Table 2. Adverse Reactions to Uracil–Tegafur.

Adverse Reaction	Grade of Toxicity*			
	1	2	3	4
	% of patients			
Leukopenia	2	1	0	0
Thrombocytopenia	<1	0	0	0
Anemia	1	<1	0	0
Increase in bilirubin	1	<1	0	0
Increase in aspartate aminotransferase	6	2	<1	0
Increase in alanine aminotransferase	6	2	0	0
Increase in alkaline phosphatase	2	<1	0	0
Anorexia	9	8	1	0
Nausea or vomiting	10	3	1	0
Diarrhea	2	1	<1	0
Alopecia	<1	0	0	0

* Toxicity was graded according to criteria of the Japan Society of Clinical Oncology. Grades range from 1 to 4, with a higher grade indicating a more severe reaction.

We also evaluated interactions between the four prognostic factors (sex, age, pathological tumor category, and size of the tumor) (Fig. 2) and the treatment. We included tumor size in the analysis because the tumor category is determined mainly by the maximal diameter of the primary tumor. As Figure 2 shows, there were significant interactions between the tumor category and size of the tumor and the treatment.

The survival rate among patients with T2 disease in the uracil–tegafur group was significantly higher than that in the control group, whereas among patients with T1 disease, there was no significant difference in survival between the uracil–tegafur and control groups. The five-year survival rate among patients with T2 disease was 85 percent (95 percent confidence interval, 79 to 91 percent) in the uracil–tegafur group and 74 percent (95 percent confidence interval, 66 to 81 percent) in the control group (Fig. 1B). The difference in overall survival between the two groups was statistically significant (P=0.005 by the log-rank test). The five-year survival rate among patients with T1 disease was 89 percent in the uracil–tegafur group and 90 percent in the control group (Fig. 1C). In the subgroups of patients with a tumor that was less than 2 cm in diameter, 2 to 3 cm, and greater than 3 cm, the five-year survival rate was 89 percent, 89 percent, and 85 per-

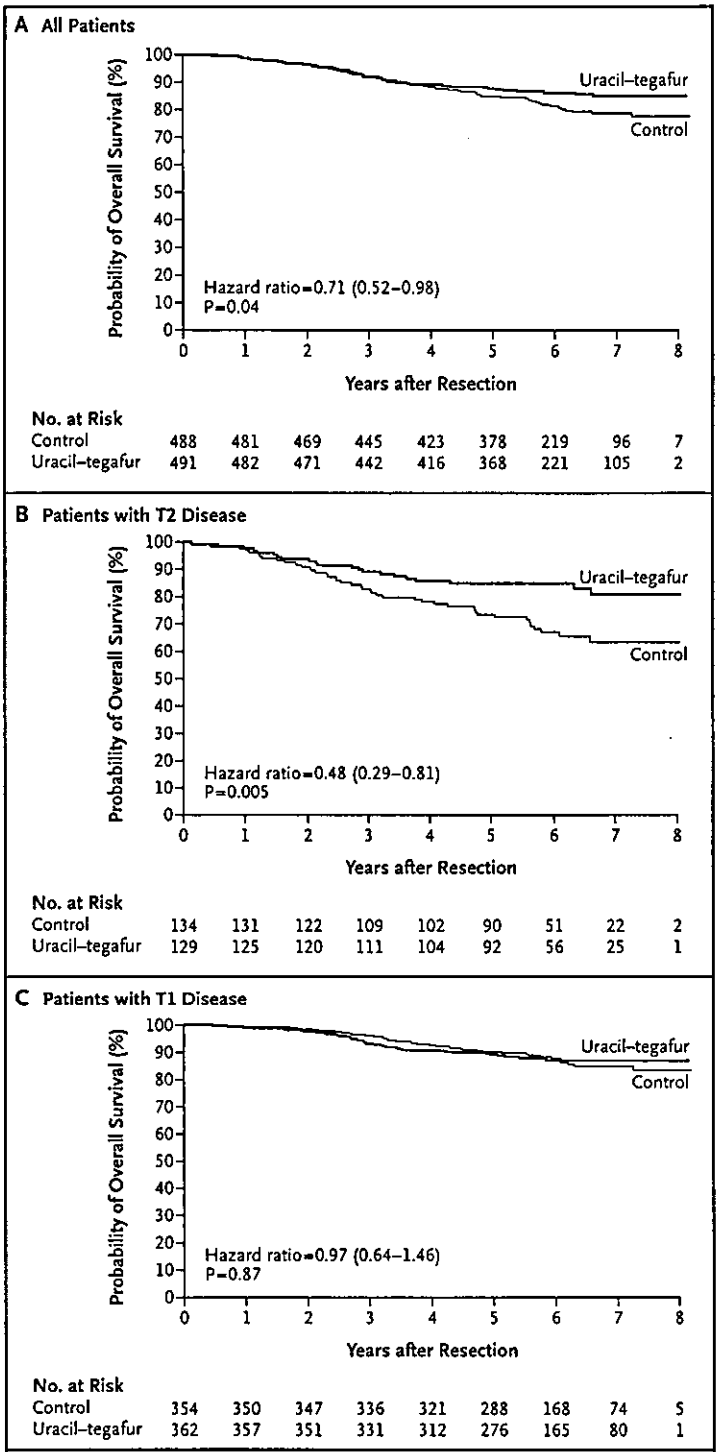

Figure 1. Overall Survival among All 979 Eligible Patients (Panel A), 263 Patients with T2 Disease (Panel B), and 716 Patients with T1 Disease (Panel C) Who Were Randomly Assigned to the Uracil–Tegafur Group and the Control Group.

The hazard ratios indicate the risk of death in the uracil–tegafur group as compared with the control group; 95 percent confidence intervals are shown in parentheses. P values were calculated with the use of the stratified log-rank test.

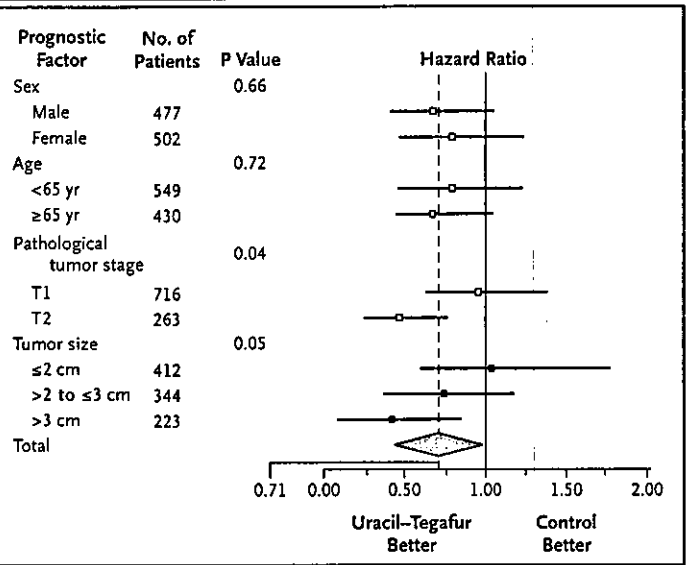

Figure 2. Hazard Ratios for Death in Patients in the Uracil–Tegafur Group as Compared with the Control Group, According to Four Prognostic Factors.

