The Prognostic Impact of Main Bronchial Lymph Node Involvement in Non-Small Cell Lung Carcinoma: Suggestions for a Modification of the Staging System

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Background. The therapeutic strategies for non-small cell lung carcinoma (NSCLC) with N1 and N2 disease differ remarkably. Debate exists about the definition of the borderline between N1 and N2 stations. This study evaluated the prognostic effect of N1 disease, especially focused on the significance of the main bronchial node (No. 10) vs N2 disease.

Methods. The records of 1601 patients who underwent complete pulmonary resection for NSCLC were reviewed to examine the clinical features of lymph nodal involvement.

Results. There were 1086 patients (67.8%) with pN0 disease, 202 (12.6%) with pN1, and 274 (17.1%) with pN2 disease; overall 5-year survival rates were 74.7%, 56.1% and 28.9%, respectively ($p < 0.001$). Overall 5-year survival rates were 60.2% in hilar N1 and 49.6% in intralobar N1. Overall 5-year survival rates were 58.6% in N1 without node 10 and 35.1% in N1 with node 10. A significant difference was observed between N0 and N1 without node 10 ($p < 0.001$), and N1 without node 10 and N1 with node 10 ($p = 0.033$); however, the difference between N1 with node 10 and N2 was not significant. The status of node 10 involvement was an independent prognostic factor of pN1 patients, as well as age and gender.

Conclusions. Patients with node 10-positive N1 disease have an unfavorable prognosis, and the disease behaves like N2 disease. The definition of clear borderline between N1 and N2 is mandatory to achieve a uniform classification map. This study offers further information for clinical and therapeutic purposes.

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Staging of lung cancer based on the T N M classification is the method internationally accepted for the clinical setting of the disease to evaluate the prognosis, decide appropriate management, and analyze the results of treatment. The current T N M classification was initially proposed by Mountain in 1986 [1] and revised in 1997 [2].

Although this staging classification has been accepted, the anatomic definition of lymph node location—especially the boundary between N1 and N2 stations—has not been completely accorded. Currently, some variations of the lymph node map can be found, and thus considerable discordance exists regarding the designation of sites among investigators in the United States, Europe, and Japan [3]. The American Joint Committee on Cancer (AJCC) [4], Naruke and colleagues [5], and The American Thoracic Society (ATS) [6] introduced the concept of lymph node maps in 1973, 1978, and 1983, respectively.

The Mountain and Dresler modification of the ATS (MD-ATS) map was promulgated in 1997 [2]. Mountain and coworkers defined the boundary between N1 and N2 at the pleural reflection. The Naruke-Japanese map did not mention pleural reflection, however; they defined the lymph node station in relation to the bronchial tree and mediastinal structures [5, 7]. The main discrepancy between these two maps is that the Narke-Japanese map considers lymph nodes around the main bronchus and in the subcarinal space among the inferior border of the main bronchus to be station 10 (N1), whereas most of those are labeled as station 4 or 7 (N2) in the MD-ATS map [8].

A rational approach to the management of lung cancer requires accurate staging to plan the most appropriate treatment and to estimate the prognosis. Patients with pathologically proven N2 are no longer indicated for initial resection. Chemotherapy, chemoradiotherapy, or induction therapy, followed by resection, is the standard treatment of choice [9, 10]. Because the therapeutic strategies for patients with N1 and N2 disease differ greatly, the boundary between N1 and N2 stations where metastasis is confirmed pathologically is most essential. More-

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over, these discordant classifications may lead to a nonunivocal staging, rendering the comparison of different clinical studies difficult. Therefore, we need to define the boundary of lymph node location more precisely and reach consensus on the basis of the most recent evidence.

We reviewed the records of patients with completely resected non-small cell lung cancer (NSCLC) to examine the clinical features of lymph nodal involvement. The purpose of our study was to evaluate the prognostic impact of N1 disease, with a special focus on the significance of involvement of the main bronchial node (No. 10) compared with N2 disease.

Patients and Methods

Of 1601 patients who underwent complete pulmonary resection for NSCLC from 1990 to 2004 at Tokyo Medical University, 202 pN1 patients (12.6 %) without distant metastasis were the focus. Data collection and analyses were approved, and the need for obtaining informed consent from each patient was waived by the Institutional Review Board.

All of those patients underwent lobectomy or pneumonectomy with systemic lymph nodal dissection of the hilum and mediastinum. The histologic tumor type was determined according to the World Health Organization classification. Staging was determined according to the international T N M staging system [2]. All dissected lymph nodes were pathologically examined and classified according to anatomic location by the numbering system of Naruke and colleagues [5].

The station of N1 lymph nodes were classified main bronchial lymph node as No. 10, interlobar as No. 11, lobar bronchial as No. 12, segment bronchial as No. 13, and subsegmental as No. 14. N1 lymph nodes were generally classified into two groups as follows, hilar lymph nodes as No. 10 and 11, and intralobar lymph nodes as No. 12, 13, and 14. We further classified N1 lymph nodes involvement into two groups: pN1 disease who were No. 10-positive as the No. 10+ N1 group, and pN1 disease who were No. 10-negative as the No. 10− N1 group. Single-station metastasis was defined as involvement of only one station, whereas multiple-station metastasis was defined as involvement of more than one station.

For staging, all patients underwent a physical examination, chest roentgenogram, computed tomography (CT) imaging of the thorax, brain, and upper abdomen; bone scintigraphy, and bronchoscopy. The tumor marker, carcinoembryonic antigen (CEA) was also examined preoperatively. Serum CEA levels were measured using Latex photometric immunoassay (Mitsubishi Chemical Medience, Tokyo, Japan), and the upper limit of normal serum CEA levels was 3.0 ng/mL according to the manufacturers.

After resection, the patients were examined at 3-month intervals for 3 years, at 6-month intervals for the next 2 years, and thereafter at 1-year intervals in general. The evaluations included physical examination, chest roentgenogram, CT of the chest, and tumor marker measurement. Abdominal and brain CT as well as bone scintigraphy were done each year.

Table 1. Clinicopathologic Profiles of Patients With pN1 and pN2 Non-Small Cell Lung Cancer, 1990 to 2004

Variable	pN1 (n = 202)	pN2 (n = 274)
Age, median (range), y	64 (31–82)	65 (25–87)
Gender, No.		
Male	158	193
Female	44	81
pT status, No.		
T1	72	63
T2	99	153
T3	19	31
T4	12	27
Location, No.		
Right	117	176
Left	85	98
Histology, No.		
Adenocarcinoma	94	178
Squamous	84	68
Large	14	20
Adenosquamous	3	3
Other	7	5
Operation, No.		
Pneumonectomy	25	36
Lobectomy	177	238
Serum CEA, median (range) ng/mL	3.0 (1.0–213.5)	2.0 (1.0–140.0)

CEA = carcinoembryonic antigen.

Patients with cancer recurrences were carefully divided into two groups according to the site of initial relapse: locoregional or distant. Locoregional recurrence was defined as any recurrent site within the ipsilateral hemithorax, mediastinum, or supraclavicular lymph nodes. All other sites of recurrence were considered distant metastases.

Survival was calculated by the Kaplan-Meier method, and differences in survival were determined by log-rank analysis in which the initial day of treatment was the day of operation. The cause of death was recorded as cancer-related, due to other diseases, or unknown. Deaths that were not because of cancer were censored. Multivariate analysis of clinicopathologic factors was performed using the Cox proportional hazard regression model. A value of $p < 0.05$ was considered statistically significant. Hazard ratios (HR) and 95% confidence intervals (CI) are presented.

Results

Demographics

Of 1601 patients who underwent complete pulmonary resection for NSCLC from 1990 to 2004 at Tokyo Medical University, lymph node involvement was recognized in 1086 (67.8 %) as pN0, 202 (12.6 %) as pN1,

Table 2. Survival at 5 Years in Patients with pN1 Non-Small Cell Lung Cancer According to Prognostic Factors, 1994 to 2002

Variables	Patients, No.	5-Year Survival, %	*p* Value
Age, years			
<65	105	63.4	0.006
≥65	97	48.5	
Gender			
Male	158	50.7	0.007
Female	44	78.0	
pT status			
T1	72	58.7	0.319
T2/T3/T4	130	54.8	
Location			
Right	117	56.3	0.858
Left	85	56.0	
Histology			
Adenocarcinoma	94	55.7	0.830
Not adenocarcinoma	108	56.4	
Operation			
Pneumonectomy	25	46.4	0.303
Lobectomy	177	57.5	
Serum CEA, ng/mL			
<3.0	115	54.7	0.662
≥3.0	45	56.7	
pN1 status			
Intralobar[a]	124	60.2	0.146
Hilar[b]	78	49.6	
No. 10−	181	58.6	0.033
No. 10+	21	35.1	

[a] No. 12, 13, 14 lymph node metastasis. [b] No. 10, 11 lymph node metastasis.

