Prognostic Factors in Small Cell Lung Cancer: A New Prognostic Index in Korean Patients

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Soo Jung Hong

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ABSTRACT

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The aims of this study were to identify prognostic factors for overall survival, progression-free survival, and response to chemotherapy in patients with small cell lung cancer (SCLC), and to construct a prognostic index on the basis of their expected overall survival. We also characterized about long-term survivors. We retrospectively analyzed 193 patients diagnosed with SCLC from January 2002 to September 2007 at Severance Hospital, Seoul, Republic of Korea. Pre-treatment variables were included both clinical and tumor-related markers, and treatment-related factors were also evaluated.

There were 91 (47.2%) limited-disease (LD) patients and 102

(52.8%) extensive-disease (ED) patients. Objective response to chemotherapy was 74.3%. The median survival time was 14.1 months (95% CI, 11.4-16.8) in all patients, 28.7 months (95% CI, 19.1-38.4) for LD patients, and 10.2 months (95% CI, 8.4-11.9) for ED patients. The median progression-free survival was 8.7 months (95% CI, 7.3-10.0). Independent prognostic factors for overall survival were extent of disease, performance status, weight loss, LDH level, and CYFRA 21-1 level. Unlike our expectations, smoking history did not affect outcome.

We classified all patients into four groups based on the results of the multivariate analysis, using classification and regression trees (CART) analysis ($p<0.001$). Median survival times were 32.0, 12.4, 8.0, and 3.5 months, respectively.

A total of 40 (20.7%) patients from the entire study population were evaluated for long-term survival which was defined as more than two year survival. Their median survival time was 45.3 months, and extent of disease and prophylactic cranial irradiation (PCI) were independent predictive factors for long-term survival.

We confirmed the well-known prognostic values of disease extent and performance status in our patients, but further identified weight loss, LDH level, and CYFRA 21-1 level as independent prognostic factors.

A prognostic index was constructed to create four classifications of SCLC considering these variables. The independent value of CYFRA 21-1 level should be validated by further studies.

Key words: prognostic factors, small cell lung cancer, survival

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I. INTRODUCTION

Small cell lung cancer (SCLC) accounts for 15~20% of all lung cancers and is highly sensitive to both chemotherapy and radiation therapy.[1] Despite the use of more active and intensive regimens, however, the survival time of SCLC patients has improved only modestly over the past two decades due to the aggressive nature of the disease. Without treatment, the median survival time is still only 2 to 4 months.

SCLC is currently categorized into a two-stage system although the criteria remain controversial.[2] Limited disease (LD) is defined as disease confined to

the ipsilateral chest within a single radiation field. Extensive disease (ED) is defined as disease beyond the ipsilateral hemithorax. Extent of disease is the most important predictor of improved response and survival.[1, 3-5]

While it is accepted that combination chemotherapy is superior to single agent chemotherapy, the best chemotherapy combination has yet to be identified. Standard chemotherapy, combining etoposide and cisplatin (EP), in use since the 1980s, has resulted in a median survival of 8-10 months and 17-20 months for patients with ED and LD, respectively.[6] In 2002, the Japanese Clinical Oncology Group (JCOG) phase III trial demonstrated the superiority of irinotecan and cisplatin (IP) over EP.[7] This result was not confirmed by a subsequent comparative trial in the U.S., however, which found both treatments to be equally effective.[8] In LD, early concurrent thoracic radiation therapy improves overall and progression-free survival.[9] Brain metastases develop in more than 50% of SCLC patients, and previous studies have shown that prophylactic cranial irradiation (PCI) during complete remission in LD patients decreases the risk of intracranial metastasis and improves both overall and disease-free survival.[10, 11]

There has been active discussion of prognostic factors for SCLC since 1981. The anatomic extent of disease, performance status, and weight loss have traditionally been used to predict the outcome of patients with SCLC,[1] but there is still no consensus that these are the best prognostic factors. The aims of this study were as follows; first, to evaluate the impact of pre-treatment patient characteristics on the outcome of SCLC with respect to response and

survival; second, to classify patient subsets with different survival potentials based on clinically available information identified according to multivariate analysis and; third, to characterize the clinical parameters of long term survivors.

