Title: Candidates for intensive local treatment in cIIIA-N2 non-small cell lung cancer: deciphering the heterogeneity

Short running title: Refining the heterogeneous IIIAN2 NSCLC

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Summary

We conducted a detailed examination of clinic-pathological characteristics of patients with cIIIA-N2 NSCLC to refine the heterogeneity in this patients population. Those with a discrete appearance of the involved mediastinal lymph nodes and a limited extent of mediastinal lymph nodes involvement at diagnosis could show favorable survival outcomes but relatively high local recurrence rate after definitive chemoradiotherapy. These patients could be candidates for multimodality approach including surgical resection after induction therapy.

Abstracts

Objective

To refine the heterogeneous clinical stage IIIA non-small cell lung cancer (NSCLC) with N2 nodes status (cIIIA-N2) by clinico-pathological characteristics before treatment.

Methods and materials

We analyzed the data of consecutive patients with cIIIA-N2 NSCLC diagnosed between 1997 and 2010 and treated by chemoradiotherapy (CRT). The appearance of the mediastinal lymph nodes (MLNs) was classified into discrete (D) or infiltrative (I) according to the criteria proposed by the ACCP. 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 was as follows; male/female, 118/30; median age, 62 years; appearance of the involved MLNs (D/I), 83/63; extent of MLNI (limited [L] /extensive [E]), 81/64; histology (squamous [sq] /non-squamous [non-sq]), 36/112. 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 (D/I), 24.6/18.9%; extent of MLNI (L/E), 25.9/17.9%.

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.

Introduction

About 30% of patients with non-small cell lung cancer (NSCLC) 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. conducted an important phase III trial (INT-0139) comparing chemoradiotherapy (CRT) and CRT followed by surgery in patients with clinical stage IIIA NSCLC with N2 nodal involvement (cIIIA-N2) (3). Although the trial did not yield positive results in respect of the primary endpoint, CRT followed by surgery appeared to confer possible benefit in patients who were eligible for lobectomy. The RTOG 0617 study evaluated both loco-regional and systemic reinforcements in a phase III trial with a factorial design: a higher dose (72 Gy) versus a standard dose (60 Gy) of definitive thoracic radiotherapy (TRT) plus systemic treatment using cetuximab versus treatment without cetuximab. However, Bradley et al. reported that the primary endpoint was not achieved in either treatment arm (4). Therefore, the standard treatment for patients with cIIIA-N2 NSCLC remains definitive CRT.

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.

Materials and methods

Patients

Patients with cIIIA-N2 NSCLC who received definitive thoracic radiotherapy (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 the seventh edition of the UICC, 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 XXX Hospital (Approval number: 2013-261).

Treatment

Patients usually received concurrent TRT with platinum-based combination chemotherapy as the standard treatment. TRT was delivered with megavoltage equipment (≥6 MV) using anterior/posterior opposed fields, at the dose 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 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes to a total dose of 60-66 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/or PET ([^{18}F]-fluorodeoxyglucose positron emission tomography) findings. The staging and diagnosis of lymph node involvement (the N status) were initially conducted by experienced radiologists and independently reviewed by another investigator. All the metastatic lymph nodes were classified according to the International Association for the Study of Lung Cancer (IASLC) node map (6). The appearance of the mediastinal lymph nodes (MLNs) was classified into discrete or infiltrative according to the criteria

proposed by the American College of Chest Physicians (ACCP) (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 (8,9). (Table 1)

The N2 status was diagnosed based on pathological and/or imaging studies. The pathological diagnosis were based on examination of mediastinoscopic, surgical or transbronchial needle biopsy specimens. Infiltrative MLNs were diagnosed as N2 based on the CT findings, irrespective of the PET findings. Discrete MLNs were diagnosed as N2 if they had a short diameter of ≥1 cm on CT, irrespective of the PET findings. Routine screening using PET-CT was started in 2005at our institution.

Statistical analysis

The clinical outcomes were analyzed using the Kaplan-Meier method, and the log-rank test was used to compare the outcomes. The Cox proportional hazard model was used for the 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 the RECIST criteria (Ver. 1.1) (10). The STATA 13 for Windows software package (StataCorp LP, College Station, TX, USA) was used for the statistical analyses.

