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Analysis of the Prognostic Factors of Extensive Disease Small-Cell Lung Cancer Patients in Tokushima University Hospital

Hirokazu Ogino[1], Masaki Hanibuchi[1], Soji Kakiuchi[1,2], Atsuro Saijo[1], Toshifumi Tezuka[1], Yuko Toyoda[1], Makoto Tobiume[1], Kenji Otsuka[1], Satoshi Sakaguchi[1,3], Hisatsugu Goto[1], Kokichi Arisawa[4], and Yasuhiko Nishioka[1]

[1]*Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan,* [2]*Department of Oncology, Tokushima Municipal Hospital, Tokushima, Japan,* [3]*Department of Respiratory Medicine, Tokushima Prefectural Central Hospital, Tokushima, Japan,* [4]*Department of Preventive Medicine, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan*

Abstract : Background : Small-cell lung cancer (SCLC) presents aggressive clinical behavior, and its prognosis is still poor. Previously, performance status (PS), or the existence of brain, bone, or liver metastasis were reported to be unfavorable prognostic factors. Given the recent progress of treatment modalities such as radiotherapy techniques and bone modifying agents, the prognostic factors might be different from previous findings. Therefore, we analyzed the prognostic factors of extensive disease SCLC (ED-SCLC) in recent years. Methods : ED-SCLC patients treated in Tokushima University Hospital between 2010 and 2016 were analyzed. Log-rank test and the Cox proportional hazards regression model was used in univariate and multivariate analysis, respectively. Results : Totally, 79 patients were analyzed. In the univariate analysis, age, PS, interstitial pneumonia (IP), liver metastasis, pleural dissemination, neutrophil counts, hypoalbuminemia, hypercalcemia and several liver and biliary enzymes were identified as poor prognostic factors. In the multivariate analysis, age, PS, IP, and liver and biliary enzymes were identified. Moreover, the PS in patients with liver metastasis was significantly worsened. Conclusions : In this study, we newly demonstrated that IP was a significant poor prognostic factor of ED-SCLC. Although liver metastasis was not extracted in multivariate analysis, it may have an impact on the prognosis of ED-SCLC. J. Med. Invest. 63 : 286-293, August, 2016

Keywords **:** *extensive disease small-cell lung cancer (ED-SCLC), prognostic factor, liver metastasis, interstitial pneumonia*

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for 15-20% of lung cancer (1) and presents aggressive clinical behavior characterized by rapid growth, metastatic spread to the distant organs (2). Despite the high response rate to initial chemotherapy, most patients subsequently experience a relapse of the primary tumor or distant metastasis, and the prognosis is still poor. SCLC is clinically categorized as two stages, limited disease (LD) and extensive disease (ED). LD-SCLC is defined as to be confined to the ipsilateral hemithorax and regional nodes, and able to be included in a single tolerable radiotherapy port. LD-SCLC is primarily treated with a combination of chemotherapy and radiotherapy, and its prognosis is improved by the development novel effective radiation therapy, such as accelerated hyperfractionated thoracic radiotherapy (AHF-TRT) (3). On the other hands, for ED-SCLC which is beyond the boundaries of LD including distant metastases, malignant pericardial, or pleural effusion and contralateral supraclavicular and contralateral hilar involvement, platinum-based combination chemotherapy alone is used as the initial therapy (4-6). Despite the several novel anticancer agents against non-small cell lung cancer were developed and shown to have favorable outcome, the chemotherapy regimens against SCLC were not making any progress in recent decade, which leads to the poor prognosis of ED-SCLC.

In the past, several studies were performed to reveal the prognostic factors in SCLC (7-19). In these studies, male, poor performance status (PS) and weight loss as the host factors, and the extent of disease, number of metastatic sites, brain metastasis, bone metastasis, liver metastasis, elevated white blood cell (WBC) counts, neutrophil counts, serum lactate dehydrogenase (LDH), alkaline phosphatase (ALP), decreased platelet (PLT) counts, albumin (ALB), sodium, and C-reactive protein (CRP) as the tumor-related factors were reported to be unfavorable prognostic factors in multivariate analysis. Among these factors, existence of distant organ metastasis become easily a major problem of treatment in clinics, and metastatic involvement of the central nervous system, the bone marrow, or the liver is usually unfavorable compared with other sites.