CEA = carcinoembryonic antigen.

and 274 (17.1 %) as pN2 disease. The 202 pN1 patients (158 men, 44 women) were a median age of 64 years (range, 31 to 82 years). Operative procedures included 177 lobectomies and 25 pneumonectomies. The histologic classification was adenocarcinoma in 94 patients, squamous cell carcinoma in 84, large cell carcinoma in 14, adenosquamous in 3, and others in 7. The median value of preoperative serum CEA was 3.0 ng/mL (range, 1.0 to 213.5 ng/mL) (Table 1).

The distribution of pathologic T status was 72 pT1, 99 pT2, 19 pT3, and 12 pT4. The mean value of preoperative serum CEA was 3.0 ng/mL (range, 1.0 to 213.5 ng/mL). Among 202 patients with p-N1 disease, 124 had metastasis of intralobar nodes but not hilar nodes. Patients with hilar N1 nodes metastases were further categorized as 21 with No. 10+ N1 disease and 181 with No. 10− N1 disease (Table 2).

Prognosis

The median follow-up for survivors was 55 months (range, 1 to 200 months). The survival curves for the 1086 pN0, 202 pN1, and 274 pN2 patients are shown in Figure

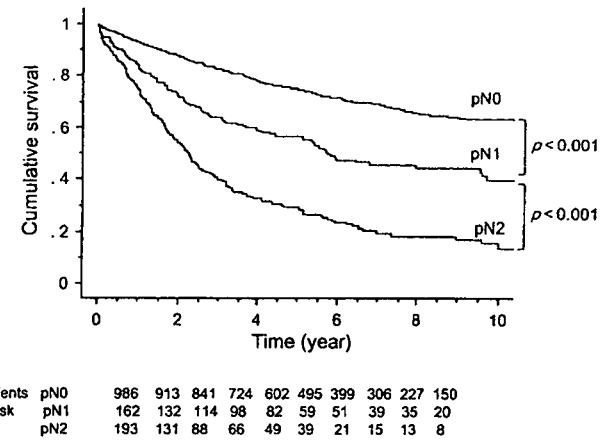

Fig 1. Kaplan-Meier curves show cumulative survival of patients undergoing complete resection for non-small cell lung carcinoma according to pathologic nodal status.

1. The overall 5-year survival rates were 74.7%, 56.1%, and 28.9%, respectively, and this difference was statistically significant ($p < 0.001$).

The association of various prognostic factors was examined by univariate analysis in 202 pN1 patients. Age and gender had a significant effect on survival ($p = 0.006$ and $p = 0.007$, respectively). The 21 No. 10+ N1 patients had significantly worse outcome than the 181 No.10− patients ($p = 0.033$). The overall 5-year survival of No. 10+ N1 patients was 35.1%, which was similar to that of pN2 patients (28.9%; Fig 2; Table 2). However, there was no significant difference in survival when pN1 patients were divided into hilar N1 (No. 10 and No. 11; n = 78) and intralobar N1 (No. 12, 13, and 14; n = 124; $p = 0.146$; Fig 3). There were also no significant differences on survival between the 156 patients with pN1 disease who had single-station metastasis and the 46 with multiple-station metastasis ($p = 0.742$; data not shown). This result implied that lymph node involvement of No. 10 is a poor

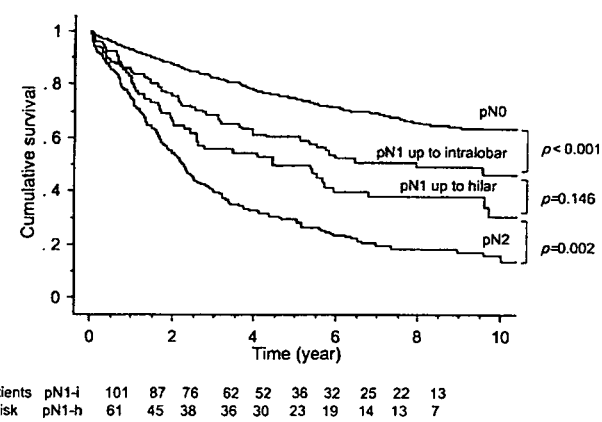

Fig 2. Kaplan-Meier curves show cumulative survival of patients undergoing complete resection for pN1 non-small cell lung carcinoma according to pathologic nodal status. Disease was classified as pN0, intralobar pN1, hilar pN1, and pN2. (Intralobar = No. 12, 13, 14 regional lymph nodes; hilar = No. 11, 10 regional lymph nodes.)

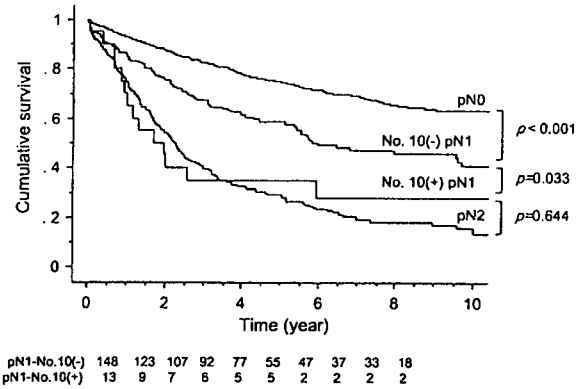

Fig 3. Kaplan-Meier curves show cumulative survival of patients undergoing complete resection for pN1 non-small cell lung carcinoma according to pathologic nodal status. Disease was classified as pN0, pN1 without No. 10 lymph nodes metastasis, pN1 with No. 10 lymph nodes metastasis, and pN.

prognostic marker in pN1 patients compared with No. 10 and No. 11 hilar lymph nodes. In multivariate analysis, the status of No. 10 lymph node involvement was an independent prognostic factor of pN1 patients as well as age and gender (HR, 1.933; 95% CI, 1.089 to 3.430; p = 0.024; Table 3).

We evaluated postoperative cancer recurrence in 100 pN1 patients for limited period, from 1996 to 2002, and 43 (43.0%) had cancer recurrence. Detailed data on cancer recurrence were not available for 6 patients. The initial relapse site was analyzed in the remaining 37 patients. The recurrences were locoregional in 10 (27.0%) and distant in 27 (73.0%). No statistical difference was observed in the distribution of the site of recurrence, locoregional or distant, between No. 10+ N1 and No. 10− N1 patients. Locoregional relapse occurred in 2 No. 10+ N1 patients (33.0%) and distant metastasis occurred 4 patients (67.0%). For those without No. 10 lymph node involvement, locoregional relapse occurred in 8 patients (25.8%) and distant metastasis in 23 (74.2%). The lung was the most common site for distant metastasis in both groups (data not shown).

Comment

During the past 30 years, different types of lymph node maps have been proposed. The distinction of lymph node stations is a most crucial topic that is still not entirely resolved by many lung cancer surgeons. One of the most significant problems concerning lymph node involvement under debate among thoracic oncologists is the definition of the borderline between N1 and N2 stations, which must be clarified, because this discordance could distort therapeutic strategies and stages reported in different studies.

In Naruke's map, lymph nodes in the subcarinal space along the inferior border of the mainstem bronchus are station No. 10 [5], whereas in MD-ATS map, these are labeled as level 7, hence N2 nodes [8]. The borderline between the N1 and N2 station is not clearly defined in Naruke's map. The No. 10 station is defined simply as "nodes around the main bronchus," and adjacent No.4 and No.7 were defined as "nodes at the tracheobronchial angle" and "nodes below tracheal carina," respectively [7].

In the MD-ATS map, the pleural reflection was set as a clear borderline for N1-N2 stations [8], with N1 nodes as those located distal to the mediastinal pleural reflection and within visceral pleura. This definition involves the proximal part of the hilar lymph nodes being classified within the N2 category because the proximal part of the mainstem bronchus lies within the mediastinal pleural envelope. However, concerning the borderline between N1 and N2 station, Asamura and colleagues [11] reported that the pleural reflection is recognized as a plane rather than as a line, and the reflecting line can be easily moved by retracting the lung anteriorly or posteriorly.

Some patients considered to have T1 2N1 M0 stage II disease in Japan would be considered to have T1 2N2 M0 stage IIIA disease in all other countries. This difference in nodal diagnosis might be a cause of staging migration.

In this study, we used Naruke's lymph node map to review the records of 1601 consecutive patients who had undergone complete resection for NSCLC. We also examined the spread pattern of lymph node metastases and investigated the outcome according to the level of the involved nodes.