Results

Patient characteristics

Between 1997 and 2010, a total of 188 patients were diagnosed as having unresectable cIIIA-N2 NSCLC at the XXX Hospital, Japan. Of these, we excluded 40 patients and included the remaining 148 patients as eligible for this analysis. The reasons for exclusion of 40 of the 188 patients were as follows; treated by radiotherapy alone (n=7), treated by radiotherapy at a total radiation dose of lower than 50 Gy (n=2), treated by chemotherapy alone (n=1), chemotherapy component of the CRT based on non-platinum chemotherapy regimens (n=1), non-availability of clinical data (n=4), included as subjects in other clinical trials (n=25).

The characteristics of the 148 patients included in this study were as follows: median age (range) 62 (33-77) years; male/female ratio 118/30; body weight loss (≥5% / <5%) 17/131; ECOG PS (0/1) 61/87; tumor histology (non-squamous / squamous) 112/36. According to the pretreatment evaluation, 83 patients (57%) had a 'discrete' appearance of the MLNs, 81 patients (56%) had 'limited' MLNI. The N2 diagnoses were based on imaging studies (CT and/or PET-CT) in 116 (79%) and on pathological examinations in 31 (21%) cases. (Table 2)

Treatment summary

Of the 148, 133 (90%) received concurrent TRT and the remaining 15 (10%) received sequential TRT with a 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 in, 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% as 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 ORR (%, 95% confidence interval [CI]), median PFS time (months, 95% CI) and the median OS time (months, 95% CI) in the entire study population were as follows; ORR 66.2% (58.5-73.9), median PFS 9.9 months (9.0-12.3) and median OS 34.7 months (28.8-41.1). (Figure 1)

In the univariate analyses, the median PFS was significantly better in patients with discrete MLNs and limited MLNI. The hazard ratio for overall survival (HR with 95% CI) and 5-year PFS rate (% with 95% CI) in patients with discrete MLNs and limited MLNI were as follows; 0.69 (0.48-1.00) and 23.1% (14.0-33.4), and 0.57 (0.39-0.82) and 24.7% (15.5-35.1), respectively. The same patient population also showed a better HR for OS (HR, 95% CI) and 5-year OS rate (%with 95% CI), as follows; 0.67 (0.43-1.04) and 39.2% (26.3-51.9), and 0.53 (0.34-0.83) and 45.1% (31.5-57.7), respectively, in patients with discrete MLNs and limited MLNI. (Figure 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]) as 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 (95% CI) for the PFS and OS were as follows; PFS 0.62 (0.41-0.95) and 0.50 (0.33-0.73), and OS 0.64 (0.38-1.08) and 0.53 (0.33-0.85), respectively, in the 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 3)

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 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.

While 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) as 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 about 40% were achieved in patients with discrete MLNs and/or 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.

Concerning local control patients with in stage III NSCLC, higher-dose TRT

has failed to exert any clinically meaningful impact on the efficacy/toxicity. (4,24) In addition to better chemotherapy regimens or targeted therapies (e.g. 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 III 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 (e.g. 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 that in prospective trials, especially trials of induction therapy followed by surgery. 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 X-ray, CT, MRI, and PET-CT every 3 to 6 months for a year after completion of the CRT, and every 6months subsequently.

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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Reference

1. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: Experience at mayo clinic from 1997 to 2003. *Chest* 2005;128:452-62.
2. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage iii non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e314S-40S.
3. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage iii non-small-cell lung cancer: A phase iii randomised controlled trial. *Lancet* 2009;374:379-86.
4. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage iiia or iiib non-small-cell lung cancer (rtog 0617): A randomised, two-by-two factorial phase 3 study. *The lancet oncology* 2015;16:187-99.
5. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest* 2009;136:260-71.
6. Rusch VW, Asamura H, Watanabe H, et al. The iaslc lung cancer staging project: A proposal for a new international lymph node map in the forthcoming seventh edition of the tnm classification for lung cancer. *J Thorac Oncol* 2009;4:568-77.
7. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e211S-50S.
8. Ichinose J, Murakawa T, Hino H, et al. Prognostic impact of the current japanese nodal classification on outcomes in resected non-small cell lung cancer. *Chest* 2014;146:644-9.
9. The 7th edition of general rule for clinical and pathological record of lung cancer. *Japan Lung Cancer Society* 2010.
10. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). *European journal of cancer* 2009;45:228-47.
11. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase iii study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage iii non-small-cell lung cancer: West japan thoracic oncology group wjtog0105. *J Clin Oncol* 2010;28:3739-45.
12. Segawa Y, Kiura K, Takigawa N, et al. Phase iii trial comparing docetaxel and cisplatin

combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: Olcsg 0007. *J Clin Oncol* 2010;28:3299-306.

