

## Clinical Investigation

# Candidates for Intensive Local Treatment in cIIIA-N2 Non-Small Cell Lung Cancer: Deciphering the Heterogeneity



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## Summary

We examined pathological characteristics of patients with cIIIA-N2 non-small cell lung cancer to refine the heterogeneity in this patient

**Purpose:** The purpose of this study was to refine the heterogeneous clinical stage IIIA non-small cell lung cancer (NSCLC) with N2 nodes status (cIIIA-N2) by clinicopathological characteristics before treatment.

**Methods and Materials:** We analyzed data of consecutive patients with cIIIA-N2 NSCLC diagnosed between 1997 and 2010 and treated by chemoradiation therapy (CRT). The appearance of the mediastinal lymph nodes (MLNs) was classified into

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population. Those with a discrete appearance of the involved mediastinal lymph nodes and limited extent of mediastinal lymph node involvement at diagnosis showed favorable survival outcomes but relatively high local recurrence rates after definitive chemoradiation therapy. These patients could be candidates for multimodality approach including surgical resection after induction therapy.

discrete or infiltrative according to the criteria proposed by the American College of Chest Physicians. In addition, the extent of MLN involvement (MLNI) was classified as limited (close to the primary tumor) or extensive (including upper MLNI in the case of tumors in the lower lobes and vice versa).

**Results:** A total of 148 patients with cIIIA-N2 NSCLC was treated by CRT. The patient characteristics were as follows: males: 118; females: 30; median age: 62 years; appearance of the involved MLNs: 85 discrete, 63 infiltrative; extent of MLNI: 82 limited, 66 extensive; histology: 36 squamous, 112 nonsquamous. The median progression-free survival (PFS) and median overall survival (OS) in the entire subject population were 9.9 and 34.7 months, respectively. A discrete appearance of the involved MLNs and a limited extent of MLNI contributed significantly to a better PFS and OS. The percentages of cases with relapses within the irradiated field classified according to the characteristics of the MLNs were as follows; appearance of the MLNs (24.6% discrete, 18.9% infiltrative); extent of MLNI (25.9 limited, 17.9% extensive).

**Conclusions:** Those with a discrete appearance of the involved MLNs and a limited extent of MLNI at diagnosis could show relatively more favorable outcomes and could be candidates for multimodality therapy. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Approximately 30% of patients with non-small cell lung cancer (NSCLC) are diagnosed as having stage III disease at the point of initial treatment (1). Constant efforts have been directed at finding better loco-regional and systemic treatments for patients with stage III NSCLC (2). Albain et al (3) conducted an important phase 3 trial (INT-0139) comparing chemoradiation therapy (CRT) and CRT followed by surgery in patients with clinical stage IIIA NSCLC with N2 nodal involvement (cIIIA-N2). Although the trial did not yield positive results in respect to the primary endpoint, CRT followed by surgery appeared to confer possible benefit in patients who were eligible for lobectomy. Radiation Therapy Oncology Group study 0617 evaluated both loco-regional and systemic reinforcements in a phase 3 trial with a factorial design: a higher dose (72 Gy) versus a standard dose (60 Gy) of definitive thoracic radiation therapy (TRT) plus systemic treatment using cetuximab versus treatment without cetuximab. However, Bradley et al (4) reported that the primary endpoint was not achieved in either treatment arm. Therefore, the standard treatment for patients with cIIIA-N2 NSCLC remains definitive CRT with 60 Gy of TRT.

These findings suggest that a rigorous research to select potential candidates for intensive local therapy is needed. We investigated the influence of the appearance of the involved MLNs and the extent of mediastinal lymph node involvement at diagnosis on the frequency of local relapses and the outcomes in patients with cIIIA-N2 NSCLC treated by definitive CRT.