Some investigators reported hilar lymph node metastasis is a significant unfavorable prognostic factor in p-N1 disease [12–18]. First, we divided N1 lymph nodes into two stations as follows, hilar lymph nodes (No. 10 and 11) and intralober lymph nodes (No. 12, 13, and 14). However, the difference in survival between hilar N1 and intralobar N1 was not significant.

Second, we further categorized patients with hilar N1 node metastases as those with and those without main bronchus node (No. 10) involvement. Among the 202 p-N1 patients, the 21(10.4%) identified with No. 10-positive N1 disease had a significantly worse prognosis than those with No. 10− N1 disease (p = 0.031). Moreover, the overall 5-year survival of patients with No. 10+

Table 3. Factors Influencing Survival in Patients With pN1 Non-Small Cell Lung Cancer by Multivariate Analysis

Variables	Favorable	Unfavorable	OR (95% CI)	p Value
Gender	Female	Male	2.109 (1.152–3.862)	0.016
Age, y	<65	≥65	1.771 (1.188–2.639)	0.005
No. 10 LN involved	Negative	Positive	1.933 (1.089–3.430)	0.024

CI = confidence interval, LN = lymph node; OR = odds ratio.

N1 disease was 35.1%, which was similar to the 28.9% survival in N2 disease. Multivariate analysis demonstrated that No. 10 lymph node involvement was one of the independent prognostic factors of pN1 patients as well as age and gender. Although the number of patients who were No. 10+ in this study is relatively small, we found that pN1 with No. 10+ disease behaves like a more advanced stage. Matsuoka and colleagues [19] reported the same results, including multivariate analysis, as ours concerning the survival benefit for the N1 disease with or without No. 10 involvement.

Several authors reported that the mode of metastasis in interlobar N1 tended to resemble that of N0, whereas that of hilar N1 behaved like N2 disease [12, 13, 15, 17, 18]; however, the modality of recurrence in our study for the limited period was not affected by the level of pN1 involvement. Our result that distant metastasis was predominant in the recurrent pattern over locoregional recurrence in p-N1 patients implies that nodal involvement might be a surrogate marker for distant metastasis, even if the site of metastasis is the interlobar lymph nodes.

Previous studies suggest that multiple levels of N1 stations are associated with a worse outcome than single-level disease [14, 20–23]. We were unable to identify the differences. Concerning the prognostic effect of the number of involved N1 stations, which may be one of the strong predictable factors for poor survival, it is possible that these analysis did not include enough patients to lead to a valid conclusion.

When taken together, the discrepancy between the Naruke map and the MD-ATS map might contribute to borderline cases between N1 and N2, such as multiple-station N1 disease or hilar N1 disease. The staging committee of the International Association for the Study of Lung Cancer (IASLC) is proposing a new international lymph node map that provides very precise definitions of the anatomic boundaries of each lymph node station and reconciles the differences between the Naruke map and the MD-ATS map [22].

The nodes around the junction of the hilum and mediastinum are key points at issue. Indeed, one of the most important problems is to decide whether the main bronchus nodes belong to the N1 or N2 station in relation to prognosis as well as anatomy. In this study, we found a difference in survival among patients with nodal metastasis up to either station 11 or station 10, whereas survival did not differ among patients with nodal metastases up to either station 10 or N2 station. This result suggested that nodes could be designated as intermediate between N1 and N2 and that there might be a borderline between N1 and N2 nodes around the main bronchus in accordance with the Naruke map. Moreover, our study demonstrated that the involvement of main bronchial nodes has a prognostic significance similar to that of single-station N2 and could be considered as an early N2 disease.

We fervently hope to have a single, accurate map of lymph node stations that can be used universally. Otherwise, it will be difficult to make progress in therapeutic strategies for lung cancer.

In conclusion, survival in patients with pN1 disease differs according to the type of lymph node involvement. Patients with No. 10 involvement have an unfavorable prognosis, and the disease behaves like N2 disease. The definition of a clear borderline between N1 and N2 is mandatory to achieve a uniform classification map. Further clinical studies may give more accurate information about the real prognostic value of No. 10 involvement to improve the clinical assessment and therapeutic strategies.

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Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: An analysis of Japan Multinational Trial Organisation LC00-03

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ABSTRACT

We examined the impact of pretreatment neutrophil count on survival in patients with advanced non-small-cell lung cancer (NSCLC). A total of 388 chemo-naïve patients with stage IIIB or IV NSCLC from a randomised controlled trial were evaluated. The effects of pretreatment peripheral blood neutrophil, lymphocyte and monocyte counts and neutrophil–lymphocyte ratio on survival were examined using the proportional hazards regression model to estimate hazard ratios after adjustment for covariates. The optimal cut-off value was determined by proportional hazards regression analysis with the minimum P-value approach and shrinkage procedure. After adjustment for prognostic factors, the pretreatment elevated neutrophil count was statistically significantly associated with short overall ($P = 0.0008$) and progression-free survival ($P = 0.024$), whereas no association was found between prognosis and lymphocyte or monocyte count. The cut-off value selected for neutrophil count was 4500 mm^{-3} (corrected hazard ratio, 1.67; 95% confidence interval (CI), 1.09–2.54). The median survival time was 19.3 months (95%CI, 16.5–21.4) for the low-neutrophil group (<4500 mm^{-3}, $n = 204$) and was 10.2 months (95%CI, 8.0–12.3) for the

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high-neutrophil group ($\geqslant$4500 mm^{-3}, n = 184). We confirmed that pretreatment elevated neutrophil count is an independent prognostic factor in patients with advanced NSCLC receiving modern chemotherapy. Neutrophil count is easily measured at low cost, and it may be a useful indicator of patient prognosis.

1. Introduction

The prognosis for patients with advanced non-small-cell lung cancer (NSCLC) (TNM stage IIIB with a positive pleural effusion, or stage IV) has improved with recent advances in systemic chemotherapy, but still remains poor, with a median overall survival time between 4 and 15 months.[1] Prognostic factors identified in previous studies include tumour stage, performance status (PS), weight loss, sex, plasma lactate dehydrogenase (LDH) level and the presence of bone, liver or skin metastases.[2] Although novel immunological and histological biomarkers have been identified, these are often time-consuming to measure, and this is not part of the standard practice.

It is now evident that inflammatory cells in the tumour microenvironment have significant effects on tumour development.[3–6] Elevation in the pretreatment neutrophil count has been proposed as a prognostic factor for poor survival in patients with metastatic renal cell carcinoma,[7–9] and elevated neutrophil, monocyte or leucocyte count has been associated with poor survival in patients with metastatic melanoma.[10,11] A high-neutrophil–lymphocyte ratio may be related to poor prognosis in patients with colorectal cancer[12] and in those with advanced gastric cancer.[13] The European Lung Cancer Working Group found that the high-neutrophil count was an independent prognostic factor for poor survival in patients with unresectable advanced NSCLC[14] and in those with small-cell lung cancer.[15] A retrospective study found that neutrophil count was of prognostic value in patients with lung cancer.[16]

The aim of this study was to examine and confirm the impact of pretreatment peripheral blood neutrophil, monocyte and lymphocyte counts on overall and progression-free survival in a well-defined population of patients with advanced NSCLC being treated with regimens using newer chemotherapeutic agents in a randomised controlled clinical trial.

2. Patients and methods

2.1. Study population

A total of 401 chemo-naïve NSCLC patients with stage IIIB with pleural effusion or stage IV without brain metastasis, who had Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, were enrolled from 45 institutions in Japan between March 2001 and April 2005 into Japan Multinational Trial Organisation LC00-03[17] (registered with ClinicalTrials.gov identifier NCT00079287). Patients underwent one of two treatment regimens: intravenous vinorelbine (25 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 every 21 d for three cycles, followed by intravenous docetaxel (60 mg/m^2) on day 1 every 21 d for three cycles [VGD arm, n = 196] versus intravenous paclitaxel (225 mg/m^2) and carboplatin (area under the curve = 6) for 3 h on day 1, every 21 d for six cycles [PC arm, n = 197]). As there were no significant differences between treatment groups in terms of either overall (hazard ratio: 0.996, P = 0.974) or progression-free survival (hazard ratio: 0.966, P = 0.742), the combined data from the two arms were analysed in this study. Of 393 eligible patients, information regarding pretreatment neutrophils in peripheral blood was not available for five patients. Thus, data from 388 patients were included in the present study.