13. Hultborn KA, Tornberg B. Mammary carcionma. The biologic character of mammary carcionma studied in 517 cases by a new form of malignancy grading. *Acta radiologica Supplementum* 1960;196:1-143.
14. Suemasu K NT. Prognostic significance of extranodal cancer invasion of mediastinal lymph nodes in lung cancer. *Japanese journal of clinical oncology* 1982;12:207-212.
15. Zacho A, Fischermann K, Sorensen BL. Prognostic role of breach of lymph node capsule in nodal metastates from gastric carcinoma. *Acta chirurgica Scandinavica* 1963;125:365-9.
16. Ellenhorn JD, Shah JP, Brennan MF. Impact of therapeutic regional lymph node dissection for medullary carcinoma of the thyroid gland. *Surgery* 1993;114:1078-81; discussion 1081-2.
17. Singletary SE, Shallenberger R, Guinee VF. Surgical management of groin nodal metastases from primary melanoma of the lower extremity. *Surgery, gynecology & obstetrics* 1992;174:195-200.
18. Michikawa C, Uzawa N, Sato H, et al. Epidermal growth factor receptor gene copy number aberration at the primary tumour is significantly associated with extracapsular spread in oral cancer. *British journal of cancer* 2011;104:850-5.
19. Dhanda J, Triantafyllou A, Liloglou T, et al. Serpine1 and sma expression at the invasive front predict extracapsular spread and survival in oral squamous cell carcinoma. *British journal of cancer* 2014;111:2114-21.
20. Yoshino I, Yoshida S, Miyaoka E, et al. Surgical outcome of stage iiia- cn2/pn2 non-small-cell lung cancer patients in japanese lung cancer registry study in 2004. *J Thorac Oncol* 2012;7:850-5.
21. Ichinose Y, Kato H, Koike T, et al. Overall survival and local recurrence of 406 completely resected stage iiia-n2 non-small cell lung cancer patients: Questionnaire survey of the japan clinical oncology group to plan for clinical trials. *Lung Cancer* 2001;34:29-36.
22. Ichinose Y, Kato H, Koike T, et al. Completely resected stage iiia non-small cell lung cancer: The significance of primary tumor location and n2 station. *The Journal of thoracic and cardiovascular surgery* 2001;122:803-8.
23. Matsunaga T, Suzuki K, Takamochi K, et al. Time to refine n2 staging? Cn2alpha and cn2beta based on local regional involvement provide a more accurate prognosis in surgically treated iiia non-small-cell lung cancer than n2 alone or the number of

node stations involved. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2013.

24. Hidehito Horinouchi IS, Minako Sumi, Miyako Satouchi, Hiroshi Isobe, Masao Harada, Seiji Niho, Kiyoshi Mori, Tomohide Tamura. Multicenter phase ii study of concurrent high-dose (72gy) three-dimensional conformal radiotherapy (3d-crt) without elective nodal irradiation with chemotherapy using cisplatin and vinorelbine for unresectable stage iii non-small cell lung cancer (nsclc). *J Clin Oncol* 2012;30:suppl; abstr 7070.
25. Yagishita S, Horinouchi H, Katsui Taniyama T, et al. Epidermal growth factor receptor mutation is associated with longer local control after definitive chemoradiotherapy in patients with stage iii nonsquamous non-small-cell lung cancer. *International journal of radiation oncology, biology, physics* 2014.
26. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage iiia-n2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442-50.
27. Barnett SA, Rusch VW, Zheng J, et al. Contemporary results of surgical resection of non-small cell lung cancer after induction therapy: A review of 549 consecutive cases. *J Thorac Oncol* 2011;6:1530-6.
28. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and ct for lymph node staging of lung cancer. *Chest* 2006;130:710-8.