For the brain metastasis of SCLC, whole brain radiotherapy (WBRT) was mainly performed currently in the combination with chemotherapy. Moreover, novel stereotactic irradiation (STI) techniques were developed recently, such as stereotactic radiosurgery (SRS) or volumetric-modulated arc therapy (VMAT), resulted in improving the management of adverse events and prognosis (20-23). For the bone metastasis, not only palliative radiotherapy (24), but also novel bone modifying agents (BMAs), such as zoledronic acid or denosumab can be used in recent days (25-26). On the other hands, we still have few treatment strategies against liver metastasis, and frequently faced lethal clinical courses of aggressive and uncontrollable liver metastasis.

Given that most of data regarding the prognostic factors in SCLC were reported in 1980s or 1990s, the prognostic factors might be

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Address correspondence and reprint requests to Yasuhiko Nishioka, Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-2134.

different from previous findings because of recent progress of novel treatment modalities. Therefore, in this study we analyzed the prognostic factors of SCLC patients, especially the status of distant organ metastasis, in recent days.

PATIENTS AND METHODS

Participants

This was a retrospective study to evaluate ED-SCLC patients who were admitted to Tokushima University Hospital between March 1, 2010 and June 30, 2016. Totally, 81 patients who were in extensive stage at diagnosis were enrolled to this study. We excluded one patient who did not have enough data for the analysis, and one patient who refused any treatments.

The statement on consent to participate in this study was obtained from patients by written informed consent forms, if applicable, or by the disclosure of information for participation. The study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Tokushima University Hospital (approval number : 2366, approval date : 2015/8/31).

Data collection

We collected several pretreatment factors, such as age, gender, performance status (PS), smoking status (Brinkman Index), comorbidities in the lungs such as chronic obstructive pulmonary disease (COPD) or interstitial pneumonia (IP), distant metastatic sites at diagnosis (brain, bone, liver, adrenal gland, lung, and pleura), and several laboratory data which were previously reported as prognostic factors of lung cancer. The laboratory data at the start of treatments were analyzed in this study. We also collected the data about radiotherapies after BMAs during treatments, the total number of chemotherapy regimens, and overall survival. The data were collected retrospectively from the medical records of Tokushima University Hospital, and in some patients, who moved to other hospital during treatments, the additional data were supplied from those hospitals.

Statistical analysis

For univariate analysis, median survival times (MSTs) were estimated by the Kaplan-Meier method, and statistical analyses were performed by the Log-rank test (27). The factors which P-value was < 0.2 in the univariate analysis, as well as the other clinically important factors, such as distant metastatic sites at diagnosis and CRP were included in the multivariate analysis. The Cox proportional hazards regression model was used for the multivariate analysis (28). Clinical parameters and laboratory parameters were analyzed separately. In the laboratory data, significant correlations in the Pearson product-moment correlation coefficient were seen between liver and biliary enzymes, therefore, only ALP, which was the most significant parameter of the liver and biliary enzymes in univariate analysis, was induced to the multivariate analysis. The continuous variables, such as age, PS, and the laboratory data were categorized according to the previous reports before analysis. The differences of PS between two groups (with or without distant metastasis in each organ) were evaluated with Mann-Whitney U Test. All analysis were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (29).