Each square represents the estimated treatment effect, the horizontal lines represent the 95 percent confidence intervals, and the diamond corresponds to the 95 percent confidence intervals for the entire group of patients. The P value for the tumor size is for the comparison of patients who had tumors that were 2 cm or less in diameter with patients who had tumors that were more than 3 cm.

cent, respectively, in the uracil–tegafur group and 91 percent, 86 percent, and 74 percent, respectively, in the control group.

PATTERN OF FAILURE AND CANCER-FREE SURVIVAL

A recurrence or a second primary cancer as the first treatment failure after surgery was documented in 23 percent of the uracil–tegafur group and 26 percent of the control group (Table 3). Among the 716 patients with T1 disease, recurrence or a second primary cancer was observed in 69 of 362 patients (19 percent) in the uracil–tegafur group and 76 of 354 patients (21 percent) in the control group; among the 263 patients with T2 disease, 42 of 129 patients (33 percent) in the uracil–tegafur group and 53 of 134 patients (40 percent) in the control group had recurrence or a second primary cancer as the first treatment failure. On the basis of a Kaplan–Meier analysis, the difference in cancer-free survival between the two groups was not statistically significant (P=0.25 by the stratified log-rank test). The survival of patients after the diagnosis of a recurrence or a second primary cancer did not differ significantly between the groups (P=0.14 by the log-rank test): the one-year and two-year survival rates after diagnosis were 65 percent and 50 percent, respectively, in the uracil–tegafur group and 65 percent and 42 percent, respectively, in the control group.

DISCUSSION

The Japanese Association for Chest Surgery and Japan Lung Cancer Society recently reported the long-term survival rate of 7408 patients with lung cancer who had undergone a surgical resection in 1994, the year that our trial started.[23] The main histologic types were adenocarcinoma (in 56 percent of the patients) and squamous-cell carcinoma (in 33 percent). Among patients with pathological stages T1N0M0 and T2N0M0, the five-year survival rates were 79 percent and 60 percent, respectively. In our study of adenocarcinoma, the five-year survival rate in the control group was 90 percent among patients with T1N0M0 disease and 74 percent among those with T2N0M0 disease. Although the figures in the two studies cannot be directly compared, owing to different histologic patterns and times when the data were collected, the excellent five-year survival rate for the control patients in our study[24,25] indicates that our collaborative group has made improvements in the quality of the surgical treatment and the accuracy of surgical staging.

Our study shows that adjuvant chemotherapy with uracil–tegafur has a beneficial effect on the survival of patients with resected stage I adenocarcinoma of the lung. This benefit, however, was not observed in patients with T1N0 disease. In the past few years, the number of patients in whom small adenocarcinomas have been discovered has increased owing to the increased use of computed tomography. In our study, 412 of 979 patients (42 percent) had an adenocarcinoma that was less than 2 cm in diameter. Adenocarcinomas of this size often include bronchoalveolar carcinoma, which is unlikely to recur after resection.[26] Therefore, a small adenocarcinoma usually has a very good prognosis[26,27]: in our study, the five-year survival rate of patients with tumors that were 2 cm or less in diameter was 91 percent. For this reason, we believe that patients with small tumors should be excluded from adjuvant trials unless a subgroup with a poor prognosis is identified.

In contrast, treatment with uracil–tegafur tended to improve the survival rate among patients with a tumor that was 2 to 3 cm in diameter and provided

a definitive survival benefit for patients with a tumor that was more than 3 cm in diameter. These findings indicate that the effect of uracil–tegafur may be related to certain biologic factors. In a retrospective study, Tanaka et al.[28] found that the prognosis was good for patients with non–small-cell lung cancer characterized by a high apoptotic index and no aberrant expression of p53 who received postoperative uracil–tegafur.

Patient compliance is usually a problem in trials of adjuvant chemotherapy. In trials of cisplatin-based chemotherapy, which was scheduled to be administered in three or four cycles postoperatively, only 50 to 70 percent of the planned treatment was given.[29-32] In our trial, we planned to give uracil–tegafur daily for two years. However, only 61 percent of patients assigned to the treatment completed the two-year course. The main reasons for discontinuing uracil–tegafur were adverse reactions (which were infrequent and usually mild) and the patient's decision, which suggests that compliance in trials of adjuvant chemotherapy may not be related to the severity of adverse events.

The main difference between trials of cisplatin-based adjuvant chemotherapy and trials of adjuvant chemotherapy with uracil–tegafur is the duration of the treatment. The cisplatin-based regimens entail three or four cycles (9 to 16 weeks) of chemotherapy,[29-32] whereas uracil–tegafur is taken daily for 1 or 2 years.[13,33-36] Fluorouracil is not a dose-dependent drug but a time-dependent agent. Therefore, a daily regimen of uracil–tegafur is an effective way of maintaining the blood level of fluorouracil. In addition, uracil–tegafur and its metabolites have an inhibitory effect on tumor angiogenesis in mice.[37] If this effect occurs in humans, then the daily, long-term administration of uracil–tegafur may be beneficial.

So far, six randomized trials,[13,33-36] including the present one, have been conducted that compare surgery alone with adjuvant chemotherapy with uracil–tegafur. Among them, three trials have shown a survival benefit from treatment with uracil–tegafur.[13,34] A meta-analysis of those six trials showed that adjuvant chemotherapy with uracil–tegafur improved the overall survival (hazard ratio for death, 0.77; 95 percent confidence interval, 0.63 to 0.94; P=0.01).[38] It is unclear whether patients with stage II or stage III disease benefit from treatment with uracil–tegafur and whether treatment for one year is equivalent to treatment for two years. However, our study indicates that patients with completely resected stage I disease, especially T2N0 adenocarcinoma, will benefit from adjuvant chemotherapy with uracil–tegafur.

Table 3. Pattern of Treatment Failure.

Pattern	Uracil–Tegafur Group (N=491)	Control Group (N=488)
	no. of patients (%)	
Intrathoracic only		
Local recurrence	17	8
Pulmonary metastases	36	38
Local recurrence plus pulmonary metastases	3	12
Second cancer	11	11
Extrathoracic only		
Recurrence	23	33
Second cancer	14	18
Intrathoracic plus extrathoracic recurrence	7	9
Total	111 (22.6)	129 (26.4)

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APPENDIX

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*Deceased.

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Editorial

Treatment of Peripheral Early Stage Lung Cancer

Harubumi Kato, Haruhiko Nakamura, Masahiro Tsuboi, Norihiko Ikeda, Takaaki Tsuchida, Yasufumi Kato, and Takashi Hirano

Introduction

Not only is the incidence of lung cancer increasing around the world, this disease has become the leading cause of cancer death. Since lung cancer kills 85% to 90% of its victims, it is recognized as one of the most difficult to cure diseases. Although the therapeutic results are quite unsatisfactory as a whole, earlier stages of lung cancer, stages IA and IB show better therapeutic results (Table 1).[1] To improve the therapeutic results of lung cancer, efforts for early detection and treatment are essential. In our institution, the 5-year survival rate has gradually improved over the past five decades. These results could be due to improvement of therapeutic procedures including surgery, chemotherapy, radiotherapy, laser therapy and immunotherapy. Furthermore, the improvement of survival may be partially due to lung cancer mass screening made by the Health Insurance Act of 1987.