2.2. Statistical analysis

Overall survival was defined as the time from randomisation until death from any cause, and progression-free survival was defined as the time from randomisation until objective tumour progression or death. Survival curves were estimated with the Kaplan–Meier method. Associations between the factors and the prognosis were examined with the log-rank test in univariate analyses. The prognostic impact of pretreatment peripheral blood neutrophil, lymphocyte and monocyte counts, and neutrophil–lymphocyte ratio were examined using the proportional hazards regression model to estimate hazard ratios after adjustment for covariates without variable selection. Optimal cut-off points for continuous variables were selected using the minimum P-value approach with correction of the P-value.[18] The corrected hazard ratio and its 95% confidence interval (CI) were estimated using a shrinkage procedure with bootstrap resampling.[19] All statistical analyses were done using SAS version 9.1 (SAS Institute, Cary, NC).

3. Results

3.1. Patients' characteristics

Of 388 patients, 276 patients had died, and the median follow-up time for the 112 surviving patients was 567 d (range: 70–1711 d). The characteristics of the 388 patients (276 men [71%], 112 women [29%], median age 65 years [range, 33–81 years]) included in the present study are shown in Table 1. Median pretreatment counts of neutrophils, lymphocytes and monocytes were 4304 mm^{-3}, 1386 mm^{-3} and 404.2 mm^{-3}, respectively. Spearman's rank correlations were 0.351 for neutrophils and monocytes, 0.034 for neutrophils and lymphocytes and 0.352 for monocytes and lymphocytes.

3.2. Relationship between pretreatment neutrophil, lymphocyte and monocytes counts and survival

In univariate analyses, pretreatment elevated counts of neutrophils were statistically significantly associated with short

Table 1 – Baseline patients characteristics (n = 388).

Characteristics	No.	%
Age, years, median (range)	65 (33–81)	
Sex		
Male	276	71
Female	112	29
Smoking history		
Non-smokers	96	25
Former smokers	107	28
Current smokers	168	43
Unknown	17	4
Stage		
IIIB	68	18
IV	320	82
Histologic type		
Squamous cell	76	20
Adenocarcinoma	274	70
Others	38	10
ECOG performance status		
0	154	40
1	234	60
Weight loss (from 6 months before enrolment)		
<5%	317	82
≥5%	71	18
LDH		
Normal (<ULN)	279	72
High (≥ULN)	109	28
Bone metastases		
No	280	72
Yes	108	28
Liver metastases		
No	357	92
Yes	31	8
Skin metastases		
No	379	98
Yes	9	2
Neutrophils, mm^{-3}, median (range)	4304 (205–17,100)	
Lymphocytes, mm^{-3}, median (range)	1386 (243–4200)	
Monocytes, mm^{-3}, median (range)[a]	404.2 (0–1620)	
Red blood cells, $\times 10^4$ mm^{-3}, median (range)	420 (286–579)	
Platelets, $\times 10^4$ mm^{-3}, median (range)[b]	26 (11–380)	

ULN: upper limit of normal.
a One missing value.
b Two missing values.

overall (Fig. 1A, $P < 0.0001$) and progression-free survival (Fig. 1B, $P = 0.0001$). Although lymphocyte count did not correlate with survival, there were significant relationships between high-neutrophil–lymphocyte ratio and short overall ($P < 0.0001$) and progression-free survival ($P = 0.005$). The elevated monocyte count was also significantly associated with short overall survival ($P = 0.004$), and was moderately related to short progression-free survival ($P = 0.052$). We selected sex, smoking history, stage, ECOG PS, weight loss, plasma LDH and the presence of bone, liver or skin metastases as the known pretreatment prognostic factors.[2,14] Adjusted hazard ratios for the relationship between pretreatment neutrophil, lymphocyte and monocyte counts and neutrophil–lymphocyte ratio and overall and progression-free survival after adjustment for the known prognostic factors are shown in Table 2. There was a statistically significant association between elevated neutrophil count and short overall ($P = 0.0008$) and progression-free survival ($P = 0.024$), and between high-neutrophil–lymphocyte ratio and short overall ($P = 0.011$) and progression-free survival ($P = 0.040$), whereas no association was found between lymphocyte or monocyte count and prognosis. The relationship between neutrophil count and both overall and progression-free survival was linear, whereas the relationship between neutrophil–lymphocyte ratio and overall survival was to some degree non-linear.

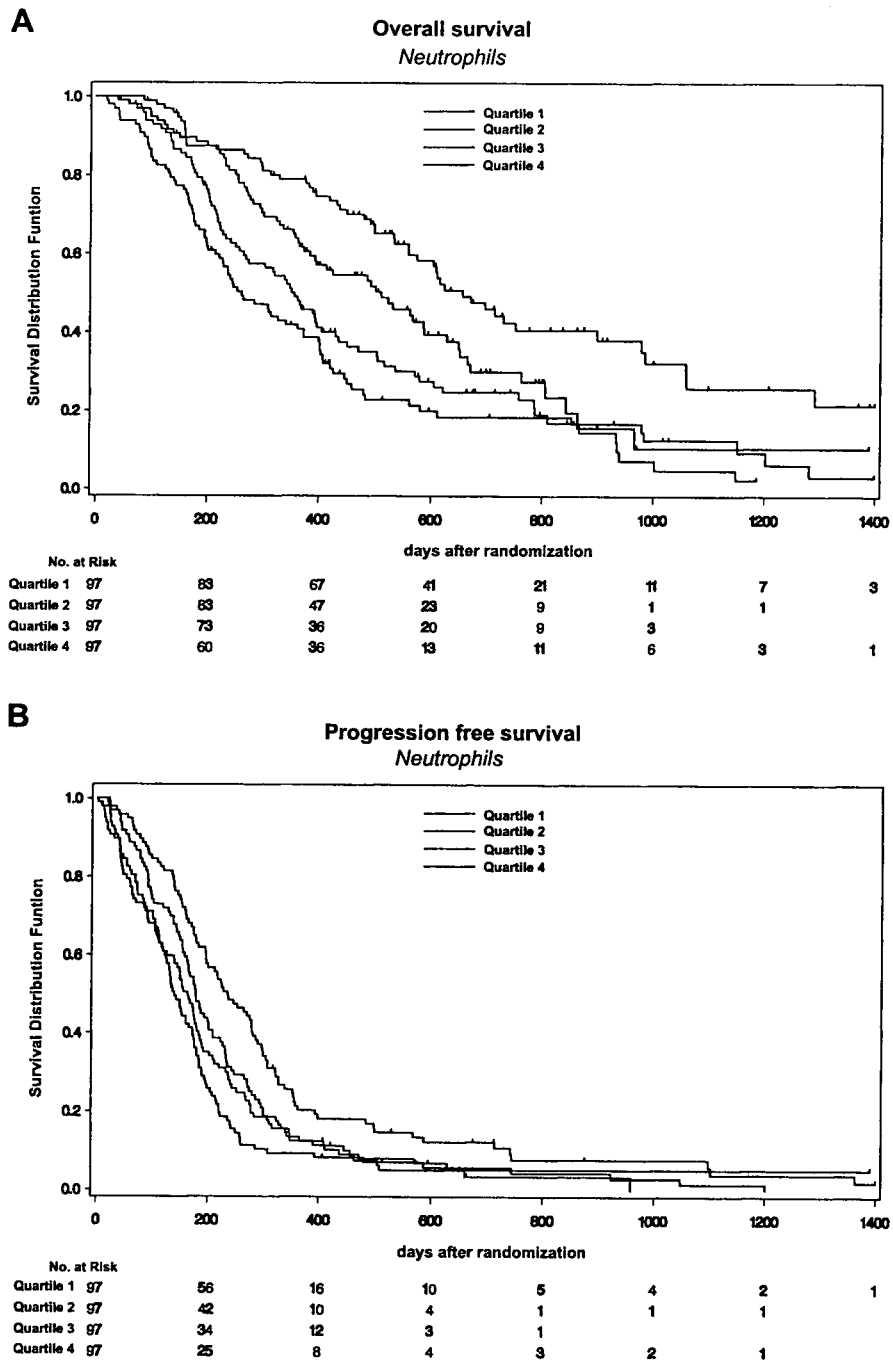

Fig. 1 – Kaplan–Meier estimates according to quartiles for the effect of pretreatment neutrophil count on (A) overall survival and (B) progression-free survival.

3.3. *Optimal cut-off value for pretreatment neutrophil count*

In selecting optimal cut-off values for the effect of neutrophil count on overall survival, the range between the 5th percentile (2205 mm^{-3}) and the 95th percentile (9657 mm^{-3}) for distribution of neutrophils was selected, and the possible cut-off points at intervals of 500 mm^{-3} from 2500 mm^{-3} to 9500 mm^{-3} were considered (giving 15 candidate cut-off points). Using the minimum P-value approach, the selected cut-off value for neutrophil count was 4500 mm^{-3} (corrected $P = 0.0009$) and the corrected shrunk hazard ratio was 1.67 (95%CI, 1.09–2.54, from 100 bootstrap samples; Table 3). The selected optimal cut-off value did not change even when we used the stratified proportional hazards model, stratified by the combination of all covariates. The median survival time was 19.3 months (95%CI, 16.5–21.4) for the low-neutrophil group (<4500 mm^{-3}, $n = 204$) and was 10.2 months (95%CI, 8.0–12.3) for the high-neutrophil group (≥4500 mm^{-3}, $n = 184$) (Fig. 2). The results of prognostic factor analysis for overall survival are shown in Table 4. In terms of the relative order of significance, neutrophil count was one of the most important

Table 2 – Multivariate Cox regression analysis for neutrophil, lymphocyte and monocyte counts.