## Methods and Materials

### Patients

Patients with cIIIA-N2 NSCLC who received definitive thoracic radiation therapy (TRT) with platinum-based chemotherapy regimens between 1997 and 2010 were eligible for the analysis. Patients who had received TRT alone, TRT at a total radiation dose of under 50 Gy, chemotherapy alone or treatment based on clinical trials were excluded. Data on the pretreatment patient characteristics, including the age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), and smoking history, and the tumor characteristics including the histology and tumor-node-metastasis (TNM) stage according to Union for International Cancer Control, seventh edition, were retrieved from the medical records (5). The treatment characteristics, including the radiation dose and the timing of the TRT (concurrent or sequential) and the chemotherapy regimens employed, were also evaluated. This study was conducted in accordance with the principles laid down in the amended Declaration of Helsinki. The study protocol was approved by the institutional review boards of the National Cancer Center Hospital (number: 2013-261).

### Treatment

Patients usually received concurrent TRT with platinum-based combination chemotherapy as the standard treatment. TRT was delivered with megavoltage equipment ( $\geq 6$  MV) using anterior/posterior opposed fields, at 40 Gy delivered

in 20 fractions, with the radiation field including the primary tumor, the metastatic lymph nodes, and the regional nodes (elective nodal irradiation). A booster dose of 20 to 26 Gy in 10 to 13 fractions was given to the primary tumor and the metastatic lymph nodes to a total dose of 60 to 66 Gy using bilateral oblique fields. Computed tomography (CT)-based treatment planning was used in the majority of the patients.

### Staging

The T, N, and M staging were performed based on the CT and <sup>18</sup>F-labeled fluorodeoxyglucose positron emission tomography (PET) findings. The staging and diagnosis of lymph node involvement (N status) were initially conducted by experienced radiologists and independently reviewed by another investigator. All metastatic lymph nodes were classified according to the International Association for the Study of Lung Cancer node map (6). The appearance of the mediastinal lymph nodes (MLNs) was classified into MLNs with discrete appearance or with extensive infiltration (abbreviated to “infiltrative” in this study) according to the criteria proposed by the American College of Chest Physicians (ACCP) mainly for surgical decision making in the multidisciplinary team discussion (7). The extent of MLN involvement (MLNI) was classified as N2a-1 (limited) or N2a-2 and N2b (extensive) according to the Japanese nodal classification proposed by the Japan Lung Cancer Society (JLCS), which is usually applied to surgically resected lung cancer (Table 1) (8, 9).

N2 status was diagnosed based on pathology and imaging studies. The pathology diagnoses were based on examination of mediastinoscopic and surgical or trans-bronchial needle biopsy specimens. Infiltrative MLNs were

diagnosed as N2 based on CT findings, regardless of PET findings. Discrete MLNs were diagnosed as N2 if they had a short diameter of ≥1 cm on CT, regardless of the PET findings. Routine screening using PET-CT was started in 2005 at our institution.

### Statistical analysis

Clinical outcomes were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare outcomes. Cox proportional hazard model was used for multivariate analyses performed to evaluate the effect of the appearance of the involved MLNs and extent of MLNI on the progression-free survival (PFS) and overall survival (OS) with adjustment for known and important co-factors such as the age, sex, body weight loss (<5% or ≥5%), ECOG PS (0 or 1), smoking history, histology, method used to diagnose N2, timing of the TRT, and the initial date of treatment. The overall response rate (ORR) was measured in patients who had measurable lesions according to Response Evaluation Criteria In Solid Tumors version 1.1 criteria (10). STATA version 13 software (StataCorp, College Station, TX) for Windows (Microsoft, Redmond, WA) was used for statistical analyses.

### Results

#### Patient characteristics

Between 1997 and 2010, unresectable cIIIA-N2 NSCLC was diagnosed in a total of 188 patients at the National Cancer Center Hospital, Japan. Of these, we excluded 40 patients and included the remaining 148 patients as eligible for this analysis. Forty of the 188 patients were excluded because they were treated by radiation therapy alone (n=7), treated by radiation therapy at a total radiation dose lower than 50 Gy (n=2), or treated by chemotherapy alone (n=1), their chemotherapy component was based on non-platinum chemotherapy regimen (n=1), nonavailability of clinical data (n=4), or they were included as subjects in other clinical trials (n=25).