Lung cancer mass screening by chest computed tomography (CT) was begun in Japan 10 years ago and now is becoming subsequently used in the United States and Europe. Since large numbers of peripheral tiny lung shadows were detected in many of the CT screening pilot trials,[2,3] it is important to establish an internationally accepted definition of peripheral type early stage lung cancer.

In this editorial the authors describe the present status and prospects for the treatment of early stage lung cancer.

The Criteria of Early Stage Lung Cancer

Since there are no authorized international criteria of early stage lung cancer, establishment of criteria is urgently required. According to the location of the tumor, early stage lung cancers are classified into two categories; central type and peripheral type.

In Japan, the criteria of early stage lung cancer were first proposed about 30 years ago, in 1975. Peripheral type early stage lung cancer was defined as a tumor located in an airway more peripheral than subsegmental bronchi, and the longest dimension of the tumor should be 2 cm or less and with no recognized lymph node and distant metastases. In central type early stage lung cancer, the tumor should be located in a segmental bronchus or more proximal airway, and the depth of tumor invasion should be limited to within the bronchial wall with no lymph node or distant metastases. These criteria of central type early stage lung cancer were first defined pathologically in a resected lung by Ikeda in a study supported by the Ministry of Health and Welfare in Japan. Now we have criteria of endoscopically diagnosed central type early stage lung cancer defined by the Japan Lung Cancer Society.[4]

Therapeutic Guidelines of Early Stage Lung Cancer

In Japan, the therapeutic guidelines of lung cancer established on Evidence-based Medicine were made with the support of the Ministry of Health, Labor and Welfare in 2002. In these guidelines, surgical resection and PDT are recommended for treatment of central type early stage lung cancer.[5]

The Possibility of Limited Resection by Video-assisted Thoracoscopic Surgery (VATS)

The standard therapeutic procedure for peripheral type early stage lung cancer is believed to be lobectomy with mediastinal lymph node dissection. However the question was raised whether lobectomy is really needed for tiny tumors, particularly those less than 1 cm in greatest

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Table 1. Survival rates according to pathologic stages (n=7,047)

p-stage	n	1 year	2 year	3 year	4 year	5 year
IA	2,142	96.5	92.8	87.9	82.7	79.2
IB	1,488	90.2	80.3	72.4	65.6	60.1
IIA	261	90.7	78.6	68.4	62.9	58.6
IIB	785	81.3	64.5	52.7	47.6	42.2
IIIA	1,337	74.7	53.8	40.3	32.6	28.4
IIIB	759	64.6	40.2	28.4	22.5	20
IV	275	60.3	39.4	29.9	22.5	19.3

n: numbers of patients with lung cancer

dimension. There are several reports on limited resection of small lung cancer.[6,7] Some of these results showed satisfactory 5-year survival rates. Clinical trials to clarify the possibility of limited resection are needed for particularly small lung cancers showing ground glass opacity (GGO), or ground glass attenuation (GGA) . Most of these lesions showed no lymph node metastases, and a 100% 5-year survival was obtained in such cases who underwent resection. A multi-center clinical trial sponsored by the Japan Clinical Oncology Group (JCOG) just started to examine the suitability of limited resection for peripheral small lung cancer. Wedge resection of small lung cancer by VATS without lymph node dissection is one type of the minimally invasive surgery. If some types of lung cancer could be shown to be resected by VATS without any increase of local recurrence, this method could become a future standard treatment for peripheral small lung cancer.

The Rate of Lymph Node Metastasis of Peripheral Small Nodular Cancer

In the past five years, 783 patients with lung cancer underwent surgery in our institution. Among them there were 150 patients with peripheral nodules less than 2 cm in diameter, including 135 adenocarcinomas. Lobectomy was performed in 93 cases and limited resection was performed in 42 cases. The pathological prognostic factors were investigated for the future selection of surgical procedures in the peripheral small nodules. Of cases less than 1 cm, 97.5% of cases showed no lymph node involvement, however even in such tiny tumors 2.5% of them already showed N2 disease. In the cases between 1 and 1.5 cm, 91.9% of cases showed no metastasis, however 8.1% showed either N1 or N2 involvements. In the cases between 1.5 and 2 cm, lymph node involvement was recognized in 12%. Therefore it seems that the tumor size does not have a large correlation with lymph node involvement.

According to Noguchi's classification,[8] bronchioloalveolar cell carcinoma showing findings of GGO on CT images did not have any nodal metastases.[9] The CT images of our cases were classified into four categories according to the percentages of areas of GGO findings in relation to the entire tumor; 100% GGO, between 50% and 100%, less than 50% and 0% GGO findings. According to these criteria, 16 cases consisted of GGO in 100% of the tumor area and 21 cases consisted of between 50% and 100% GGO. These two groups showed no lymph node metastases. Furthermore, in cases with GGO findings consisting of less than 50% or 0% of the lesion, cases with a tumor size of less than 1 cm showed no lymph node metastasis. However, two cases with a tumor size more than 1 cm had nodal metastases. In the cases with 0% GGO, the presence of lymph node metastases was not related to the sizes of the tumor. The overall 5-year survival rate in adenocarcinoma 2 cm or less in tumor size was 93.3%.

The survival curves according to the postoperative stage showed a 98.1% 5-year survival rate in stage IA, 54.7% in stage IIIA and no 5-year survivals in stages IIA and IV. Since the number is small in stages IIA and IV, it is necessary to increase the number for accurate evaluation. In the survival curves according to the tumor size, tumors less than 1 cm showed a 100% 5-year survival rate. In tumors between 1 and 1.5 cm the survival rate was 86.5%, and in cases between 1.5 and 2 cm, the 5-year survival rate was 92.4%. On the survival curves according to area of GGO finding, the cases consisting of more than 50% GGO showed 100% 5-year survival rate and the cases consisting of less than 50% GGO had 91.1% 5-year survival rate. From these data it seems that the proportion of GGO in the tumor may be related to prognosis. The survival rate was 100% in cases of limited operation and 91.5% in lobectomy cases. The better result of limited resection than lobectomy might be due to selection bias.

Future Surgical Procedures for Peripheral Early Stage Lung Cancer

Tumors with 100% GGO findings on CT images could indicate the suitability of surgical limited resection by VATS. Lesions consisting of between 50% and 100% of GGO in area may also be indication for limited resection in cases less than 2 cm in diameter, and also perhaps in cases consisting of between 10% and 50% GGO finding with a tumor size less than 1 cm in diameter.

The evaluation of limited resection for the small peripheral nodules were reported previously by several researchers,[6,7,9] however different opinions concerning these modalities have been reported.[10,11] There are still controversies concerning limited resection of peripheral small lung cancers. A randomized clinical trial by the Lung Cancer Study Group (LCSG) demonstrated disadvantages of limited resection for T1N0 tumors in relation to lobectomy.[11] Therefore clinical evidence of the usefulness of limited resection for peripheral early stage lung cancers should be proven. The features of peripheral lung cancers suitable for limited resection without lymph node dissection should be clarified. That will make it possible to determine the optimal CT findings for limited resection.

In our experience, even if the primary lesion was less than 1 cm in size, nodal involvement was confirmed histologically in some cases. Prognostic factors may not solely depend on tumor size but also on the percentage of the area of GGO. It is necessary to clarify the findings of CT images of non-invasive cancer by a clinical multicenter study.