Factors	Overall survival				Progression-free survival			
	Hazard ratio[a]	95%CI	P	P[b]	Hazard ratio[a]	95%CI	P	P[b]
Neutrophil count (mm^{-3})								
Quartile 1 (<3278)	1	–	–	0.0008	1	–	–	0.024
Quartile 2 (<4304)	1.25	0.86–1.82	0.251		1.19	0.88–1.61	0.258	
Quartile 3 (<5873)	1.76	1.22–2.53	0.002		1.32	0.97–1.78	0.076	
Quartile 4 (⩾5873)	1.94	1.35–2.79	0.0003		1.61	1.18–2.19	0.003	
Lymphocyte count (mm^{-3})								
Quartile 1 (<1082.3)	1	–	–	0.251	1	–	–	0.545
Quartile 2 (<1386.1)	1.14	0.81–1.61	0.438		1.10	0.82–1.47	0.535	
Quartile 3 (<1821.8)	0.83	0.58–1.19	0.303		0.88	0.65–1.20	0.424	
Quartile 4 (⩾1821.8)	1.13	0.80–1.59	0.495		0.95	0.70–1.28	0.732	
Neutrophil–lymphocyte ratio								
Quartile 1 (<2.093)	1	–	–	0.011	1	–	–	0.040
Quartile 2 (<2.914)	1.42	0.98–2.05	0.065		1.39	1.02–1.88	0.035	
Quartile 3 (<4.744)	1.83	1.27–2.62	0.001		1.50	1.09–2.06	0.012	
Quartile 4 (⩾4.744)	1.56	1.09–2.24	0.015		1.48	1.09–2.02	0.013	
Monocyte count (mm^{-3})								
Quartile 1 (<289.9)	1	–	–	0.381	1	–	–	0.969
Quartile 2 (<402.3)	0.93	0.65–1.32	0.674		1.05	0.78–1.41	0.755	
Quartile 3 (<550.4)	1.07	0.75–1.52	0.712		0.99	0.72–1.35	0.924	
Quartile 4 (⩾550.4)	1.26	0.89–1.78	0.203		1.04	0.76–1.42	0.792	

CI: confidence interval.
a Adjustment for sex, smoking, stage, ECOG PS, weight loss, LDH, bone metastases, liver metastases and skin metastases.
b P-values for global association.

Table 3 – Cutpoint analysis for neutrophil count and overall survival.

Neutrophil count (cut-off points, mm^{-3})	Uncorrected hazard ratio[a]	Uncorrected P-value
2500	1.95	0.016
3000	1.78	0.001
3500	1.40	0.021
4000	1.57	0.0007
4500	1.72[b]	<0.0001[c]
5000	1.49	0.002
5500	1.51	0.002
6000	1.46	0.008
6500	1.75	0.0004
7000	1.62	0.005
7500	1.59	0.015
8000	1.88	0.004
8500	1.86	0.007
9000	1.78	0.017
9500	1.89	0.009

a (Hazard of death in patients on or above the cut-off point) divided by (hazard of death in patients below the cut-off point), after adjustment for sex, smoking, stage, ECOG PS, weight loss, LDH, bone metastases, liver metastases and skin metastases.
b Corrected hazard ratio: 1.67 (95%CI, 1.09–2.54).
c Corrected P = 0.0009.

prognostic factors along with ECOG PS ($P < 0.0001$), LDH ($P = 0.001$) and smoking history ($P = 0.002$). The adjusted hazard ratios for the relationship between neutrophil count (<4500 mm^{-3} versus ⩾4500 mm^{-3}) and survival according to the treatment groups were 1.62 (95%CI, 1.14–2.30) in the PC arm ($n = 195$) and 1.74 (95%CI, 1.22–2.48) in the VGD arm ($n = 193$). There was no interaction between the neutrophil count and the treatment arms (P for interaction = 0.437).

3.4. *Relationship between pretreatment neutrophil count and intensity of chemotherapy*

In order to evaluate the effect of neutrophil count on administration of chemotherapy and toxicity, we analysed the dose intensity of chemotherapeutic agents and the incidence of toxicity in each arm. In the VGD arm, there was no significant difference in the relative dose intensity of vinorelbine or

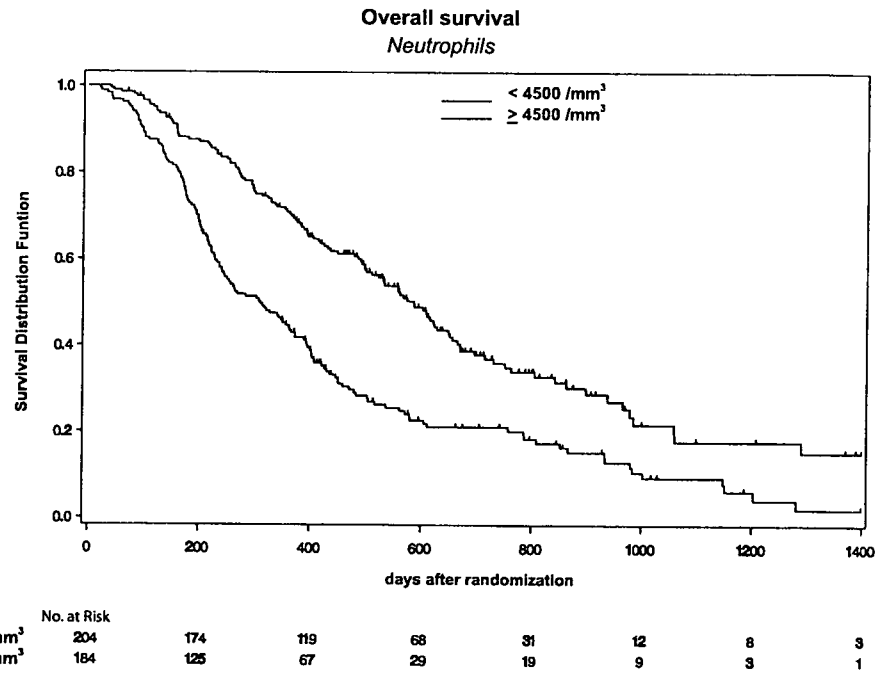

Fig. 2 – Kaplan–Meier estimates according to optimal cut-off point (4500 mm^{-3}) for the effect of pretreatment neutrophil count on overall survival.

gemcitabine between the low-neutrophil group (<4500 mm^{-3}) and the high-neutrophil group (≥4500 mm^{-3}). However, the relative dose intensity of docetaxel was significantly lower in the high-neutrophil group (median, 33%) than in the low-neutrophil group (median, 87%) ($P = 0.040$, Wilcoxon test).

The toxicity due to treatment was also analysed. In the VGD arm, the incidence of grade 3 or 4 non-haematological toxicity within the first three cycles of treatment was significantly higher in the high-neutrophil group than in the low-neutrophil group (26.5% versus 8.5%; $P = 0.002$, Fisher's exact test). Significantly fewer cycles were administered in the high-neutrophil group than in the low-neutrophil group (mean, 2.9 cycles versus 4.7 cycles; $P < 0.0001$, Wilcoxon test). None of the patients in the high-neutrophil group who experienced grade 3 or 4 non-haematological toxicity within the first three cycles completed the planned six cycles. The proportion of patients requiring reductions in the doses of vinorelbine or gemcitabine within the first two cycles of treatment was significantly higher in the low-neutrophil group (45.2%) than in the high-neutrophil group (26.4%) ($P = 0.007$, Fisher's exact test). No such differences in dose intensity or toxicity were seen in the PC arm.

4. Discussion

In multivariate analysis after adjustment for known prognostic factors, we found linear associations between pretreatment elevated neutrophil count and short overall and progression-free survival. As there was no such association for the lymphocyte count, the relationship between neutrophil-lymphocyte ratio and overall survival was also found, however, it was to some degree weak and non-linear. As a consequence, we consider that absolute neutrophil count may better serve as a prognostic factor. An optimal cut-off value for the relationship between neutrophil count and overall survival was identified as 4500 mm^{-3} (corrected hazard ratio, 1.67; 95%CI, 1.09–2.54). In the VGD arm, the low-neutrophil group (<4500 mm^{-3}) tended to have a lower incidence of severe non-haematological toxicity and tolerated longer administration of the chemotherapeutic agents compared with the high-neutrophil group. However, no such association was found in the PC arm, and pretreatment neutrophil count was equally predictive of prognosis in both treatment arms when analysed separately. We therefore do not consider it likely that the pretreatment neutrophil count serves as an indicator of intolerance to chemotherapy, rather than as an indicator of poor prognosis.