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. The median age was 72 years, and 41 patients (52%) were ≥ 70 years. Most patients were male (71 patients, 90%), and clinical stage IV (74 patients, 94%), and 52 patients (66%) had PS 0-1. Thirty-three patients (42%) and 21 patients (27%) were associated with COPD and IP, respectively. The metastasis to the brain (BRA), the bone (OSS), the liver (HEP), the adrenal glands (ADR) and the lungs (PUL), and the dissemination in the pleural cavity (PLE) were detected in 38%, 19%, 35%, 20%, 16%, and 25% of the patients at diagnosis, respectively. Four patients (5%) were treated with radical thoracic radiotherapy (AHF-TRT). Most patients with brain metastasis were treated with radiotherapy, such as WBRT or STI, and bone metastasis were treated with radiotherapy and BMAs. Most patients were treated with platinum-based chemotherapeutic regimens, and the median number of chemotherapy regimens was two. In the laboratory data, hypoalbuminemia and elevation of LDH was seen in 37 (59%) and 56 patients (72%), respectively. The tumor markers such as Pro-gastrin-releasing peptide (ProGRP) and Neuron-specific enolase (NSE) were elevated in most patients.

Results of the univariate analysis

The results of the univariate analysis for demographic, clinical, and laboratory variables are shown in Table 2 and Figure 1. In the demographic and clinical variables, five of twelve factors were determined to have prognostic significance. Elderly patients (≥ 70 years) or the patients with poor PS (PS 2-4) survived shorter than the others ($P < 0.001$). Moreover, IP but not COPD as comorbid disease was selected as a poor prognostic factor. The prognosis of patients with liver metastasis was significantly deteriorated compared with those without liver metastasis, while this was not the case for brain and bone metastasis. We also evaluated the pretreatment laboratory data which are reported to be prognostic factors in lung cancer patients, such as WBC or neutrophil counts, ALB, and calcium corrected for albumin (cCa). Among them, elevation of neutrophil counts, hypoalbuminemia and hypercalcemia were selected as prognostic factors. Interestingly, the elevation of alanine amino transferase (ALT), ALP and γ-glutamyl transpeptidase (γ-GTP), those were thought to be caused by liver metastasis, significantly associated with poor prognosis.

Results of the multivariate analysis

The Cox proportional hazard regression analysis was performed by using variables with P-value was < 0.2 in the univariate analysis and other clinically important factors, such as distant metastatic sites at diagnosis. In this study, we analyzed the significance of clinical parameters and laboratory parameters separately in several reasons. First, only 79 patients were analyzed in this study. Because the statistical power seems to be dependent on the total number of events, that is patient's death, there is a limitation in the number of parameters to be analyzed in multivariate analysis. Therefore, we thought it is better to reduce the parameters in multivariate analysis model. Second, there were some correlations between clinical factors and laboratory factors, such as liver metastasis and the elevation of liver enzymes, therefore we thought it is not better to induce these correlated parameters in multivariate analysis model at the same time. When we performed the analysis with only clinical variables, age, PS, IP were determined as independently significant poor prognostic factors (Table 3a). The multivariate analysis of the laboratory data was performed with the essential clinical variables such as age, gender and PS, and laboratory data which P-value was < 0.2 in the univariate analysis. Moreover, since the significant correlations in the Pearson product-moment correlation coefficient were seen between liver and biliary enzymes, only