Characteristics of the 148 patients were as follows: median age 62 (range: 33-77) years; male-to-female ratio 118:30; body weight loss (≥5% in males, <5% in females) 17:131; ECOG PS (0/1) 61/87; and tumor histology (non-squamous/squamous) 112/36. According to the pretreatment evaluation, 85 patients (57%) had a “discrete” appearance of the MLNs, 82 patients (55%) had “limited” MLNI. N2 diagnoses were based on imaging studies (CT and PET-CT) in 117 cases (79%) and on pathology examinations in 31 cases (21%) (Table 2).

#### Treatment summary

Of the 148 patients, 133 (90%) received concurrent TRT and the remaining 15 (10%) received sequential TRT with a

**Table 1** Definition of the extent of MLNI\* according to JLCS†

	Right			Left		
	Upper	Middle	Lower	Upper		Lower
				Upper (lingula)	Lower	
N2a-1 (limited MLNI)	2R 4R	2R 4R	7 8	4L 5	4L 5	7 8
		7	9	6	6	9
N2a-2 and N2b (Extensive MLNI)	7 3a 3p	3a 3p	2R 4R	7 2L	2L 3a	4L 5
	8 9	9	3a 3p	3a 3p	8 9	6 2L 3a 3p

Abbreviations: JLCS = Japan Lung Cancer Society; MLNI = mediastinal lymph node involvement.

\* Each number refers to the station of lymph nodes in the International Association of the Study of Lung Cancer staging atlas (7).

† Modified from the Japanese nodal classification for resected lung cancer (10).

**Table 2** Patient characteristics

Characteristic	No. of patients (N = 148)	% or range
Median age (y)	62	33-77
Sex		
Male	118	80
Female	30	20
Body weight loss		
≥5%	17	11
<5%	131	89
Performance status		
0	61	41
1	87	59
Smoking history (median pack-years)	43	0-156
Appearance of the MLNs		
Discrete	85	57
Infiltrative	63	43
Extent of MLNI		
Limited	82	55
Extensive	66	45
Tumor histology		
Non-squamous	112	76
Squamous	36	24
N2 diagnosis		
Imaging study	117	79
Pathological	31	21
Radiation therapy, timing		
Concurrent	133	90
Sequential	15	10
Median radiation therapy dose	60	52-66
Chemotherapy		
CDDP + VNR	95	64
Nedaplatin + PTX	16	11
CBDCA + PTX	10	7
MVP	9	6
Others	18	12
Treatment begun		
Before 2005	85	57
After 2005	63	43

*Abbreviations:* CBDCA = carboplatin; CDDP = cisplatin; MLNI = mediastinal lymph node involvement; MVP = mitomycin C + vindesine + cisplatin; PTX = paclitaxel; VNR = vinorelbine.

median radiation dose of 60 Gy (range: 52-66 Gy). The combined chemotherapy regimens were as follows; cisplatin plus vinorelbine, 95 patients; nedaplatin plus paclitaxel, 16 patients; carboplatin plus paclitaxel, 10 patients; mitomycin plus vindesine plus cisplatin, 9 patients; others, 18 patients.

### Patterns of the initial relapses

Of the 148 patients included in this study, 112 (76%) developed disease recurrences. The initial site of relapse was local alone in 21.4% of patients, mixed in 17.9% of patients, and distant alone in 60.7% of patients, including 17% with brain metastasis as the sole site of recurrence. The frequency of local relapses was higher in patients with

limited MLNI (25.9%), discrete appearance of the MLNs (24.6%) and a squamous histology (52%). (Table 3)

In the subgroup with pathologically proven N2 disease, the frequency of local and mixed relapses was higher in patients with limited MLNI than in those with extensive MLNI (41.7% compared to 25.0% in patients with extensive MLNI), but similar between patients with discrete and infiltrative MLNs (35.3% compared to 33.3% in patients with infiltrative MLNs).