A number of studies in the last two decades have suggested an association between the neutrophil count or neutrophil–lymphocyte ratio and the prognosis of cancer patients,[7–16] although no acceptable explanations for the mechanisms underlying these observed associations have been proposed. Moreover, although neutrophilia often accompanies the diagnosis of cancer, the causes of neutrophilia in cancer patients are not fully understood, and are likely to be the result of a combination of factors. One obvious cause of neutrophilia is paraneoplastic production of myeloid growth factors by cancer cells themselves. Granulocyte-colony stimulating factor (G-CSF) is a growth factor that acts selectively on bone marrow granulocytic lineage cells, and is considered to play a central role in granulopoiesis. Administration of G-CSF was reported to increase bone marrow neutrophil precursors and shorten bone marrow transit time in mice and humans,[20–22] resulting in marked increases in the production of neutrophils. Granulocyte macrophage-colony stimulating factor (GM-CSF) and macrophage-colony stimulating factor

Table 4 – Prognostic factor analysis for overall survival using proportional hazards regression model without variable selection.

Factors	Hazard ratio	95%CI	P-value
Performance status			
0	1.00	–	–
1	2.03	1.54–2.67	<0.0001
Neutrophil count			
<4500 mm^{-3}	1.00	–	–
⩾4500 mm^{-3}	1.72	1.34–2.19	<0.0001
LDH			
Normal	1.00	–	–
High	1.57	1.20–2.05	0.001
Smoking history			
Non/former smokers	1.00	–	–
Current smokers	1.56	1.18–2.06	0.002
Liver metastases			
No	1.00	–	–
Yes	1.62	1.08–2.43	0.020
Sex			
Male	1.00	–	–
Female	0.74	0.54–1.02	0.064
Weight loss			
<5%	1.00	–	–
⩾5%	1.30	0.96–1.76	0.092
Skin metastases			
No	1.00	–	–
Yes	1.78	0.85–3.72	0.124
Bone metastases			
No	1.00	–	–
Yes	1.21	0.90–1.63	0.204
Stage			
IIIB	1.00	–	
IV	1.24	0.88–1.75	0.222

are the other examples of haematopoietic growth factors that cause neutrophilia by *in vivo* administration.[23,24] A variety of non-haematopoietic malignant tumours including mesothelioma,[25] squamous cell carcinoma of the oropharynx,[26] melanoma,[27] glioblastoma[28] and carcinoma of the lung[29] have been reported to secrete G-CSF or GM-CSF and cause significant leucocytosis. Although there have been several reports of the existence of autocrine growth loops for G-CSF and GM-CSF in non-haematopoietic tumour cells, implying G-CSF- and GM-CSF-producing tumours are more aggressive,[30,31] the relationship between paraneoplastic production of myeloid growth factors and prognosis remains unclear. Furthermore, considering the linear relationship we observed between pretreatment neutrophil count and survival in this study, ectopic production of myeloid growth factors, which often causes marked neutrophilia, does not seem to be the sole reason for the observed association between neutrophil count and prognosis.

Other possible factors that cause neutrophilia are coexistent infection and cancer-related inflammation. In this study, patients with active infection were excluded based on the eligibility criteria of the trial, and there is no clear reason to assume the existence of latent infection as the cause of neutrophilia and poor prognosis.

The association between cancer and inflammation was initially pointed out during the 19th century. However, recent advances in understanding of tumour biology have stimulated renewed interests in searching for links between cancer and inflammation.[3–6] Today, it is widely accepted that chronic inflammation contributes to the initiation and progression of cancer. Furthermore, it is now known that inflammatory processes almost always accompany cancer, and persistence of chronic inflammation-like processes within cancer tissue causes suppression of anti-tumour immunity by several mechanisms, such as activation of type 2 T-helper responses, recruitment of regulatory T cells and activation of the chemokine system, and results in promotion of cancer growth and metastasis. Thus, inflammation may result in the aggressive growth of a tumour. The cytokines interleukin (IL)-6 and tumour necrosis factor-alpha (TNFα), which are implicated in the pathogenesis of cancer-related inflammation as well as of acute inflammatory processes, are also known to induce neutrophilia.[32–34] It is possible that the neutrophil count at diagnosis indicates the severity or nature of inflammation occurring within the tumour, and thus reflects prognosis. In a recent report, a proportion of patients with metastatic cancer were shown to have IL-6-mediated elevation in serum cortisol levels. This may partly explain the neutrophilia of cancer

patients, although its contribution to outcome is not yet known.[35]

We did not measure inflammatory markers such as C-reactive protein or haemogram of total white cell count in this study. However, we are investigating correlations between several cytokines and prognosis in a correlative study of another clinical trial (ClinicalTrials.gov identifier NCT00616031).

Besides inflammation in cancer tissue, host factors may influence the prognosis of cancer patients. It is now known that lifetime exposure to infectious diseases and other sources of inflammation not only is related to the pathogenesis of cancer, but also plays an important role in ageing and influences longevity.[36,37] Ageing is a complex process, and numerous genes are known to have associations with longevity.[38] Polymorphisms of the genes that encode proteins involved in inflammatory processes (e.g. IL-1, IL-6, IL-10 and TNFα) are suspected to affect ageing and longevity. Given the close relationship between cancer and inflammation, it is natural to speculate that genetic polymorphisms in inflammation-related genes may also influence host responses to cancer and prognosis; peripheral neutrophil count may be an indicator of this association.

Another possibility is that neutrophil directly down-regulates host cellular immunity against cancer, thereby affecting the prognosis. *In vitro* studies showed that neutrophils suppress the cytolytic activity of lymphocytes and natural killer cells when co-cultured with neutrophils and lymphocytes from normal healthy donors; the degree of suppression was proportional to the number of neutrophils added.[39–41] The clinical relevance of these effects seen in *in vitro* studies is currently unknown. The biological basis for the multi-factorial and complex association is also unknown, and merits further research.

5. Conclusion

Using the dataset from a randomised controlled trial, we have confirmed that pretreatment peripheral blood neutrophil count is an independent prognostic factor in patients with advanced NSCLC receiving modern chemotherapy. The results need to be investigated for generalisability in other populations. Since neutrophil count is easily measured at low cost, it may be a useful predictor of prognosis in clinical practice. Considering the strength of the association reported here, neutrophil count should be taken into account as a stratification factor in future randomised clinical trials of patients with advanced NSCLC.

Conflict of interest statement

Kaoru Kubota has received honoraria from Eli Lilly, Sanofi-Aventis, and Chugai. All other authors declared no conflicts of interest.

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Postoperative Adjuvant Chemotherapy for Node-Positive Cervical Adenocarcinoma

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Abstract: We examined the effectiveness of postoperative adjuvant chemotherapy for node-positive cervical adenocarcinoma. During the period from 1994 to 2002, 98 consecutive patients with clinical stage I and II cervical adenocarcinoma were treated surgically without having undergone any prior treatment. Surgical procedures included radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Postoperatively, 21 patients were found to have lymph node metastasis, and all were treated with chemotherapy in the absence of radiotherapy. All patients were followed up for at least 5 years. Recurrence developed in 9 of the 21 patients, all 9 died of the disease. Six of the 9 recurrences were extrapelvic lesions. Five-year disease-free survival and overall survival were 57% and 67%, respectively. Recurrence was more common in patients with 6 or more positive nodes than in those with fewer than 3 positive nodes. These data suggest the potential role of postoperative chemotherapy for treatments of cervical adenocarcinoma. However, the effectiveness of chemotherapy alone in node-positive cervical adenocarcinoma was likely not as high as that in squamous cell carcinoma. Despite our use of postoperative chemotherapy in the absence of pelvic radiation, the disease recurred predominantly at distant sites.

Key Words: Cervical cancer, Adenocarcinoma, Chemotherapy

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Although the efficacy of radical hysterectomy and pelvic lymphadenectomy has been shown for early-stage cervical adenocarcinoma,[1] the presence of surgically detected pelvic lymph node metastasis correlates with treatment failure.[2–8] Node-positive patients with cervical adenocarcinoma have traditionally been treated with radiotherapy (RT) alone, but improving the prognosis for such patients has been a major issue in gynecologic oncology. In 2000, Peters et al[9] reported that concurrent chemoradiotherapy (CCRT) was more effective for treatment of high-risk cervical cancer, including cervical adenocarcinoma, than RT alone.