Tables

Figure legends

Tables

Table 1. Definition of the extent of MLN involvement according to JLCS

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

MLN: mediastinal lymph node

MLNI: MLN 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

	N=148	% or range
Age (yr, median)	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 (pack-year, median)	43	0-156
Appearance of the MLNs		
Discrete	83	57
Infiltrative	63	43
Extent of MLNI		
Limited	81	56
Extensive	64	44
Tumor histology		
Non-squamous	112	76
Squamous	36	24
N2 diagnosis		
Imaging study	116	79
Pathological	31	21
Radiotherapy, timing		
Concurrent	133	90
Sequential	15	10
Radiotherapy, dose (median)	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

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

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				
Infiltrative (N=53)	18.9	15.1	66.0	26.4
Discrete (N=57)	24.6	21.1	54.4	7.0
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

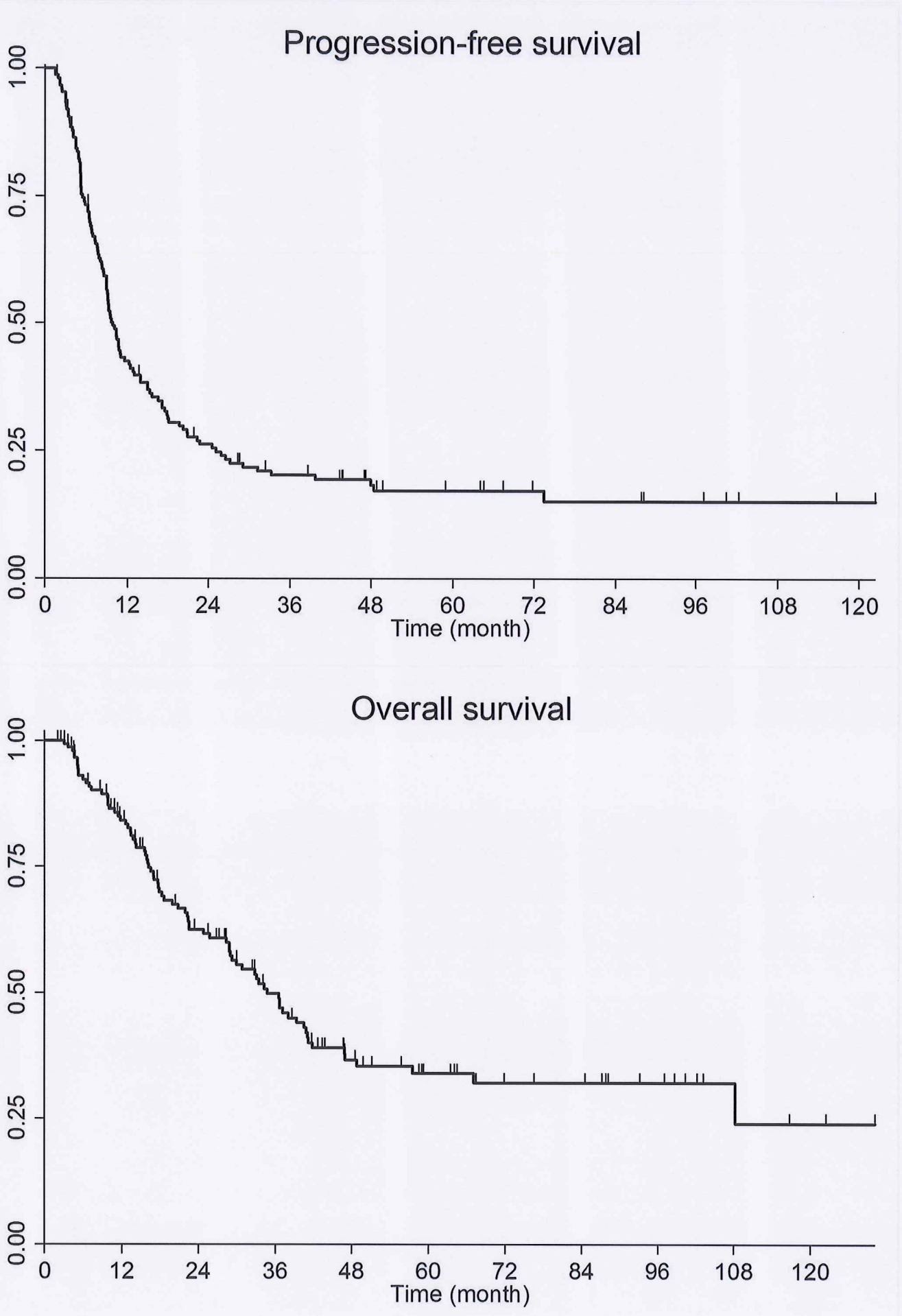
MLN: mediastinal lymph node, MLNI: MLN involvement