### Efficacy

At the point of data cutoff, the median follow-up time was 50.9 months. The percentage of ORR (95% confidence interval [CI]), median PFS time (months) and median OS time (months) in the entire study population were: ORR 66.2% (95% CI: 58.5-73.9), median PFS 9.9 months (95% CI: 9.0-12.3), median OS 34.7 months (95% CI: 28.8-41.1), and 5-year OS rate 34.0 (95% CI: 25.1-43.1) (Fig. 1).

In the univariate analyses, the median PFS was significantly better in patients with discrete MLNs and limited MLNI. The hazard ratio (HR) for PFS and 5-year PFS rates in patients with discrete MLNs were 0.70 (95% CI: 0.49-1.01) and 22.5% (95% CI: 13.7-32.6), respectively. The same survival parameters in patients with limited MLNI were 0.59 (95% CI: 0.41-0.85) and 24.4% (95% CI: 15.3-34.7), respectively. The same patient population also showed a better HR for OS and 5-year OS rate, as follows; 0.68 (95% CI: 0.44-1.06) and 37.9% (95% CI: 25.3-50.4), respectively and 0.55 (95% CI: 0.35-0.85) and 44.1% (95% CI: 30.7-56.7), respectively, in patients with discrete MLNs and limited MLNI (Fig. 2).

In an exploratory analysis in the subgroup with a pathological N2 (31 patients), patients with limited MLNI showed a better median PFS (15.0 months vs 7.6 months; HR: 0.43 [95% CI: 0.19-0.99]) and median OS (46.9 months vs 22.3 months; HR: 0.54 [95% CI: 0.21-1.38]) compared to those with extensive MLNI.

Based on the Cox proportional hazard model analysis with adjustment for known and important co-factors, the adjusted HR for the PFS and OS were as follows: PFS: 0.63 (95% CI: 0.41-0.96) and 0.53 (0.36-0.78), respectively, and OS: 0.65 (95% CI: 0.39-1.09) and 0.56 (0.35-0.88), respectively, in patients with discrete MLNs and limited MLNI. It is also noteworthy that patients who received CRT after the start of routine PET-CT scanning had at our institution showed better PFS and OS. (Table 4)

### Discussion

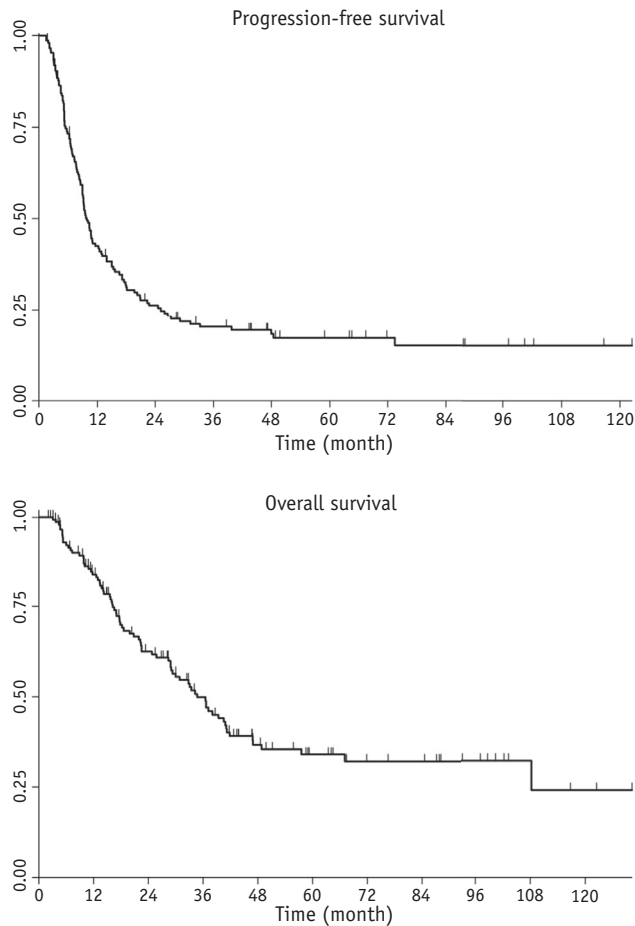
To the best of our knowledge, this is the first and most detailed analysis of the efficacy of definitive CRT in NSCLC patients with cIIIA-N2 according to the classification of the appearance of the involved mediastinal lymph nodes and extent of mediastinal lymph node involvement proposed by the ACCP and JLCs guidelines. Although