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An increase in the percentage of HLA-DR-positive peripheral leukocytes predicts a poor prognosis in patients with squamous cell carcinoma of the lung

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Abstract. Immunologic factors that predict survival in patients with lung cancer have not been established. We examined the relationship between the percentage of HLA-DR-positive peripheral leukocytes [HLA-DR$^+$ (%)] and survival of patients with squamous cell carcinoma of the lung. Before initiating therapy, peripheral blood was taken from 105 patients with squamous cell carcinoma of the lung. HLA-DR positivity was determined by flow cytometry. Patients were divided into 2 groups; a high and a low percentage group. The significance of the intergroup difference in the Kaplan-Meier survival curves was determined by the log rank test. Multivariate analysis was performed using the Cox proportional hazards model. The average HLA-DR$^+$ (%) was 25.9±10.6% (mean ± SD). Survival in the high percentage group (HLA-DR$^+$ (%) ≥25.9%, n=44) was much worse than that in the low percentage group (HLA-DR$^+$ (%) <25.9%, n=61; p=0.0002). The 5-year survival rate in the high percentage group was only 7.4%, while that in the low group was 54.3%. Multivariate analysis identified a significant association between survival and lymph node metastasis (p=0.0028) and HLA-DR$^+$ (%) (p=0.0004). Survival of patients with stages I, II, and IIIA was worse in the high percentage group (n=32) than that in the low percentage group (n=43; p<0.0001). However, survival of patients with more advanced disease, stages IIIB and IV, was similar in the high percentage (n=12) and low percentage groups (n=18; p=0.7610). The peripheral HLA-DR$^+$ (%) predicts survival of patients with resectable squamous cell carcinoma of the lung.

Introduction

Immunologic interactions between host and tumor are an important determinant of survival in cancer patients. However, the immunologic factors that predict survival in lung cancer have not been well characterized. We previously investigated several cell surface markers, NK activity, and lymphoblastogenesis in peripheral blood leukocytes taken from lung cancer patients looking for factors that correlate with a prognosis (1,2). Although other investigators have reported some of these cellular immunologic factors predicted survival (3-7), we found that the percentage of HLA-DR-positive peripheral leukocytes [HLA-DR$^+$ (%)] was the most reliable prognostic factor in lung cancer. The present study analyzed clinical data from 105 patients with squamous cell carcinoma of the lung during a longer follow-up period than the previous study to determine whether or not HLA-DR$^+$ (%) predicts survival.

Patients and methods

One hundred and five patients with squamous cell carcinoma of the lung, treated from April 1995 to November 1998 in our institute, were enrolled in this study. These 98 men and 7 women had an average age of 67.7 years (range, 40-90 years). The diagnosis of squamous cell carcinoma was based upon cytologic or histologic examinations. American Joint Committee on Cancer criteria were used for TNM staging of lung cancer (8). Stages IA and IB patients were grouped together as stage I, and stages IIA and IIB patients were grouped as stage II. Pathologic staging was used when resection was performed, and clinical staging when it was not. When surgery was not performed, the presence of lymph node metastasis was determined by chest computed tomography (CT). The presence of distant metastases was determined by brain CT, chest CT, abdominal CT, and bone scintigraphy. Thirty-nine patients had stage I disease, 10 had stage II, 26 had stage IIIA, 24 had stage IIIB, and 6 had stage IV. Fifty-eight patients underwent surgery and 47 patients did not undergo surgery. Photodynamic therapy (9) was performed for centrally located early squamous cell carcinoma. The mean follow-up period for patients alive was 45.6 months.

Before initiation of therapy, peripheral blood samples were obtained. The HLA-DR$^+$ (%) was determined as described previously (1). In short, the HLA-DR$^+$ cells were stained using a lysed whole blood method: 50 ml of blood from each patient was stained with 50 ml of diluted fluorescein isothiocyanate (FITC)-labeled anti-HLA-DR monoclonal antibody, Leu HLA-DR (Becton-Dickinson, Franklin Lakes, NJ), for 30 min at 4˚C in the dark. Then the red blood cells were lysed in lysing buffer. After 15 min, the samples were analyzed by flow cytometry using the FCM-1 (Nihon-bunko, Tokyo,

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Key words: tumor immunity, lung cancer, squamous cell carcinoma, HLA-DR, leukocyte, survival

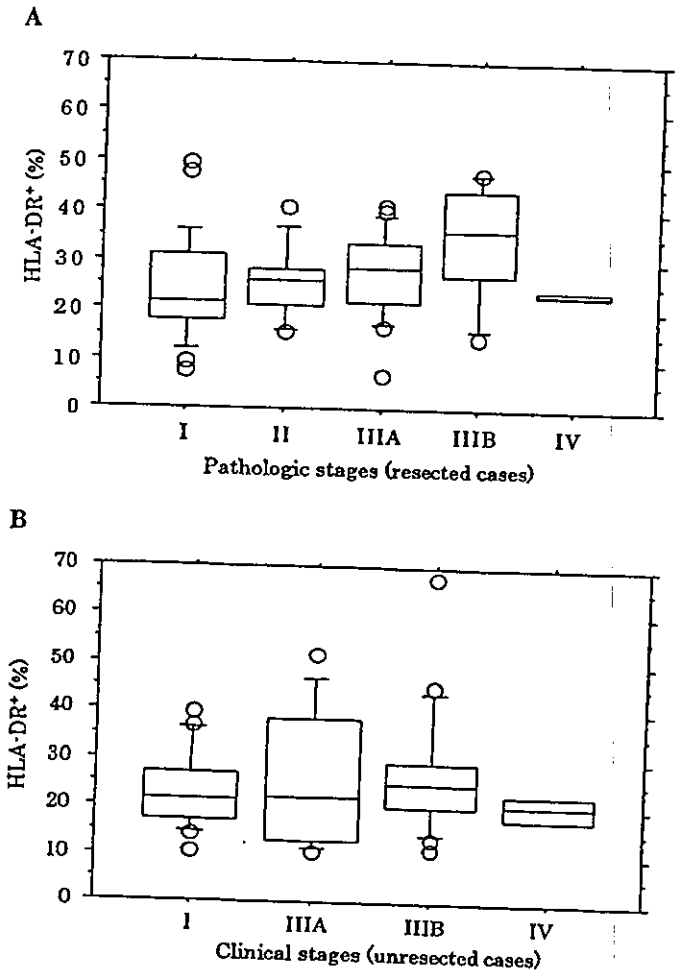

Figure 1. A, Comparison of the percentages of HLA-DR-positive peripheral leukocytes as a function of the pathologic stage in patients who underwent resection of squamous cell carcinoma of the lung. Differences between stages were not significant by the Kruskal-Wallis test (p=0.2976). B, Comparison of the percentages of HLA-DR-positive peripheral leukocytes as a function of the clinical stage in patients who did not undergo resection of squamous cell carcinoma of the lung. Differences between stages were not significant by the Kruskal-Wallis test (p=0.5406).