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

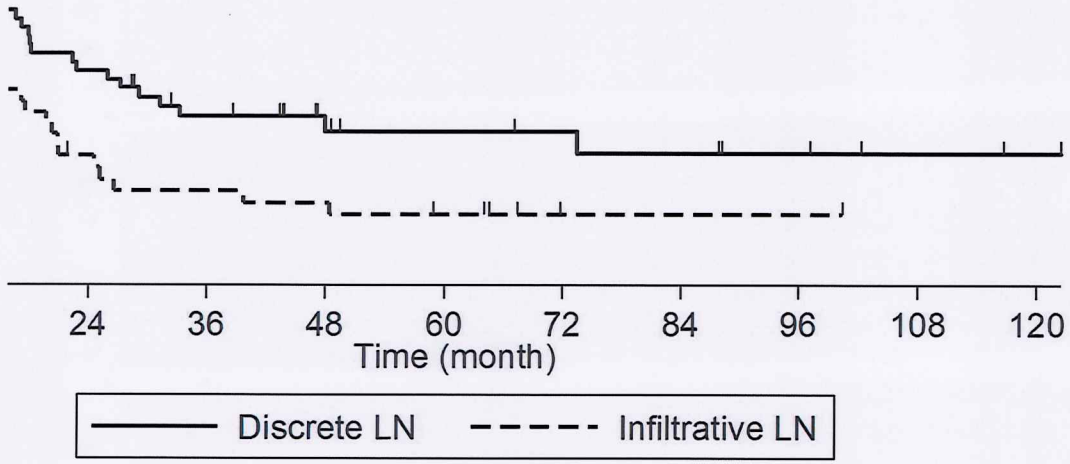
	PFS			OS		
	HR	95% C.I.	p value	HR	95% C.I.	p value
Age (yr)						
<62	1			1		
≥62	1.15	0.78-1.70	0.472	1.26	0.80-2.01	0.320
Sex						
Male	1			1		
Female	0.63	0.34-1.19	0.157	0.68	0.30-1.53	0.354
Body weight loss						
<5%	1			1		
≥5%	0.86	0.47-1.58	0.632	0.93	0.46-1.89	0.849
PS						
0	1			1		
1	0.85	0.56-1.29	0.451	0.82	0.50-1.37	0.456
Smoking history (pack-year)						
≥10	1			1		
<10	0.77	0.42-1.42	0.401	0.78	0.35-1.77	0.558
Appearance of the MLNs						
Infiltrative	1			1		
Discrete	0.62	0.41-0.95	0.029	0.64	0.38-1.08	0.094
Extent of MLNI						
Extensive	1			1		
Limited	0.50	0.33-0.73	0.000	0.53	0.33-0.85	0.008
Histology						
Squamous	1			1		
Non-squamous	1.60	0.98-2.62	0.060	0.76	0.44-1.30	0.320
N2 diagnosis						
Imaging study	1			1		
Pathological	0.93	0.57-1.53	0.789	0.90	0.51-1.59	0.723
Radiotherapy, timing						
Concurrent	1			NE	NE	NE
Sequential	1.70	0.85-3.40	0.137			
Treatment began						
before 2005	1			1		
after 2005	0.67	0.45-0.99	0.045	0.51	0.31-0.86	0.011