Concurrent chemoradiotherapy is accepted as a standard treatment of high-risk cervical cancer,[10] but alternative treatments have been investigated in an attempt to improve survival or more importantly to reduce treatment-related morbidity. Several studies have suggested the potential role of chemotherapy (CT) alone for treatment of node-positive cervical cancer.[11–14] At our facility, cervical cancer patients with lymph node involvement have been treated with CT alone since 1993. Here, we report the results of treatment of node-positive cervical adenocarcinoma with CT alone and discuss the possible use of this treatment.

PATIENTS AND METHODS

During the period from 1994 to 2002, 98 consecutive patients with clinical stage IB to IIB adenocarcinoma of the uterine cervix were treated surgically at the Cancer Institute Hospital (Tokyo, Japan). Patients with adenosquamous carcinoma and those who had received neoadjuvant CT were excluded from the study. Surgical procedures consisted of radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. A median of 32 (range, 15–61) lymph nodes was obtained in this series. Of the 98 patients, 21 (21.4%) were found to have lymph node metastasis and formed the study population.

All 21 node-positive patients received CT postoperatively without RT. In 19 (90.5%) of the 21 patients, CDDP(cisplatin)-based CT regimens were administered. A CT regimen consisting of ifosfamide (700 mg/m^2 on days 1–4), epiadriamycin (50 mg/m^2 on day 5), and cisplatin (15 mg/m^2 on days 1–5) was used in 14 patients (67%). In 2 patients, a non–CDDP-based regimen consisting of irinotecan hydrochloride (120 mg/m^2 on days 1 and 15) and mitomycin C (7 mg/m^2 on day 1) was used (Table 1). These regimens were generally scheduled to be repeated every 4 weeks for 5 cycles.

Treatment outcomes, including toxicity of CT, were investigated. All patients were followed up for at least for 5 years. Disease-free survival and overall survival rates were calculated by the Kaplan-Meier method and analyzed by log-rank test. Differences in ratios were analyzed with the Fisher exact test. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (Version 3).

RESULTS

Patients' characteristics are shown in Table 1. Median age was 45 years (range, 31–69 years). Of the 21 node-positive patients, 13 showed 100% stromal invasion, and 8 showed parametrial involvement. The 5-year disease-free survival and overall survival rates in total cases were 57% and 67%, respectively (Fig. 1). Relapse rates by

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TABLE 1. Patients' characteristics (n = 21)

Age, mean (range), y	45 (31–69)
Clinical stage	
IB1	14
IB2	4
IIB	3
Pathologic type	
Endocervical type	
Well differentiated	13
Moderately differentiated	1
Poorly differentiated	5
Serous type	2
Capillary space involvement	
Yes	20
No	1
Depth of stromal invasion	
1–50%	3
51–99%	5
100%	13
Parametrial invasion	
Yes	8
No	13
Tumor size, cm	
<4	15
≥4	6
Chemotherapy regimen	
IEP	14
Other CDDP-based	5
CPT-11/MMC	2

CPT-11 indicates irinotecan hydrochloride; IEP, ifosfamide, epiadriamycin, and cisplatin; MMC, mitomycin C.

the number and sites of metastatic nodes are shown in Table 2. Recurrence was more frequent in patients with more than 6 positive nodes than in those with fewer than 3 positive nodes. Sites of relapse are shown in Table 3. Six of the 9 recurrences were extrapelvic lesions. Disease-free survival in relation to parametrial involvement is shown in Figure 2. Involvement of the parametrium decreased the 5-year disease-free survival rate from 64% to 43%, but this change was not statistical significant ($P = 0.3346$).

Toxicity was generally acceptable, and there was no treatment-related deaths. Grade 3 hematologic toxicity was observed in 47.6% of patients, and grade 4 was observed in 14.3%. Grade 3 gastrointestinal toxicity was observed in 14.3% of patients and sometimes necessitated termination of CT. Grade 2 alopecia was observed in most patients.

DISCUSSION

Although it is controversial whether there is a difference in survival between women with squamous cell carcinoma and those with adenocarcinoma of the cervix,[15,16] it seems that the most significant difference in prognosis between the 2 types of cervical cancer occurs in patients with surgically detected pelvic lymph node metastasis.[5,6] Nakanishi et al[6] analyzed the literature regarding prognosis of patients with cervical cancer treated surgically and concluded that the difference in prognosis between adenocarcinoma

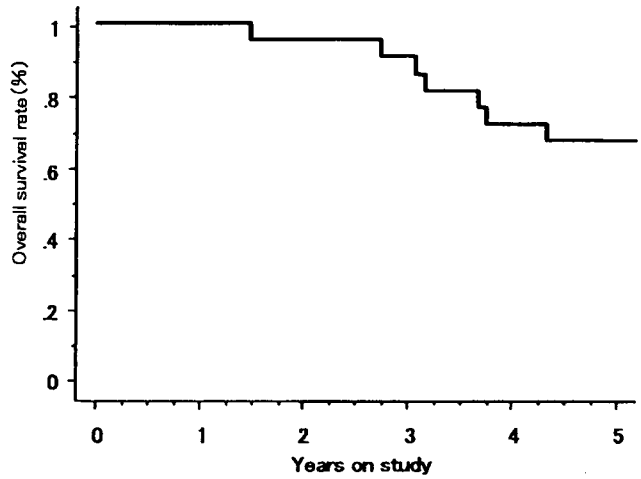

FIGURE 1. Overall survival in node-positive patients with cervical adenocarcinoma treated postoperatively with CT alone. The 5-year overall survival rate was 67% in 21 node-positive patients with cervical adenocarcinoma.

and squamous cell carcinoma depends on the ratio of node-positive cases with adenocarcinoma.

Node-positive cervical adenocarcinoma has been treated postoperatively by RT. The reported 5-year survival rates range from 33.3% to 63.2%, suggesting that node-positive cervical adenocarcinoma shows lower radiosensitivity and poorer prognosis than node-positive squamous cell carcinoma.[2–7] Recently, Chargui et al[8] reported an 8% 5-year survival rate of node-positive patients with cervical adenocarcinoma; however, RT was usually performed before surgery in their series. Yokosuka and Hasumi[4] reported a 40.9% 5-year survival rate in 25 node-positive patients with cervical adenocarcinoma; this is our historic control study in which RT was used postoperatively as adjuvant therapy (Table 4). On the basis of these observations, alternative treatments for node-positive cases have been sought.

The rationale for postoperative use of CT alone for node-positive cervical cancer is as follows. First, distant metastasis is the major problem in the treatment of high-risk cervical cancer, and CT is considered the most powerful means of eradicating subclinical metastases. Second, treatment of local recurrence is considered to be

TABLE 2. Relapse rates by the number and sites of metastatic nodes

	Relapse rate	*P*
No. metastatic nodes		
1–2 (n = 12)	25%	
3–5 (n = 5)	40%	0.012*
≥6 (n = 4)	100%	
Laterality of metastatic nodes		
Ipsilateral involvement (n = 8)	25%	0.367
Bilateral involvement (n = 13)	54%	
Involvement of common iliac nodes		
Yes (n = 7)	71%	0.159
No (n = 14)	29%	

*For 1 to 2 versus 6 or more metastatic nodes.

TABLE 3. Sites of relapse

Intrapelvic	
Pelvic lymph nodes	2
Parametrium	1
Extrapelvic	
Lung	3
Para-aortic lymph node	1
Intra-abdominal	1
Virchow node	1

easier because of the presence of RT reserved for recurrence. Finally, CT alone may yield a better quality of postoperative life by precluding radiation-related morbidities, such as small bowel obstruction and leg lymphedema. The potential role of CT for the treatment of node-positive cervical cancer has been discussed in several reports.[11–14]

The current study is the first reported study of more than 20 node-positive patients with cervical adenocarcinoma treated postoperatively with CT alone. The survival data suggest that the effectiveness of postoperative CT is equal to or better than that of RT in node-positive patients with cervical adenocarcinoma. Recurrence tends to occur more frequently in patients with many (>6) positive nodes. A similar finding was noted in patients treated with RT. Ishikawa et al[17] reported a 5-year survival rate of 61.3% in patients with cervical adenocarcinoma and fewer than 3 positive nodes but only 13.0% in those with 3 or more positive nodes. In the present study, parametrium involvement tends to be associated with poor prognosis; however, this association did not reach statistical significance. Lai et al[12] reported that postoperative CT was effective in patients with lymph node metastasis but free of parametrial extension, whereas postoperative RT was effective in those without lymph node metastasis but at high risk of recurrence.