**Table 3** Sites of first relapse

	Local (%)	Mixed (%)	Distant (%)	
			Total (%)	Brain only (%)
All patients with relapse (N=112)	21.4	17.9	60.7	17.0
Appearance of the MLNs				
Discrete (n=57)	24.6	21.1	54.3	7.0
Infiltrative (n=53)	18.9	15.1	66.0	26.4
Extent of MLNI				
Limited (n=54)	25.9	16.7	57.4	16.7
Extensive (n=56)	17.9	19.6	62.5	17.9
Histology				
Squamous (n=25)	52.0	16.0	32.0	4.0
Non-squamous (n=87)	12.6	18.4	69.0	20.7

Abbreviation: MLNI = mediastinal lymph node involvement.

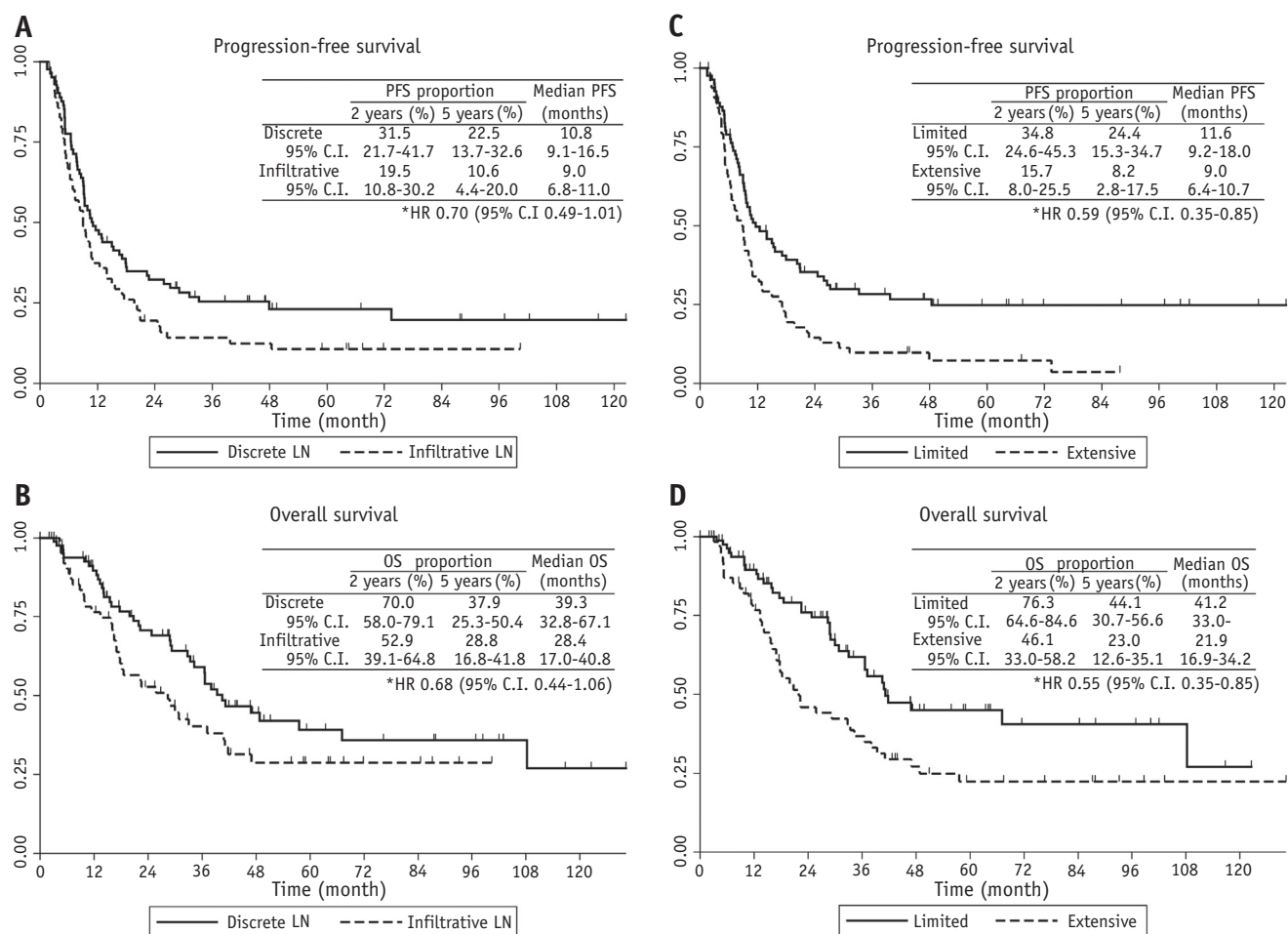
there was still room for improvement in the local control rate, more favorable outcomes were obtained in cIIIA-N2 patients with discrete MLNs and limited MLNI.