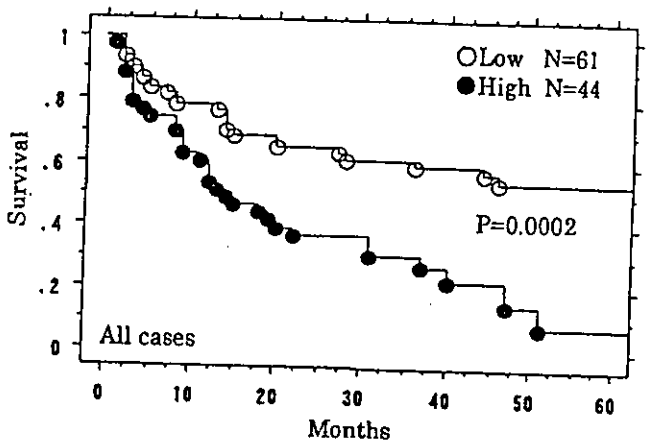

Figure 2. Kaplan-Meier overall survival curves comparing the HLA-DR-positive peripheral leukocytes high percentage group and the low percentage group in 105 patients. The difference was significant by the log rank test (p=0.0002).

Table I. Survival analysis of 105 patients with squamous cell carcinoma of the lung in a Cox proportional hazards model.

Prognostic factor	Multivariate analysis P-value (HR: 95% CI)
Age	
≥67.7 vs. <67.7	0.3934 (1.015: 0.981-1.051)
Gender	
Men vs. women	0.1399 (4.622: 0.606-35.10)
T-factor	
T_{2-4} vs. T_1	0.2555 (1.499: 0.746-3.012)
N-factor	
N_{1-3} vs. N_0	0.0028 (2.728: 1.414-5.263)
M-factor	
M_1 vs. M_0	0.2925 (1.715: 0.628-4.695)
HLA-DR+ (%)	
≥25.9 vs. <25.9	0.0004 (2.743: 1.565-4.808)

HR, hazard ratio; CI, confidence interval.

Japan). Results are expressed as percentages of the total leukocyte count.

The significance of differences in the HLA-DR+ (%) between groups were compared using the Mann-Whitney U test for 2 groups and the Kruskal-Wallis test for ≥3 groups. The patients were divided into a high percentage group, greater than or equal to the average percentage and a low percentage group, less than the average, to determine the correlation between HLA-DR+ (%) and survival. The survival rate was calculated by the Kaplan-Meier method. Survival differences were compared using the log rank test. A multivariate survival analysis was evaluated according to the Cox proportional hazards model in order to detect independent risk factors adjusting for the confounding factors. P<0.05 was considered significant.

Results

The average HLA-DR+ (%) in all 105 patients was 25.9±10.6% (mean ± SD). The HLA-DR+ (%) was similar in patients who did and did not undergo resection (p=0.3179). Additionally, HLA-DR+ (%) between stages was similar overall and in patients who did and did not undergo resection (Fig. 1).

Survival in the high percentage group [HLA-DR+ (%) ≥25.9 %; n=44] was significantly worse than in the low percentage group [HLA-DR+ (%) <25.9%; n=61] with 5-year survival rates of 7.4 and 54.3%, respectively (Fig. 2). Multivariate analysis including age, gender, T-factor, N-factor, M-factor, and HLA-DR+ (%) as co-variables indicated a significant association between survival and lymph node metastasis (p=0.0028) and HLA-DR+ (%) (p=0.0004) (Table I).

Among the 58 patients who underwent resection, survival in the high percentage group (n=29) was worse than that in the low group (n=29), with 5-year survival rates of 9.3 and 67.6%, respectively (Fig. 3). Among the 47 patients who did

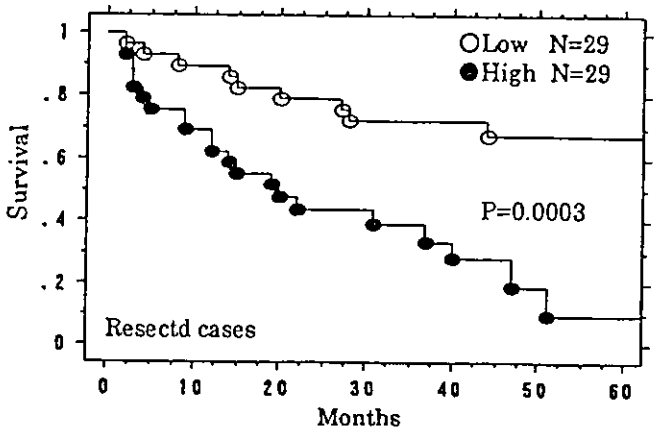

Figure 3. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in 58 patients who underwent resection of squamous cell carcinoma of the lung. The difference was significant by the log rank test (p=0.0003).

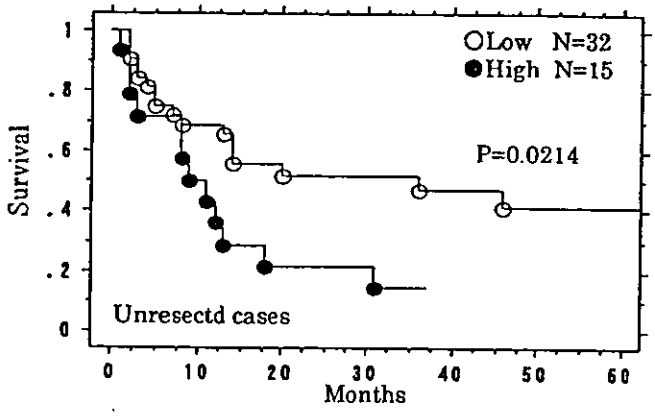

Figure 4. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in 47 patients who did not undergo resection of squamous cell carcinoma of the lung. The difference was significant by the log rank test (p=0.0214).

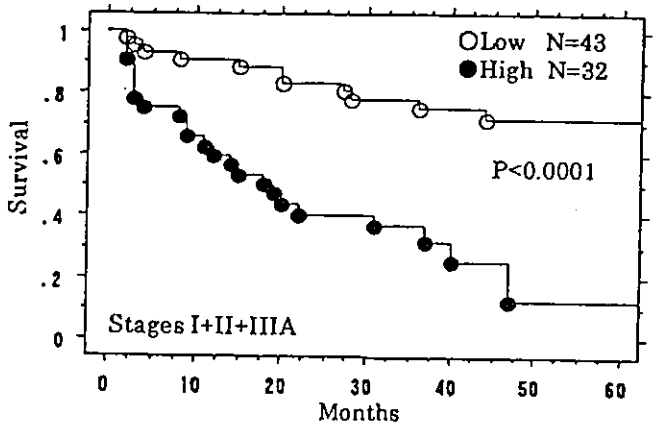

Figure 5. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in stages I, II, and IIIA of patients with squamous cell carcinoma of the lung. The difference was significant by the log rank test (p<0.0001).

not undergo resection, survival in the high percentage group (n=15) was worse than in the low percentage group (n=32), with no 5-year survivors in the high percentage group and a 41.5% survival rate in the low percentage group (Fig. 4).