II. MATERIALS AND METHODS

1. Patients

This study included patients who were newly diagnosed with SCLC from January 2002 to September 2007 in Severance Hospital, Seoul, Republic of Korea.

Staging at diagnosis included a computed tomographic (CT) scan of the chest and abdomen, radionuclide whole body bone scan, and magnetic resonance imaging (MRI) of the brain.

Performance status was defined by the Eastern Cooperative Oncology Group (ECOG) classification. Weight loss was recorded in kilograms (kg) and defined as more than 5 kg or 10% of baseline body weight in the past 6 months.[12] Smoking history was recorded as pack-years smoked. Smokers who were smoking during diagnosis or had quit for less than one year were defined as current smokers. Smokers who had quit for more than one year were classified as former smokers. A never-smoker was defined as one who had never smoked before. Information regarding secondary smoking history, and passive exposure to a smoking environment, was not available in the medical records.

The presence of co-morbidities included the following conditions: hypertension, diabetes mellitus, cerebrovascular disease, ischemic heart disease, asthma, chronic obstructive lung disease, pulmonary tuberculosis, liver cirrhosis, and end stage renal disease.

Chemotherapy given was recorded as either irinotecan-based or etoposide-based. Ideally, thoracic radiotherapy should start concurrently with the first or second cycle of chemotherapy in LD patients.[9] In our patient population, radiotherapy was often started with the second cycle of chemotherapy. PCI was given to the LD patients who were treated with curative intent.

2. Response and Survival

Response was assessed using RECIST (Response Evaluation Criteria in Solid Tumors) criteria.[13] Objective response included both complete and partial responders. Overall survival was measured from the date of diagnosis until the date of death or the date of the last follow-up day. Progression-free survival (PFS) was defined as the time from the date of diagnosis until the date of tumor progression or death. Long-term survival was defined as survival for more than 2 years after the date of diagnosis.[14]

3. Statistical Methods

Survival curves were calculated using the Kaplan-Meier method and the log-rank test was used to test for survival difference by subgroups. A *p*-value of less than 0.05 was judged to be statistically significant. The hazard ratio was estimated with the Cox proportional hazard method, which was used to choose a multivariate regression model to predict important prognostic factors. The classification and regression trees (CART) method was used to define prognostic subgroups that had similar survival.[15] In essence, the whole patient

population was partitioned into two subgroups according to the factor producing the most significant survival difference. Each of these subgroups was then again partitioned into subgroups in the same manner.

III. RESULTS

1. Patient Characteristics

Data from a total of 193 patients were analyzed, including 91 (47.2%) with LD and 102 (52.8%) with ED. Overall median follow-up duration was 11.5 months (range 0.3-63.7 months). The clinical, laboratory, and treatment-related characteristics are summarized in Table 1-1. The median age was 65 years (range 36-82 years). One hundred sixty-one (83.4%) patients were male and 32 (16.6%) patients were female. Twenty patients (10.4%) had never smoked. Most of the patients with LD (89%) had good performance status compared to ED (p=0.049). In pretreatment lab findings, leukocytosis, hypoalbuminemia, high lactate dehydrogenase (LDH) level, high C-reactive protein (CRP) level, and high serum cytokeratin fragment 19 (CYFRA 21-1) level were significantly associated with ED (Table 1-2). Paraneoplastic syndromes such as Eaton-Lambert Syndrome, Syndrome of Inappropriate Secretion of Anti-diuretic Hormone (SIADH), and hypercalcemia were present in 9.9% and 2% of LD and ED patients, respectively (Table 1-3). Brain metastasis was observed in 15 (14.7%) ED patients, and liver and bone metastasis occurred in 30 (29.4%) ED patients. Concurrent thoracic radiation and PCI were done with 93.4% and 31.9% of LD patients, respectively. Irinotecan-based chemotherapy was administrated in 86.5% of patients overall, and etoposide-based treatment was provided in the remaining 13.5% of the patients (Table 1-4).