Table 1 Patient characteristics

	No. of patients (n=79)	%
Age (years)		
Median (range)	72 (45-85)†	
< 70	38	48
≥ 70	41	52
Gender		
Male	71	90
Female	8	10
PS		
0	6	8
1	46	58
2	13	16
3	11	14
4	3	4
BI		
Median (range)	1230 (0-3,000)	
Clinical stage		
IIIB	5	6
IV	74	94
COPD	33	42
IP	21	27
BRA	30	38
OSS	15	19
HEP	28	35
ADR	16	20
PUL	13	16
PLE	20	25
WBRT	39	51
STI	17	23
AHF-TRT	4	5
Bone radiotherapy	13	18
BMA	14	19
No. of chemotherapy regimens		
0	3	4
1	26	35
2	16	22
3	15	20
4	10	14
5	3	4
6	1	1
WBC count (/μL)		0
Median (range)	7400 (2,000-15,700)	
> 10,000	14	18
Neutrophil count (/μL)		
Median (range)	5200 (570-14,370)	
> 7,500	15	21
Hemoglobin (g/dL)		
Median (range)	13.0 (8.6-16.3)	
< 12.0	21	27
Platelet count (10^4/μL)		
Median (range)	25.8 (10.4-63.4)	
< 15.0	5	6
ALB (g/dL)		
Median (range)	3.4 (1.5-4.3)	
< 3.5	37	59
Cr (mg/dL)		
Median (range)	0.76 (0.40-5.26)	
> 1.1	11	14
T-Bil (mg/dL)		
Median (range)	0.6 (0.2-7.2)	
> 1.0	9	12
AST (U/L)		
Median (range)	26 (10-251)	
> 35	23	29
ALT (U/L)		
Median (range)	20 (5-164)	
> 40	13	17
LDH (U/L)		
Median (range)	278 (152-2,258)	
> 220	56	72
ALP (U/L)		
Median (range)	269 (95-1,853)	
> 340	21	27
γ-GTP (U/L)		
Median (range)	36 (10-1,264)	
> 60	24	31
Na (mEq/L)		
Median (range)	139 (118-147)	
< 135	17	22
Ca (mg/dL)		
Median (range)	9.2 (6.9-12.2)	
> 10.2	10	17
CRP (mg/dL)		
Median (range)	1.27 (0.05-17.13)	
> 0.3	58	78
CEA (ng/mL)		
Median (range)	6.2 (0.5-2,800)	
> 5.0	38	51
Cyfra (ng/mL)		
Median (range)	3.3 (1.0-62)	
> 3.5	24	32
ProGRP (pg/mL)		
Median (range)	930 (15.2-29,200)	
> 81	60	81
NSE (ng/mL)		
Median (range)	47.7 (9.4-1,670)	
> 16.3	55	74

PS : Performance status, BI : Brinkman index, COPD : chronic obstructive pulmonary disease, IP : Interstitial pneumonia, BRA : Brain metastasis, OSS : Bone metastasis, HEP : Liver metastasis, ADR : Adrenal metastasis, PUL : Lung metastasis, PLE : Pleural dissemination, WBRT : Whole brain radiation therapy, STI : stereotactic irradiation for brain, AHF-TRT : Accelerated hyperfractionated thoracic radiotherapy, BMA : Bone modifying agents, ALB : Albumin, AST : Aspartate amino transferase, ALT : alanine amino transferase, LDH : lactate dehydrogenase, ALP : alkaline phosphatase, γ-GTP : γ-glutamyl transpeptidase, Na : sodium, Ca : calcium corrected for albumin, CRP : C-reactive protein, CEA : carcinoembryonic antigen, Cyfra : cytokeratin 19 fragment, ProGRP : pro-gastrin releasing peptide, NSE : neuron specific enolase

† : median (range)

Table 2 The univariate analysis for overall survival

Variable	Category	MST (months)	*P*-value*	Variable	Category	MST (months)	*P*-value*
Age (years)	< 70	16.4	< 0.001	ALB (g/dL)	< 3.5	7.4	0.001
	≥ 70	8.7			≥ 3.5	16.4	
Gender	Male	10.3	0.716	Cr (mg/dL)	≤ 1.1	10.3	0.948
	Female	14.9			> 1.1	17.1	
PS	0-1	14.5	< 0.001	T-Bil (mg/dL)	≤ 1.0	11.5	0.544
	2-4	4.2			> 1.0	14.4	
Clinical stage	ⅢB	9.1	0.971	AST (U/L)	≤ 35	13.2	0.113
	Ⅳ	12.4			> 35	5.3	
COPD	Yes	9.5	0.233	ALT (U/L)	≤ 40	12.4	0.049
	No	14.2			> 40	5.3	
IP	Yes	8.2	0.008	LDH (U/L)	≤ 220	13.9	0.15
	No	13.6			> 220	8.7	
BRA	Yes	13.9	0.421	ALP (U/L)	≤ 340	12.7	0.011
	No	9.4			> 340	5.3	
OSS	Yes	8.2	0.347	γ-GTP (U/L)	≤ 60	11.5	0.015
	No	13.2			> 60	8.2	
HEP	Yes	7.4	0.041	Na (mEq/L)	< 135	13.6	0.83
	No	13.3			≥ 135	11.5	
ADR	Yes	13.3	0.911	Ca (mg/dL)	≤ 10.2	11.4	0.004
	No	11.4			> 10.2	3.0	
PUL	Yes	10.3	0.949	CRP (mg/dL)	≤ 0.3	14.4	0.11
	No	12.7			> 0.3	10.3	
PLE	Yes	7.4	0.017	CEA (ng/mL)	≤ 5.0	13.6	0.473
	No	13.6			> 5.0	10.3	
WBC count (/μL)	≤ 10,000	12.7	0.664	Cyfra (ng/mL)	≤ 3.5	11.5	0.052
	> 10,000	8.6			> 3.5	8.2	
Neutrophil count (/μL)	≤ 7,500	13.3	0.005	ProGRP (pg/mL)	≤ 81	11.5	0.216
	> 7,500	5.3			> 81	12.4	
Haemoglobin (g/dL)	< 12.0	12.7	0.99	NSE (ng/mL)	≤ 16.3	17.1	0.253
	≥ 12.0	9.5			> 16.3	12.7	
Platelet count (10^4/μL)	< 15.0	2.7	0.244				
	≥ 15.0	11.5					