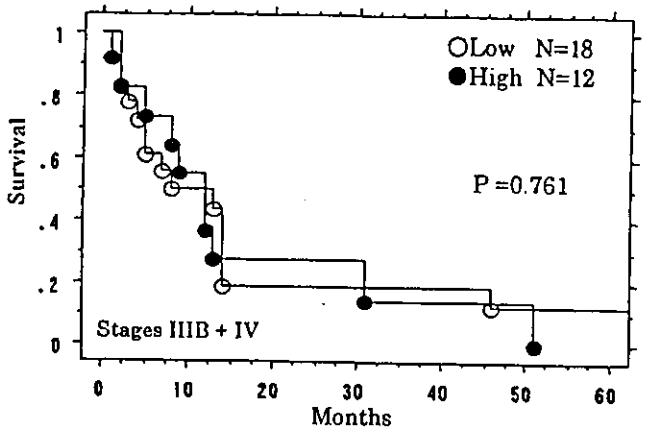

Figure 6. Kaplan-Meier survival curves comparing the HLA-DR-positive peripheral leukocytes in high and low percentage group in stages IIIB and IV of patients with squamous cell carcinoma of the lung. The difference was not significant by the log rank test (p=0.7610).

Among patients with stages I, II, or IIIA disease, survival in the high percentage group (n=32) also was worse than in the low percentage group (n=43), with 5-year survival rates of 12.5 and 71.5%, respectively (Fig. 5). However, survival in the high (n=12) and the low (n=18) percentage groups were similar in patients with more advanced disease, stages IIIA and IV (Fig. 6).

Discussion

HLA-DR antigens are shared by activated T cells, activated NK cells, B cells, monocytes, macrophages, dendritic cells, and hematopoietic progenitor cells (10). A decrease in peripheral blood monocyte HLA-DR expression has been correlated with a poor prognosis in patients with severe injury or sepsis (11-13). Conversely, our study of patients with lung cancer revealed that an increase in HLA-DR$^+$ (%) strongly correlates with a poor outcome. We performed additional flow cytometric analyses to determine the HLA-DR$^+$ subset more precisely using double-staining with combinations of HLA-DR/CD4 and HLA-DR/CD8 in another series of patients with lung cancer. In that study, the subset that best predicted poor survival was HLA-DR$^+$ CD8$^-$ leukocytes (14).

We believe the following facts are relevant: i) HLA-DR$^+$ (%) does not increase with stage progression. Since the HLA-DR$^+$ (%) does not rise to maintain a correlation with the pathologic or clinical stages, some immunologic reactions probably are induced by only some tumor cells through an increase in the number of HLA-DR$^+$ cells. ii) HLA-DR$^+$ (%) predicts survival in patients with squamous cell carcinoma, but not in patients with adenocarcinoma (2). This finding implies that tumor immunogenicity plays an important role in determining survival. For example, spontaneous regression of squamous cell carcinoma of the lung has been the subject of several reports (15-19), but this phenomenon has not been documented in adenocarcinoma of the lung, probably due to lower immunogenicity of this histologic type. iii) Survival differences related to the HLA-DR$^+$ (%) disappear in stages IIIB and IV. This may be because the host immune response is weakened in advanced disease.

The status of HLA-DR expression by peripheral leukocytes and prognosis in cancer patients has received little attention. Tisch *et al* (20) studied peripheral leukocytes in patients with head and neck squamous cell carcinoma and found a negative correlation between survival and HLA-DR6 positivity. Yacyshyn *et al* (21) reported that patients with breast cancer who showed a greater than median decrease in peripheral $CD20^{-}HLA\text{-}DR^{+}$ cells following cyclophosphamide treatment had a survival advantage over patients who had less than the median decrease in the percent of the same subset. Kikuchi *et al* (22) reported that the percentage of peripheral $CD3^{+}HLA\text{-}DR^{+}$ cells in patients with ovarian cancer with minimal residual tumors after surgery was higher than it was pre-operatively, while the value in patients with a large residual tumor volume was lower. Arista *et al* (23) reported greater numbers of peripheral $HLA\text{-}DR^{+}$ T lymphocytes in patients with colorectal cancer than in healthy volunteers. These reports on breast, ovarian, and colorectal cancer suggested that certain subsets of $HLA\text{-}DR^{+}$ cells are induced by the presence of cancer cells. We do not believe that the stimulation of leukocytes by cancer cells is always advantageous in cancer patients. Although we did not analyze cytokines in the present study, a Th1/Th2 imbalance in cancer patients (24-26) may play an important role in killing cancer cells in the host's immune response. Ito *et al* (27) reported that the Th1/Th2 ratio in infiltrative lymphocytes is elevated in patients with squamous cell carcinoma of the lung. In addition, Gerrard *et al* (28) reported that a Th2-type cytokine, interleukin 4, increases HLA-DR expression in normal human monocytes. Thus, an increase in the $HLA\text{-}DR^{+}$ (%) in patients may reflect a Th2-dominant state that makes the prognosis in these patients worse. Further studies are needed on this point.

In conclusion, $HLA\text{-}DR^{+}$ (%) can be a useful immunologic marker to predict survival in potentially respectable, stages IA to IIIA squamous cell carcinoma of the lung.

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A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

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A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304)

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KEYWORDS
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Complete resection

Summary The purpose of this study was to evaluate the efficacy of adjuvant chemotherapy with three courses of cisplatin and vindesine, in comparison to observation only, for N2 non-small cell lung cancer that had been completely resected. Patients with pathologically demonstrated mediastinal lymph node metastasis (N2), who had undergone complete resection, were randomized to observation or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8: ×3 courses). Cycles started within 6 weeks after complete resection and were repeated every 4 weeks. This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival

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was 36 months for both groups. Postoperative cisplatin with vindesine chemotherapy was not shown to be efficacious in cases of completely resected N2 non-small cell lung cancer in this setting of timing, dose and agents studied.

1. Introduction

Even completely resected non-small cell lung cancer (NSCLC) usually relapses with distant metastases. Many adjuvant chemotherapy trials have been conducted to reduce the incidence of postoperative distant metastases. Holmes et al. reported that adjuvant cyclophosphamide, doxorubicin, and cisplatin (CAP) therapy improved disease-free survival for stage II-III adenocarcinomas [1]. Since then, many cisplatin based adjuvant chemotherapy trials have been conducted around the world. Most trials for adjuvant chemotherapy have neither reduced distant metastases nor local recurrence.

Mountain and Dresler reported that some patients with stage I (70-80%) and II (50%) disease can be cured by surgery alone [2]. For these patients, adjuvant chemotherapy would be unnecessary. Postoperative stage IIIA disease relapses in more than two-thirds of cases treated surgically. There are very few stage IIIA patients who could be cured with surgery alone, in whom adjuvant chemotherapy would be unnecessary. The Japanese Clinical Oncology Group (JCOG) conducted a randomized study of postoperative adjuvant chemotherapy focusing only on stage IIIA NSCLC [3], but showed no survival benefit of adjuvant chemotherapy compared with observation alone. There were more cases of N2 disease enrolled in the adjuvant chemotherapy group than in the surgery alone group. In Ohta's report, chemotherapy had to be administered for two or three courses, and many patients received only two cycles of chemotherapy, only 41% of the patients received three cycles of chemotherapy. In the present protocol, cycles of chemotherapy should be administered three times because the low compliance of drug delivery might have contributed to the negative result of the study of Ohta et. al. Also, the present protocol included only N2 patients so as to make the population more uniform.