Table 1-1. Patient characteristics: Clinical markers

Characteristics	Total (n=193)	Limited disease (n=91)	Extensive disease (n=102)	*p*-value†
	n (%)	n (%)	n (%)	
Age				0.537
<70	138 (71.5)	67(73.6)	71 (69.6)	
≥70	55 (28.5)	24(26.4)	31 (30.4)	
Sex				0.129
Male	161 (83.4)	72 (79.1)	89 (87.3)	
Female	32 (16.6)	19 (20.9)	13 (12.7)	
Weight loss				0.162
No	146 (75.6)	73 (80.2)	73 (71.6)	
Yes	47 (24.4)	18 (19.8)	29 (28.4)	
Performance status				0.049
ECOG 0-1	161 (83.4)	81 (89)	80 (78.4)	
ECOG 2-4	32 (16.6)	10 (11)	22 (21.6)	
Co-morbidities				0.052
No	69 (35.8)	39 (42.9)	30 (29.4)	
Yes	124 (64.2)	52 (57.1)	72 (70.6)	
Smoking history				0.63
Never	20 (10.4)	12 (13.2)	8 (7.8)	
Former	42 (21.8)	20 (22)	22 (21.6)	
Current	128 (66.3)	58 (63.7)	70 (68.6)	
unknown	3 (1.6)	1 (1.1)	2 (2)	

† *p*-value: Chi-square test between limited disease and extensive disease

Table 1-2. Patient characteristics: Pretreatment laboratory findings

Characteristics		Total (n=193)	Limited disease (n=91)	Extensive disease (n=102)	*p*-value†
		n (%)	n (%)	n (%)	
Hemoglobin	≥12g/dL	158 (81.9)	76 (83.5)	82 (80.4)	0.574
	<12g/dL	35 (18.1)	15 (16.5)	20 (19.6)	
Leukocyte	≤10000/μL	156 (80.8)	80 (87.9)	76 (74.5)	0.018
	>10000/μL	37 (19.2)	11 (12.1)	26 (25.5)	
Platelet	≤400k/μL	167 (86.5)	81 (89)	86 (84.3)	0.34
	>400k/μL	26 (13.5)	10 (11)	16 (15.7)	
Sodium	≥135mmol/L	155 (80.3)	76 (83.5)	79 (77.5)	0.29
	<135mmol/L	38 (19.7)	15 (16.5)	23 (22.5)	
Albumin	≥3.3g/dL	179 (92.7)	90 (98.9)	89 (87.3)	0.002
	<3.3g/dL	14 (7.3)	1 (1.1)	13 (12.7)	
LDH	≤455 IU/L	54 (50.9)	28 (66.7)	26 (40.6)	0.009
	>455 IU/L	52 (49.1)	14 (33.3)	38 (59.4)	
ALP	≤85 IU/L	93 (48.7)	47 (52.2)	46 (45.5)	0.357
	>85 IU/L	98 (51.3)	43 (47.8)	55 (54.5)	
CRP	≤0.8mg/dL	46 (48.9)	26 (70.3)	20 (35.1)	0.001
	>0.8mg/dL	48 (51.1)	11 (29.7)	37 (64.9)	
CEA	≤5ng/dL	112 (61.2)	59 (68.6)	53 (54.6)	0.053
	>5ng/dL	71 (38.8)	27 (31.4)	44 (45.4)	
CYFRA21-1	≤3.3ng/dL	85 (58.2)	51 (71.8)	34 (45.3)	0.001
	>3.3ng/dL	61 (41.8)	20 (28.2)	41 (54.7)	

† *p*-value: Chi-square test between limited disease and extensive disease

Abbreviations: LDH, Lactate Dehydrogenase; ALP, Alkaline Phosphatase; CRP, C-reactive protein; CEA, Carcinoembryonic Antigen; CYFRA 21-1, Cytokeratin fragment 19