MST : Median survival time
* : For the univariate analysis, MSTs were estimated by the Kaplan-Meier method, and statistical significance between survivals was assessed using the Log-rank test. $P < 0.05$ was considered significant.

ALP, which was the most significant parameter of the liver and biliary enzymes in univariate analysis, was induced to the multivariate analysis. As a result, interestingly, only ALP was determined as a laboratory poor prognostic factor (Table 3b). We also analyzed the multivariate analysis using step-wise methods and confirmed that same parameters were selected in this setting (data not shown). These results suggested that, not only age and poor PS but also the existence of IP as a comorbid disease is an important clinical poor prognostic factor. Moreover, although liver metastasis was not selected as a poor prognostic factor, it may have an impact on the prognosis of ED-SCLC, because only the elevation of liver enzyme was selected as a laboratory prognostic factor.

Relationship of PS and distant metastatic sites

In the multivariate analysis, the most prominent prognostic factor was poor PS, and any distant organ metastasis at diagnosis was not determined as independent prognostic factors, indicating the correlations between PS and each distant organ metastasis. Thus, we finally compared PS with or without distant organ metastasis to evaluate their correlation. Interestingly, PS in patients with liver metastasis was significantly deteriorated compared with those without liver metastasis (Fig. 2a), while no significant differences were observed in other distant organ metastasis (Fig. 2b-f). These results suggest that the existence of liver metastasis at diagnosis deteriorates patient's general condition, and resulted in poor prognosis in ED-SCLC.

DISCUSSION

In this study, we retrospectively analyzed the prognostic factors of ED-SCLC. In the univariate analysis, age, poor PS, IP, liver metastasis, pleural dissemination, hypoalbuminemia, elevated neutrophil counts, hypercalcemia, and the elevations of liver metastasis related parameters such as ALT, ALP, γ-GTP were selected as poor prognostic factors (Table 2 and Fig. 1). In the multivariate analysis, age, poor PS, IP and the elevation of liver and biliary enzymes were extracted as independently significant poor prognostic factors (Table 3). The poor PS was the most prominent prognostic factor, and PS in patients with liver metastasis was significantly deteriorated