2. Patients and methods

The protocol was reviewed by JCOG Clinical Trial Review Committee and approved by the Institutional Review Board of each participating hospital. Patient eligibility was dependent on the following criteria: to have undergone complete resection with systematic mediastinal dissection (as described in "General rule for clinical and pathological record of lung cancer" [4]), histologically documented non-small cell lung cancer, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma or adeno-squamous cell carcinoma; age less than 75 years and World Health Organization (WHO) performance status 0-1; normal hematological data (WBC $\geq$ *4000*/mm^3, platelet count $\geq$100,000/mm^3); normal hepatic function (bilirubin $\leq$1.5 mg/dl, SGOT and SGPT within twice the normal range); and normal renal function (blood urea nitrogen $\leq$25 mg/dl, serum creatinine $\leq$1.5 mg/dl, creatinine clearance $\geq$50 ml/min). Furthermore, to be eligible, the absence of no distant metastasis prior to surgery had to be established by full staging procedures including brain computed tomography (CT) or magnetic resonance imaging (MRI), chest CT, bone scans, and abdominal CT or abdominal ultrasonography revealed. Mediastinoscopy was not mandatory before surgery. All patients had ipsilateral mediastinal lymph node metastasis. Finally, patients could not have been previously treated with chemotherapy or radiation therapy for any malignancy and could not have active secondary cancers. Written informed consent, signed by patients, was mandatory before registration.

The following were excluded.: low-grade malignant lung cancers such as carcinoid tumor, adenoid cystic carcinoma or mucoepidermoid carcinoma, N3 lymph node metastases (contralateral mediastinal, contralateral hilar, supraclavicular nodes, or scalene nodes) and cases with malignant pleural effusion or pleural dissemination, T4 disease, i.e. direct invasion to the mediastinal lymph nodes, esophagus, vertebral bodies, heart or carina. Patients with Pancoast type tumor; superior vena cava syndrome or pretracheal or paratracheal lymph node metastases from cancers in which the primary lesion was located in the left lung were also excluded.

At post-operative registration, patients were randomly assigned to either observation or adjuvant chemotherapy. Neither group was allowed to receive any other treatments for cancer other than the planned adjuvant chemotherapy until relapse.

The adjuvant chemotherapy regimen was as follows: intravenous cisplatin (CDDP) 80 mg/m^2 on day 1 and vindesine (VDS) 3 mg/m^2 on days 1 and 8, every 4 weeks for 3 cycles. Chemotherapy started within 6 weeks after surgery.

3. Statistical considerations

Randomization was carried out by a blocked arrangement that balanced the treatment assignments within each institution. All patient data, including clinical, pathological, and outcome measures were entered into a computerized database using a Stat view version 5.0 (SAS Institute Inc. Cary, NC, USA.). The chi-square test and Fischer's test were used to examine the deviation of each patient's characteristics. The Kaplan-Meier method was used to calculate survival analyses. The log-rank test and the generalized Wilcoxon test were used to determine survival differences.

We planned to enter 100 cases into each group. The benefit of adjuvant chemotherapy was assumed to be a 20% increase in the 3-year survival rate (60% in the adjuvant group and 40% in the observation group) [5,6]. Given these assumptions, 154 patients were required, assuming a type 1 error of 0.05 and a type 2 error of 0.20. The primary endpoint was overall survival. The secondary endpoints was disease-free survival. However, the accrual rate was very slow. We abandoned this study in July 1998 after acquiring permission to do so from the JCOG clinical trial review committee. The endpoint was changed to overall survival only. Follow up was done every 6 months by the JCOG data center. The final outcome was confirmed in August 2001.

4. Results

From January 1994 to July 1998, 119 cases were entered from 26 institutes. Of the 119 patients, 59 were randomized to the CDDP + VDS arm and 60 to the surgery alone arm. Only one patient was lost to follow-up.

Forty men and 19 women were included in the adjuvant chemotherapy arm, and 37 men and 23 women were included in the control arm. The median age was 62 in both groups. Pneumonectomy was performed in only six patients in each group. The two groups were well balanced in regard to sex, age, operation performed, preoperative stage, pathological T factors, pattern of combined resection and number of N2 stations (Table 1).

There were no ineligible cases. There were no toxic deaths during adjuvant chemotherapy. Thirty-five of the 59 patients assigned to the chemotherapy arm received three courses of chemotherapy, 55 patients received one or more courses of chemotherapy, and 44 patients received two or more courses. The major cause of

Table 1 Patient characteristics

	Adjuvant chemotherapy	Observation	
Gender (male/female)	40 (68%)/19	37 (62%)/23	0.48
Median age	62 (41–75)	62 (43–74)	0.93
Operation			
Pneumonectomy	6 (10%)	6 (10%)	0.97
Lobectomy	53	54	
Clinical stage			
Stage I–II	44 (75%)	41 (68%)	0.45
Stage III	15 (25%)	19 (32%)	
Pathological T			
T1–/T3	50	55	0.24
Histology			
Adenocarcinoma/squamous cell carcinoma/others	47 (80%)/9/3	40 (67%)/15/5	0.28
Combined resection			
Chest wall	6	3	0.28
Diaphragm	1	1	
Others	9	4	
None	43 (73%)	52 (87%)	
Number of N2 stations			
1	31 (52%)	28 (47%)	0.75
2	24	25	
Unknown	4	6	

Table 2 Compliance of chemotherapy and causes for discontimuation

Chemotherapy	Case no.	Cycles performed			
		0	1	2	3
Fully administered	59	4	11	10	34 (58%)
	34	0	0	0	34
Cause of discontinuation					
Adverse effect	5	0	3	2	–
Patient refusal	18	3	7	8	–
Others	2	1	1	1	–

discontinuation of the chemotherapy was patient withdrawal, which accounted for 17 cases (Table 2). There were no grade four adverse effects on hematological data during chemotherapy. The major toxicity was grade 3 neutropenia, which 50% of patients experienced. Only two patients had grade 3 bilirubinemia, and one had grade 3 creatinine elevation.

The 5-year survival was 28.2% in the chemotherapy arm and 36.1% in the control group ($P = 0.89$). The median disease-free survival was 18.3 months in the chemotherapy group and 16.1 months in the control group ($P = 0.66$). There were no statistical differences between the two groups in overall survival by either the log-rank test or the generalized Wilcoxon test (Fig. 1). Almost all deaths were from the original cancer, especially distant metastasis (46%). Lung, bone and brain were frequent sites of relapse in both groups. Lymph node relapses were more frequently seen in the observation group than the adjuvant chemotherapy group ($P = 0.049$) (Tables 3 and 4). Univariate analysis was performed to examine the following factors: treatment arm, age, gender, tumor histology, extent of surgery, existence of combined resection, and number of N2 stations (Table 5). Only an age of 61 or younger was found to be a significant favorable prognostic factor ($P = 0.042$).

5. Discussion

We set out to clarify whether adjuvant chemotherapy is effective in cases of completely resected N2 non-small cell lung cancer.