**Fig. 1.** Survival in all patients with cIIIA-N2 treated by CRT. In the overall study population (n=148), the median PFS was 9.9 months (95% CI: 9.0-12.3), the median OS was 34.7 months (95% CI 28.8-41.1), and 5-year OS rate 34.0 (95% CI; 25.1-43.1). Abbreviations: CRT = chemoradiation therapy; OS = overall survival; PFS = progression-free survival.

Although few reports have discussed the efficacy of CRT separately for cIIIA-N2 NSCLC, we analyzed the efficacy and pattern of relapses in this population of patients who tend to be candidates for multimodality therapy, including induction CRT followed by surgery. Patients with cIIIA-N2 NSCLC have been reported to show substantially better median OS (34.7 months) compared to the outcomes of standard CRT in trials including the entire stage III population (11, 12). Because of the heterogeneity of the disease anatomy and biology, we need to obtain more information to offer more appropriate local and systemic treatment for patients with stage III NSCLC. The updated guideline from ACCP recommends consideration of both definitive CRT and induction therapy followed by surgery based on assessment by a multidisciplinary team for patients with cIIIA-N2 NSCLC with discrete MLNs (2). In this study, we attempted to define subgroups of patients based on the appearance of the involved MLNs and the extent of MLNI, and found that a 5-year PFS rate of more than 20% and 5-year OS rate of approximately 40% were achieved in patients with discrete MLNs and limited MLNI after definitive CRT. These pre-treatment patients' characteristics could be important factors to consider multimodality therapies.

It has been reported infiltrative appearance (extracapsular invasion) of metastatic lymph nodes is a poor prognostic factor in surgically treated patients in various cancers, including lung cancer (13-19). Several reports suggested that the copy number of aberrations of the epidermal growth factor receptor gene, expression of alpha smooth muscle actin, and serine protease inhibitor (SERPINE1) are correlated with extracapsular invasion in patients with oral squamous cell carcinoma (18, 19). Concerning the influence of the extent of involvement of the MLNs, an abundance of articles reported poorer outcomes in the subgroup of patients with extensive MLNI among patients with completely resected clinical and pathological N2 NSCLC (8, 20-23). Our results could be the first to identify a similar impact of the appearance of the MLNs and extent of MLNI on the efficacy of CRT and the relapse pattern after definitive CRT in patients with cIIIA-N2 NSCLC.



**Fig. 2.** Survival according to characteristics of the MLNs in the patients with cIIIA-N2 treated by CRT. (A) PFS according to the appearance of the MLNs. (B) OS according to the appearance of the MLNs. (C) PFS according to the extent of MLNI. (D) OS according to the extent of MLNI. *Abbreviations:* CRT = chemoradiation therapy; MLNI = infiltrative mediastinal lymph nodes; OS = overall survival; PFS = progression-free survival.