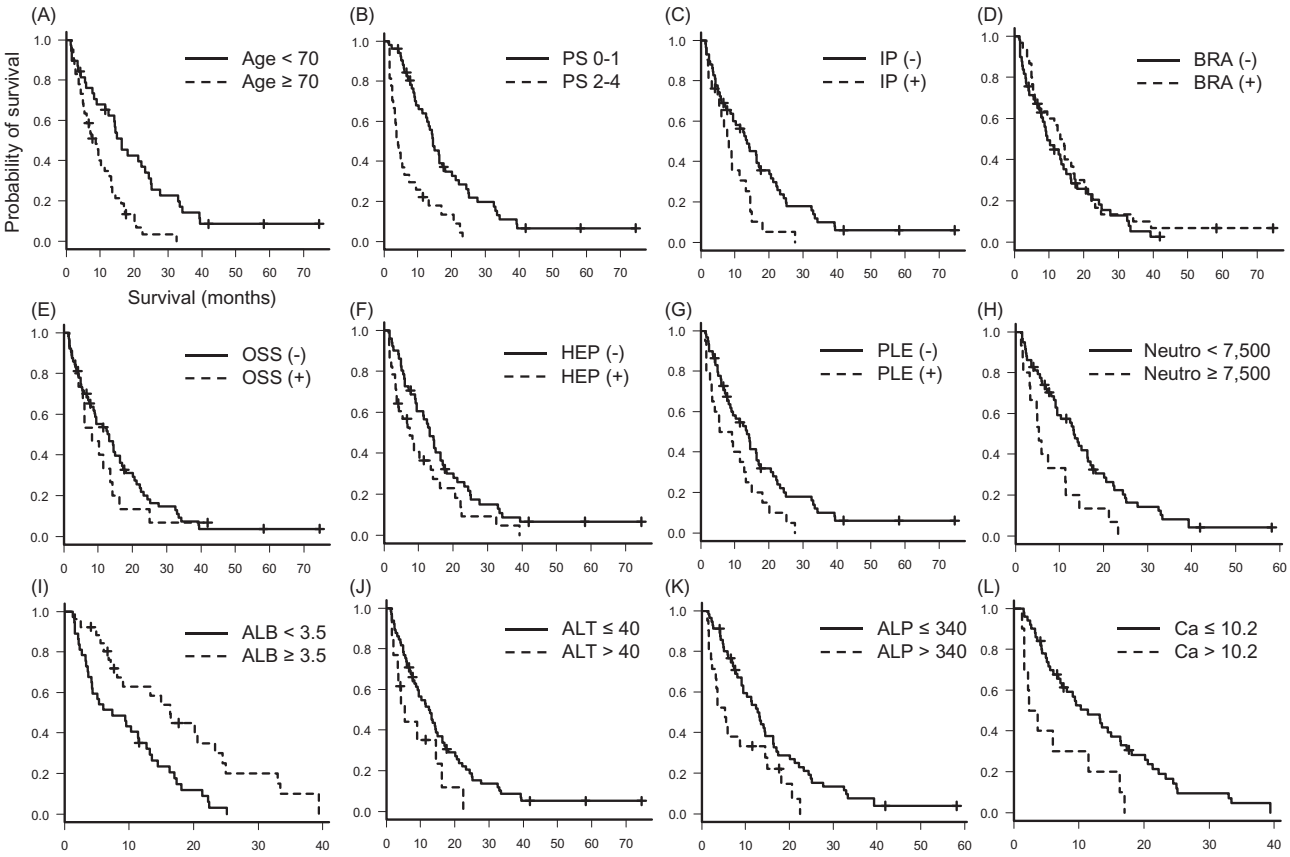

Figure 1. Kaplan-Meier estimates of the survival of patients with ED-SCLC according to several parameters which were significant in Log-rank analysis.
(A) Age. (B) PS. (C) IP. (D) Brain metastasis. (E) Bone metastasis. (F) Liver Metastasis. (G) Pleural dissemination. (H) Neutrophil counts. (I) ALB. (J) ALT. (K) ALP. (L) Calcium.