MLN: mediastinal lymph node; MLNI: MLN involvement; NE: not evaluable

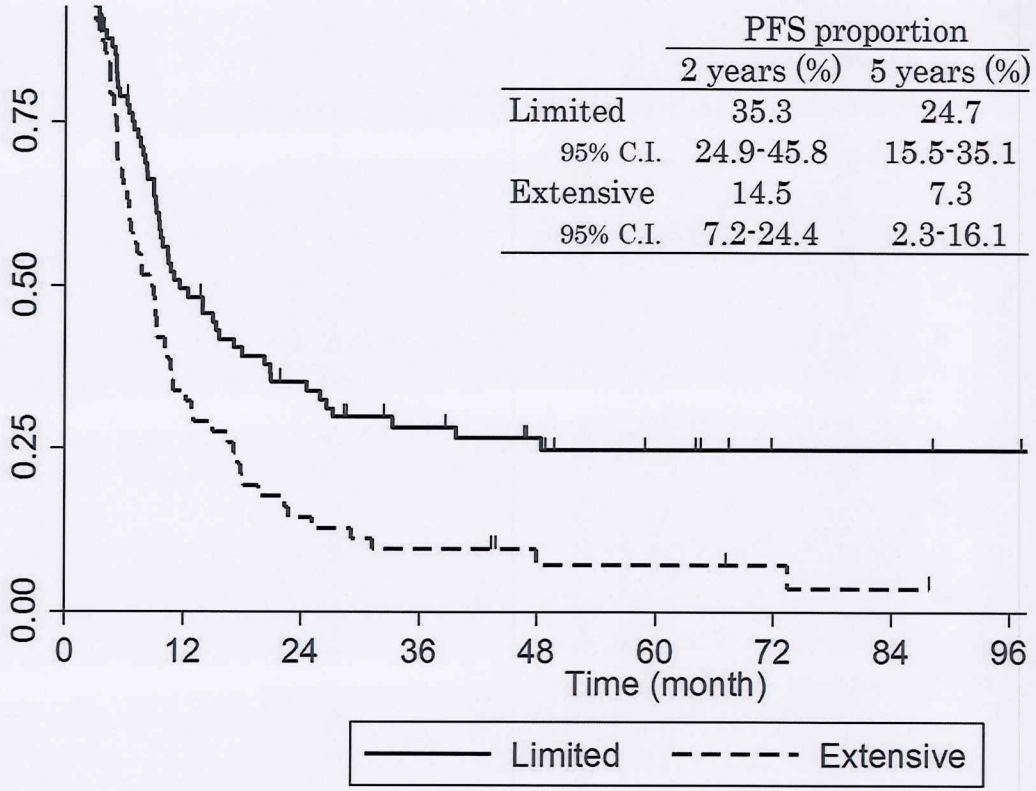
Figure 1. Survival in overall population



	PFS proportion		Median PFS
	2 years (%)	5 years (%)	(months)
Discrete	32.3	23.1	11.1
95% C.I.	22.3-42.6	14.0-33.4	9.1-17.2
Infiltrative	19.5	10.6	9.0
95% C.I.	10.8-30.2	4.4-20.0	6.8-11.0

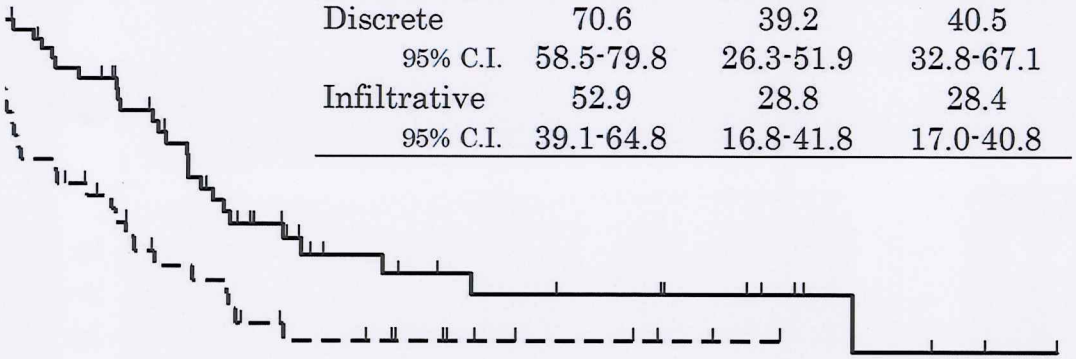


	PFS proportion	
	2 years (%)	5 years (%)
Limited	35.3	24.7
95% C.I.	24.9-45.8	15.5-35.1
Extensive	14.5	7.3
95% C.I.	7.2-24.4	2.3-16.1



Overall survival

	OS proportion		Median OS
	2 years (%)	5 years (%)	(months)
Discrete	70.6	39.2	40.5
95% C.I.	58.5-79.8	26.3-51.9	32.8-67.1
Infiltrative	52.9	28.8	28.4
95% C.I.	39.1-64.8	16.8-41.8	17.0-40.8



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Overall survival

	OS proportion	
	2 years (%)	5 years (%
Limited	76	45.1
95% C.I.	64.2-84.4	31.5-57.7
Extensive	46	22.4
95% C.I.	32.7-58.3	12.2-34.6