pN2-3	0.78	0.68
Ef 1 versus Ef 2 versus Ef 3	0.0050	0.0036

Ad, adenocarcinoma; CR, complete response; Ef, pathological effect; OS, overall survival time; PFS, progression-free survival; PR, partial resonse; PS, performance status; SD, stable disease; Sq, squamous cell carcinoma.

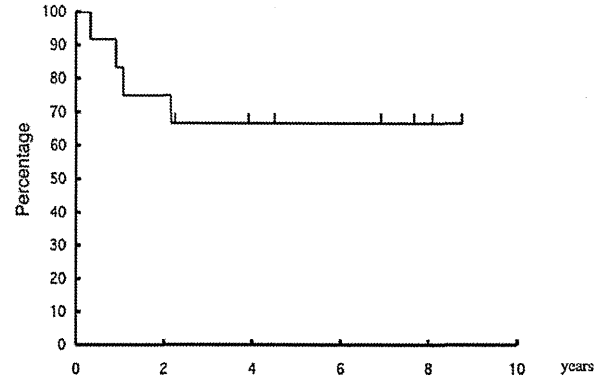

Figure 3 Survival curve for histologically proven N2 patients ($n = 13$). The 5-year survival rate was 66.7% with median follow-up period of 27.0 months (range, 9 –105 months).

unresectable stage III NSCLC. Among the 32 evaluable patients the overall response rate was 91% (CR 2, PR 27) and the median survival time by intention-to-treat analysis was 27 months. In our study the induction chemoradiation with CBDCA + DOC proved to be well-tolerated, and 100% of the scheduled chemotherapy and radiotherapy were administered. Treatment-related mortality was low: 3 versus 4–8% in other studies.[22,29]

The rate of pneumonectomy was high (range, 27–47%) in previous studies with stage IIIA-N2 NSCLC,[22,29] compared with only 3.8% in our study. In a phase III study by Albain *et al.*,[22] OS was improved in patients who underwent a lobectomy and treatment-related mortality was 7% in lobectomies and 26% in pneumonectomies. In our study the high rate of lobectomy was one cause of the longer survival times, for example, the 58.8% of 5-year survival rates. However, the sample size of our study was small, with a selection bias towards potential respectability.

Stage N2 was histologically proven in 13 (56.5%) out of the 23 N2 patients included in our study. Although clinical N2 patients diagnosed mainly with FDG-PET instead of a mediastinoscopy might include some false positive N2 patients, histologically proven N2 patients showed good 5-year survival rates of 66.7%, with a median follow-up period of 27 months (range, 9–105 months) (Fig. 3). A further study of induction chemoradiation should be conducted in patients in whom it was possible to perform a lobectomy after induction chemoradiation.

Previous studies suggested that for selected T4 NSCLC cases with mediastinal involvement, resection might provide a survival benefit.[30,31] Median survival time and 5-year survival rates of surgically treated mediastinal-invading T4 NSCLC were reported to be 24.8 months and 22.7%, respectively.[32] By induction chemoradiation with CDDP plus VP-16 for T4 NSCLC, De Leyn *et al.*[33] reported 87% disease control rates (CR + PR + SD) and 74% 5-year survival rates. Anraku *et al.*[34] reported that induction therapy including total vertebrectomies and hemivertebrectomies facilitates radical resection of T4-NSCLC invading the spine with a 43% CR rate and a 92% 3-year survival rate for pathological CR or near CR.[30] One patient underwent a hemivertebrectomy after induction therapy (Ef 2) and had RFS for 8 years. Thus, it appears that selected T4 NSCLC patients can potentially be cured with induction therapy followed by radical en bloc resection, including total vertebrectomies and hemivertebrectomies.

Lobectomy, pathological down-staging and complete resection were reported to be prognostic factors found in multivariate analysis in stage III NSCLC.[7,9–15] In the present study there was a significant difference between Ef 3, Ef 2 and Ef 1 ($P = 0.0036$). There were no significant differences among age, gender, PS, histopathological classification, clinical stage, clinical response, down-staging or complete resection. Our pathological CR (Ef 3) rate was 25.9%, which is higher than the rate of 5–15% reported in other studies.[4,9,18–23] The patients with pathological CR were reported to have a significant longer survival than those without a CR.[4,9,18–23] This study showed a significant difference of survival between Ef 1 and EF 2 among non-CR patients. We consider that

the Ef after stage III NSCLC induction chemoradiation are be better classified as Ef 3, Ef 2 or Ef 1 rather than "CR or non-CR".

A limitation of this study was that it was conducted in a highly selected patient group. Of the 1121 consecutive patients with primary lung cancer who were treated at our institution during the period April 2001 to March 2010, 30 patients with stage III NSCLC received induction chemoradiation. One of the reason that this study took 10 years to complete was that, as it was performed at a single institution, the enrolment rate was slower than would have been the case in a multicenter study. At our institution 110 out of 1121 patients with stage III received anti-cancer therapy without induction chemoradiation (46 received chemotherapy, eight radiation and 56 chemoradiation). The median survival of these 110 patients was 11.0, 17.3 and 29.4 months, respectively. Interestingly, Ef 2 and Ef 3 patients treated with induction chemoradiation had a significantly longer survival than patients treated with non-induction chemoradiation ($P = 0.04$, 0.001).

In conclusion, the present study demonstrated that Ef 1–3 was correlated with prognosis after surgery following induction chemoradiation with DOC plus CBDCA. Patients with good Ef 2 or Ef 3 had good long-term survival.

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