Table 3 Cox's regression analysis for overall survival

(a) Clinical parameters only

Factor	Hazard ratio	*P*-value*
Age	1.94 (1.07-3.51)	0.029
Gender	0.69 (0.28-1.66)	0.4
PS	2.71 (1.46-5.05)	0.002
IP	2.21 (1.13-4.33)	0.021
BRA	0.94 (0.52-1.72)	0.84
OSS	1.80 (0.91-3.58)	0.092
HEP	1.27 (0.70-2.33)	0.43
ADR	1.30 (0.70-2.41)	0.4
PUL	0.95 (0.45-1.98)	0.89
PLE	1.68 (0.81-3.47)	0.16

(b) Laboratory parameters

Factor	Hazard ratio	*P*-value*
Age	1.88 (0.91-3.89)	0.089
Gender	1.03 (0.38-2.81)	0.95
PS	1.58 (0.72-3.45)	0.25
Neutro	1.36 (0.62-2.98)	0.45
ALB	0.49 (0.22-1.07)	0.075
ALP	2.39 (1.21-4.72)	0.012
Ca	1.60 (0.65-3.94)	0.3
CRP	1.07 (0.45-2.55)	0.87

* : For the multivariate analysis, statistical significance was assessed using the Cox proportional hazards regression model. $P < 0.05$ was considered significant.

when compared with those without liver metastasis (Fig. 2). These results suggest that not only age, poor PS, IP but also the existence of liver metastasis at diagnosis may have an impact on the prognosis of ED-SCLC.

In this study, brain metastasis or bone metastasis, which are reported as poor prognostic factors in previous studies, were not selected as prognostic factors even in the univariate analysis. Moreover, the MSTs of the patients with brain metastasis tended to be longer than the patients without brain metastasis. We thought that these results were induced by the progressions of radiotherapy techniques or bone modifying agents as mentioned in introduction. Moreover, the progressions of imaging modalities, such as high resolution computed tomography (HRCT), magnetic resonance imaging (MRI), or positron emission tomography-CT (PET-CT), which enable early diagnosis and early treatment for the brain and bone metastasis, partially influenced on these results. However, in contrast to the improvement of managements for brain and bone metastasis, no specified method against the metastasis to other organs was developed, therefore the liver metastasis and pleural dissemination were still extracted as poor prognostic factors in the univariate analysis in this study.

In this study, liver metastasis was determined as a significant poor prognostic factor in the univariate analysis, but not in the multivariate analysis. There seems to be some putative explanations for the reasons of this finding. First, the numbers of patients enrolled in this study was small and only 28 patients with liver metastasis were analyzed. Thus, further larger scale studies are required to draw definite conclusions in the future. Second, there is