The first report of adjuvant chemotherapy for completely resected non-small cell lung cancer

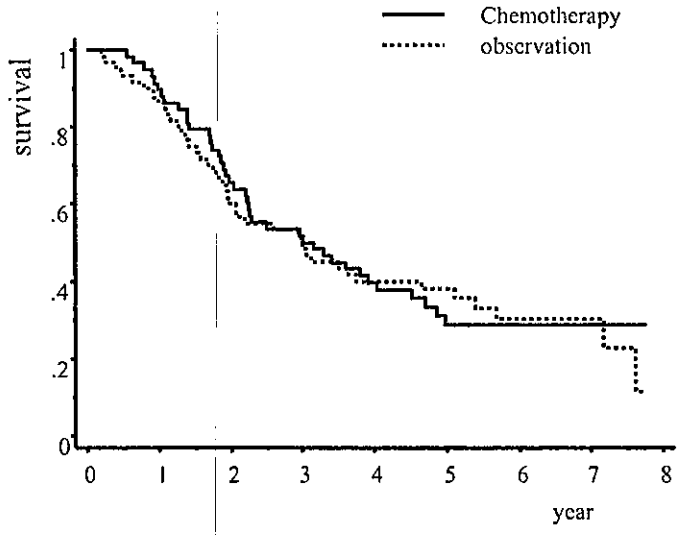

Fig. 1 Actual survival. The solid line indicates the adjuvant group and dotted line indicates the observation group ($P = 0.89$).

Table 3 Treatment-related adverse effects (WHO grade) by chemotherapy

Adverse effect	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
WBC	44	51	0
Hb	85	7	0
Plt	11	2	0
Bilirubin	11	4	0
SGOT	22	0	0
SGPT	24	0	0
Creatinine	25	1	0
Nausea/vomit	73	9	0
Diarrhea	16	0	0
Infection	5	2	0
Alopecia	78	–	–

Four patients who did not have chemotherapy were excluded from this analysis. $n = 55$.

Table 4 Relapse patterns for each group

Relapse site	Adjuvant chemotherapy	Observation	*P*-value
Bone	10 (2)	8 (1)	0.77
Brain	13 (1)	8	0.31
Lung	13 (2)	10 (4)	0.60
Mediastinal or cervical LN	7	18 (3)	0.049
Others	4 (1)	5	0.99

Data in parentheses represent metastasis found synchronously at another site. All data reflect absolute numbers of patients.

Table 5 Univariate analyses according to prognostic factors

Factors		*P*-value
Study arm	Adjuvant vs. obsevation	0.840
Age	≤61 vs. >61	0.042
Gender	Female vs. male	0.505
Histology	Adenocarcinoma (ad) vs. non-ad	0.220
Operation	Pneumonectomy vs. lobectomy	0.614
Combined resection	With vs. without	0.116
Number of N2 station	1 vs. 2	0.333

There is no significant difference between any factors.

using a CDDP-based regimen, reported by Holmes et al. [1], included stages II and III, and demonstrated slight effectiveness of adjuvant chemotherapy for large cell and adenocarcinoma cases. LCSG801 [7] also included T2N0 and T2N1 patients, but revealed no effectiveness of adjuvant chemotherapy for non-small cell lung cancer at all. Niiranen et al. reported another randomized trial for completely resected non-small cell lung cancers [8]. Although they demonstrated the efficacy of adjuvant chemotherapy for T1-3N0 patients, the higher number of pneumonectomies included in the observation group might have caused the difference. A meta-analysis of adjuvant chemotherapy by the Non-Small Cell Lung Cancer Collaborative Group reported that the hazards ratio in most trials slightly favored adjuvant chemotherapy but the *P*-value was not significant [9]. The 5-year survival rate for adjuvant chemotherapy patients was 5% better than for surgery alone. A BLT study (ASCO 2003, abstract#2543), which enrolled 381 patients from 56 institutes and included all stages, also could not show the effectiveness of chemotherapy. An 8% 2-year survival advantage was seen with chemotherapy in another meta-analysis for node positive patients [10]. Therefore, the selection of particular stages for perioperative chemotherapy may have been the key to the success seen in that adjuvant chemotherapy trial.

Dautzenberg reported a randomized trial that compared adjuvant radiation versus adjuvant radiation plus chemotherapy [11]. They found no significant difference in overall survival. However, in the subset analyses, patients with N2 disease treated with chemoradiation had a significantly better survival than radiation alone. Keller also reported no difference between survival rates for adjuvant chemo-radiotherapy and adjuvant radiotherapy for stage II and IIIa cancers [12]. Although there have been many clinical trials for non small cell lung cancer, there have been almost no reports on clinical trials of adjuvant chemotherapy for n2 disease. Only Pisters et al. [13] made a report on comparing adjuvant chemo-radiotherapy and adjuvant radiotherapy limited to 71 cases of T1-2 N2 disease including incompletely resected patients. They also did not demonstrate any therapeutic effectiveness. There are several large-scale randomized control studies of adjuvant chemotherapy for patients with completely resected lung cancers. An ALPI study (ASCO 2002, abstract#1157) reported ineffective results, while an IALT study (ASCO 2003, abstract#6) showed slight efficacy of adjuvant chemotherapy. Those two trails included radiation therapy frequently for patients with nodal metastasis. Those reports, mentioned above, aimed to

determine the efficacy of adding chemotherapy to radiation therapy after surgery for patients with nodal metastasis. PORT meta analysis reported that post operative radiation therapy was not useful even in nodal metastasis patients [14], so we aimed to determine the efficacy of adding chemotherapy after surgery for patients with mediastinal nodal metastasis without radiation therapy.

Ohta et al. reported an adjuvant trial for stage IIIa disease conducted by JCOG [3], which also revealed no effectiveness of adjuvant chemotherapy. Although the patients were randomly assigned to each group, the surgery alone group included a higher number of N2 disease patients than the adjuvant chemotherapy group, which may have been related to the negative result. We enrolled only completely resected N2 disease to reduce the heterogeneity of diseases.

Compliance is important in adjuvant chemotherapy. LCSG801 [7] was criticized for low compliance, which was seen as one possible reason for negative data. In our series, 58% of patients received the targeted dose and 75% received two or more courses without serious adverse effects. This appeared sufficient for adjuvant chemotherapy. Although the number of patients accrued was small, the two survival curves were almost identical. Thus, in pathological N2 disease, adjuvant chemotherapy using CDDP and VDS does not improve survival.

The initial target of neoadjuvant chemotherapy was only locally advanced cancer. A few small-sample trials have shown some efficacy of perioperative chemotherapy [15,16]. Recently, a Bimodality Lung Oncology Trial (BLOT) study focused on earlier stages as a target for chemotherapy [13]. The French trial for neoadjuvant chemotherapy also included stages I-IIIa [17]. These two groups hold great expectations for perioperative chemotherapy in earlier stages. Considering these studies, adjuvant chemotherapy is also warranted with new agents for earlier stages of cancer.

6. Conclusion

Patients with N2, NCSLC who had undergone complete resection, were randomized to surgery only or adjuvant chemotherapy (cisplatin 80 mg/m^2 on day 1; vindesine 3 mg/m^2 on days 1 and 8; ×3 courses). This trial was terminated before accumulation of the planned numbers for registration because of a slow accrual rate. A total of 119 patients were randomized (59 patients in the adjuvant arm and 60 with surgery alone). The median survival was 36 months for both groups. There was no significant difference in survival between the adjuvant chemotherapy group and the observation group. The efficacy of adjuvant chemotherapy for completely resected NSCLC with N2 disease might be so small that the number of patients in this study was insufficient to detect the efficacy of this classic regimen.

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