We previously reported[18] favorable results of postoperative CT as treatment of node-positive squamous cervical cancer, showing a disease-free survival rate of more than 80%. The treatment outcome of node-positive cervical adenocarcinoma in the present series was considerably worse than that of squamous cell carcinoma.

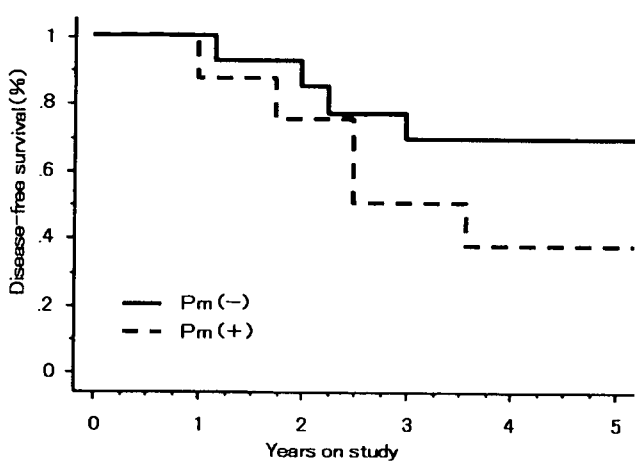

FIGURE 2. Relation between disease-free survival and parametrial involvement. The 5-year disease-free survival rate was 64% in 14 node-positive patients without parametrial involvement (pm −) and 43% in 7 node-positive patients with parametrial involvement (pm +) ($P = 0.3346$).

TABLE 4. Survival in cases of node-positive cervical adenocarcinoma

	Postoperative therapy	Clinical stage	No. cases	5-y survival rate, %
Kilgore et al[2]	RT	IB	13	42.7
Vesterinen et al[3]	RT	IB-IIB	44	40–55.6
Yokosuka and Hasumi[4]	RT	IB-IIB	25	40.9
Shingleton et al[5]	RT	IB-IIA	31	33.3
Nakanishi et al[6]	RT	IB	19	63.2
Irie et al[7]	RT	IB-IIB	18	47.9
Peters et al[9,19]	CCRT	IB-IIA	29*	82.0
Current study	CT	IB-IIB	21	66.7

*Includes 11 cases of adenosquamous carcinoma.

With respect to sites of recurrence, it is surprising that despite the use of postoperative CT in the absence of pelvic RT, recurrences occurred predominantly at distant sites. In 2000, Peters et al[9] examined 2 treatment modalities, RT and CCRT, in 243 patients with high-risk cervical cancer and obtained 4-year disease-free survival rates of 63% and 80%, respectively. Most importantly, they reported no difference in survival rate between squamous cell carcinoma and nonsquamous carcinoma when CCRT was used to treat high-risk cases. An 82.0% 5-year survival rate was reported for 29 patients with adenocarcinoma or adenosquamous carcinoma.[9,19]

Our study is limited by retrospective data collection, a small number of patients, and varying CT regimens. Nevertheless, we believe that the current study provides some information to help in the design of future trials. Prospective studies are necessary to verify the utility of postoperative adjuvant CT for cervical cancer. The Japanese Gynecologic Oncology Group has a plan to perform a phase 2 trial in this aspect. On the basis of the present results, we consider that node-positive patients with adenocarcinoma should be excluded from the study.

In summary, our findings suggest the potential role of postoperative CT for treatment of cervical adenocarcinoma. The effectiveness of CT alone for node-positive patients with cervical adenocarcinoma is equal to or better than that of RT alone. However, a high survival rate for patients with node-positive cervical adenocarcinoma has been reported only for those treated with CCRT. Although CT is probably advantageous over CCRT with respect to treatment-related morbidity,[18] at present, CCRT is considered the best treatment of node-positive cervical adenocarcinoma.

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Current Organ Topics:

Gynecologic Cancer
婦人科がん
婦人科がん治療ガイドライン策定の背景と今後の動向

Ⅰ．子宮頸癌の初回治療

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〔*Jpn J Cancer Chemother* 36(2): 205-208, *February*, 2009〕

はじめに

現在，婦人科領域の悪性腫瘍治療ではガイドラインが作成され，標準的治療というものが示されるようになった。子宮頸癌治療においても，臨床実務にガイドラインは幅広く使用されている。しかし，これらのなかでさらに検討されるべき分野も多く，今回はこのような子宮頸癌治療に関する最近の話題を概説したい。

1．縮小手術

本邦では子宮頸部癌治療の基本手術として岡林式広汎性子宮全摘出術が用いられてきたが，近年これを改良し，神経の温存を重視する手術術式が盛んに検討されてきた[1]。しかし，最近の動向として，特にⅠB1期症例のなかでも直径2cm以下のものはより縮小した手術が可能ではないかと，考えられるようになってきている。当科のⅠB1期症例の検討では，術前のMRIで腫瘍径が2cm以下の場合（59症例），2cm以上の場合（66症例）では子宮傍組織浸潤の頻度は0%と9.1%，リンパ節転移の頻度は6.8%と19.7%であった[2]。このように腫瘍径が2cm以下の場合には，従来の広汎性子宮全摘出術はover treatmentである可能性が考えられる。

当科では腫瘍径が2cm以下のⅠB1症例に対して，基靭帯処理は行うが，膀胱子宮靭帯後層処理（膀胱腟靭帯切断）を省略する縮小広汎性子宮全摘術を提唱している[3]（図1）。現在この術式による膀胱機能および予後への影響を検討中である。また，腫瘍径が2cm以下には準広汎性子宮全摘術をという意見もあり，実地適応の可能性があると思われる。基靭帯処理の必要性については微妙な問題であるが，先の当科の検討では腫瘍径が2cm以下には子宮傍組織浸潤がなかったものの，腫瘍径が2～3cmの症例において子宮傍組織浸潤例が認められた経緯がある。いずれにしても，これらの領域で今後多くの臨床試験が行われるものと考えられる。

2．術前化学療法

現在ガイドラインでは，術前化学療法（NAC）は臨床試験の下で行われるべき試験的治療と規定されている。子宮頸癌のNACの有用性を考えるのに重要な前向き研究として，日本腫瘍臨床グループ（婦人科腫瘍グループ）（以下JCOG）で行われたJCOG0102[4]と米国Gynecologic Oncology Group（以下GOG）のGOG141[5]の二つの研究がある。前者はⅠB2-ⅡB期を対象とし，後者はⅠB2期のみを対象とした。二つの研究ではNACの使い方が大きく異なり，前者では4コース前後（BOMP療法）と多くのコース数のNACを施行するのが特徴であり，後者は1コース（1週間ごと3回投与）のみの抗がん剤投与（CDDP/VCR療法）である。NACによる病理学因子（例えばリンパ節転移頻度）の改善は前者である程度認められているが，後者ではコース数が少ないためほとんど認められていない。最も重要なことは，どちらの研究でも予後の改善効果は認められていないことである。また，定義が難しいが“手術の容易さ”への影響も両研究とも明確にはされなかった。

当科で施行された，子宮頸癌ⅠB2-ⅡB期80症例（1994～2004年症例）の治療成績を紹介したい。組織型別の検討を行ったが，表1にNACの奏効率を，図2に治療成績を示した。なお，NACとして扁平上皮癌にはBOMP療法，腺癌系にはIEP（IFO/epi-ADM/CDDP）

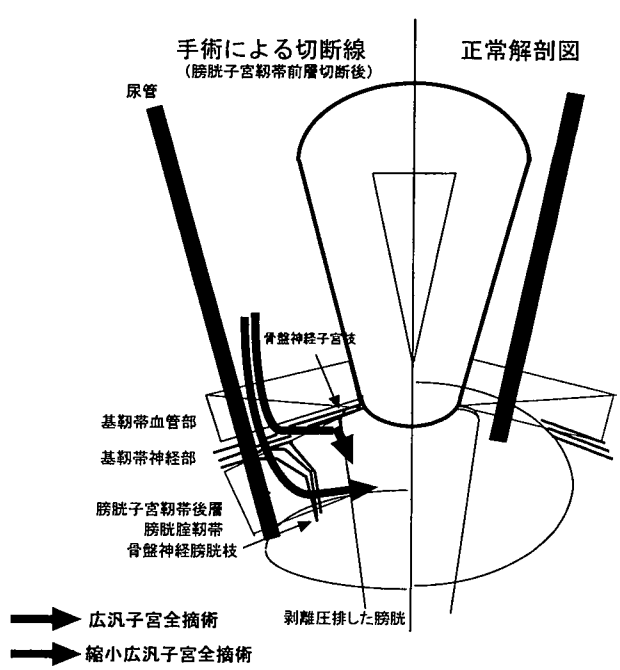

図1 縮小広汎子宮全摘の術式説明