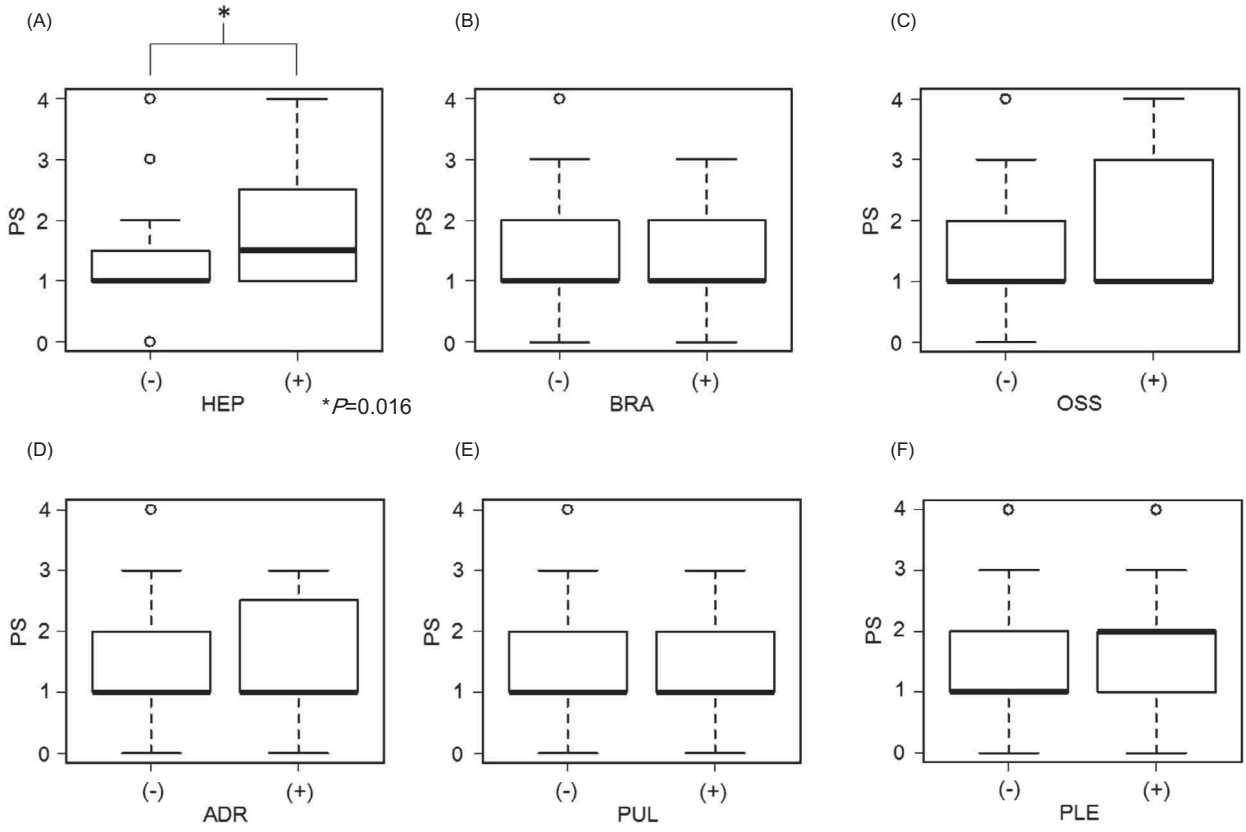

Figure 2. Comparison of PS in the presence or absence of distant organ metastasis.
Mann-Whitney *U* Test was used to investigate the relations between PS and the existence of distant organ metastasis, such as (A) liver metastasis, (B) brain metastasis, (C) bone metastasis, (D) adrenal gland metastasis, (E) lung metastasis, and (F) pleural dissemination. PS of the patients with liver metastasis was significantly deteriorated ($P=0.016$).

a significant correlation between PS and liver metastasis. Because of this correlation, liver metastasis might be difficult to be selected as an independent prognostic factor. Although liver metastasis is not extracted as a prognostic factor in the multivariate analysis, it is clinically very important that liver metastasis deteriorates patient's PS, therefore, this result also emphasizes the importance of the novel strategies against liver metastasis.

As the primary risk factor of SCLC is cigarette smoking, smoking related lung diseases, such as COPD and/or IP, are often seen as comorbid diseases in SCLC (30, 31). Among these comorbidities, IP often become a problem in the treatment of SCLC. For example, thoracic radiotherapy is contraindication, and chemotherapy and/or infection often induce the acute exacerbation of IP which results in the discontinuation of treatments. In this study, IP was extracted as a poor prognostic factor in both univariate analysis and multivariate analysis (Table 2, 3a). These findings have significance in clinics, and to our knowledge, this is the first report which show the existence of IP is a significant prognostic factor of SCLC.

This study had several limitations. First, this was a retrospective study with small number of patients. Therefore, there is a possibility that our findings may not reflect of real clinics adequately. For example, important parameters could have been missed in this analysis. Second, this study was performed in only one institution. To resolve these problems, we plan to increase the number of the patients for analysis, and to demonstrate external validation by analyzing the data in multiple hospitals. As a result, we will able to show the more clinically significant data in the future.

In summary, we showed the significance of age, PS, and the existence of IP in the prognosis of SCLC. Although liver metastasis was not extracted as an independent poor prognostic factor, the elevation of liver and biliary enzymes was significant factor in multivariate analysis, and PS in patients with liver metastasis was significantly worsened. Therefore, liver metastasis at diagnosis may have an impact on the prognosis of ED-SCLC. The findings of this study suggested the importance of developing novel therapeutic strategies against liver metastasis or interstitial pneumonia associated with SCLC, although these may not have an impact on the clinical managements directly at this time. On the basis of the obtained findings of this study, further basic studies for the development of novel therapies and clinical studies with the increased number of patients in multiple institutions will improve the prognosis of ED-SCLC patients in the future.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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