Concerning local control patients with stage III NSCLC, higher-dose TRT has failed to exert any clinically meaningful impact on the efficacy or toxicity. (4, 24) In addition to better chemotherapy regimens or targeted therapies (eg, tyrosine kinase inhibitors for patients with epidermal growth factor receptor mutations) for systemic control, better strategies for selection and treatment of the heterogeneous population of patients with stage III NSCLC are warranted (25). We thoroughly investigated the effect of the extent of MLNI and appearance of the involved MLNs and found that even those patients with discrete MLNs and limited MLNI experienced frequent local relapses within the radiation field (24.6% in patients with discrete MLNs and 25.9% in patients with limited MLNI). Although several phase 3 trials evaluating induction CRT followed by surgery showed negative results in terms of the endpoint in the pre-PET/CT era and when the trial patients included the entire stage III population, further clinical trials based on contemporary pre-treatment diagnosis (eg, PET-CT,

endobronchial ultrasound-guided biopsy) and advanced surgical management could yield different results (3,26-28).

Our study had several limitations. First, there was an inevitable bias because of the retrospective nature of the study. However, we analyzed consecutive patients in a single institution, which resulted in relatively uniform methods of diagnosis, treatment, and follow-up. Second, the proportion of patients who had pathological N2 was relatively low in comparison with trials of induction therapy followed by surgery, which may affect the survival analyses. To confirm the results with those in the overall population, we conducted a subgroup analysis in patients with pathological N2 and obtained similar trends of local relapses and survival. Third, the follow-up period was not strictly the same in all patients, which could have resulted in some imbalance. Despite the imbalance, all the patients were regularly followed-up at every 1 to 2 months at the outpatient division, and were worked up by radiography, CT, magnetic resonance imaging, and PET-CT

**Table 4** Multivariate analyses to identify factors contributing to the PFS and OS

	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age (y)						
<62	1			1		
≥62	1.17	0.80-1.71	0.428	1.26	0.80-1.98	0.322
Sex						
Male	1			1		
Female	0.72	0.39-1.31	0.278	0.73	0.34-1.59	0.426
Body weight loss						
<5%	1			1		
≥5%	0.86	0.47-1.57	0.624	0.90	0.45-1.82	0.779
PS						
0	1			1		
1	0.88	0.58-1.33	0.544	0.86	0.52-1.42	0.553
Smoking history (pack-year)						
≥10	1			1		
<10	0.92	0.51-1.66	0.786	0.91	0.41-1.99	0.806
Appearance of MLNs						
Infiltrative	1			1		
Discrete	0.63	0.41-0.96	0.033	0.65	0.39-1.09	0.106
Extent of MLNI						
Extensive	1			1		
Limited	0.53	0.36-0.78	0.001	0.56	0.35-0.88	0.013
Histology						
Squamous	1			1		
Non-squamous	1.61	0.99-2.62	0.056	0.78	0.46-1.34	0.371
N2 diagnosis						
Imaging study	1			1		
Pathological	0.95	0.58-1.54	0.829	0.93	0.53-1.61	0.788
Radiation therapy, timing						
Concurrent	1			NE	NE	NE
Sequential	1.66	0.83-3.34	0.153			
Treatment began						
Before 2005	1			1		
After 2005	0.63	0.42-0.93	0.022	0.48	0.29-0.79	0.004

Abbreviations: MLNI = mediastinal lymph node involvement; NE = not evaluable; OS = overall survival; PFS = progression-free survival; PS = performance status.

every 3 to 6 months for a year after completion of the CRT and every 6 months subsequently.

## Conclusions

In conclusion, a limited extent of MLNI and discrete appearance of the MLNs were associated with a better survival. However, local relapses were still common in these relatively favorable subgroups of NSCLC patients with cIIIA-N2 disease. Further clinical trials are warranted to explore better treatment strategies for the right patients.

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