Table 1-3. Patient characteristics: Tumor-related markers

Characteristics	Total (n=193) n (%)	Limited disease (n=91) n (%)	Extensive disease (n=102) n (%)	*p*-value†
Pleural effusion				<0.001
No	134 (69.4)	84 (92.3)	50 (49)	
Yes	59 (30.6)	7 (7.7)	52 (51)	
Pericardial effusion				0.023
No	172 (89.1)	86 (94.5)	86 (84.3)	
Yes	21 (10.9)	5 (5.5)	16 (15.7)	
Paraneoplastic syndrome				0.018
No	182 (94.3)	82 (90.1)	100 (98)	
Yes	11 (5.7)	9 (9.9)	2 (2)	
Superior vena cava syndrome				0.148
No	179 (92.7)	87 (95.6)	92 (90.2)	
Yes	14 (7.3)	4 (4.4)	10 (9.8)	
Number of metastasis				
0	113 (58.5)	91 (100)	22 (21.6)	<0.001
1	50 (25.9)	0 (-)	50 (49)	
2	20 (10.4)	0 (-)	20 (19.6)	
3	6 (3.1)	0 (-)	6 (5.9)	
4	2 (1)	0 (-)	2 (2)	
5	2 (1)	0 (-)	2 (2)	

†*p*-value: Chi-square test between limited disease and extensive disease

Table 1-4. Patient characteristics: Treatment-related markers

Characteristics	Total (n=193) n (%)	Limited disease (n=91) n (%)	Extensive disease (n=102) n (%)	*p*-value†
Thoracic radiation				<0.001
No	104 (53.9)	6 (6.6)	98 (96.1)	
Yes	89 (46.1)	85 (93.4)	4 (3.9)	
Palliative radiation therapy				<0.001
No	130 (67.4)	74 (81.3)	56 (54.9)	
Yes	63 (32.6)	17 (18.7)	46 (45.1)	
Prophylactic cranial irradiation				<0.001
No	161 (83.4)	62 (68.1)	99 (97.1)	
Yes	32 (16.6)	29 (31.9)	3 (2.9)	
Chemotherapy				0.008
Irinotecan+platinum	167 (86.5)	85 (93.4)	82 (80.4)	
Etoposide+platinum	26 (13.5)	6 (6.6)	20 (19.6)	

†*p*-value: Chi-square test between limited disease and extensive disease

2. Response to Chemotherapy

Table 2 displays the distribution of the best response to chemotherapy. Objective response rate was achieved in 74.3% of patients, and their median survival time was 18.6 months (95% CI, 12.6-24.5 months). In the univariate analyses, the characteristics associated with higher objective response rate (p<0.05) were limited disease (88.8% vs. 60.6%; p<0.001), good performance status (81.2% vs.37.9%; p<0.001), the absence of any metastasis (68.4% vs. 31.9%; p<0.001), no pleural effusion (79.8% vs. 61.1%; p=0.008), no leukocytosis (79.1% vs. 54.3%; p=0.003), normal serum sodium (78.8% vs. 56.8%; p=0.006), normal level of LDH (83% vs. 63.8; p=0.029), normal level of CYFRA 21-1 (86.4% vs. 60%; p<0.001), concurrent thoracic radiation therapy (92% vs. 58.3%; p<0.001), and PCI (96.9% vs. 69.5%; p=0.001). Patients who never smoked had a better objective response rate than smokers (89.5% vs. 73.3%), but the comparison was not statistically significant (p=0.123). There was no significant difference between patients receiving IP and EP chemotherapy (75.5% vs. 66.7%; p=0.357). Of all of these factors, only good performance status was significant in the multivariate analysis, with an HR of 6.16 (95% CI, 1.06-35.8, p=0.043).

Table 2. Response to chemotherapy

	Total	Limited disease	Extensive disease	*p*-value[†]
	n (%)	n (%)	n (%)	
CR	16 (8.7)	15 (16.9)	1 (1.1)	<0.001
PR	120 (65.6)	64 (71.9)	56 (59.6)	
SD	15 (8.2)	4 (4.5)	11 (11.7)	
PD	32 (17.5)	6 (6.7)	26 (27.7)	
Objective response				
CR+PR	136 (74.3)	79 (88.8)	57 (60.6)	<0.001

[†]*p*-value: Chi-square test between limited disease and extensive disease

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

3. Overall Survival

The median survival time was 14.1 months (95% CI, 11.3-16.8) in all patients, 28.7 months (95% CI 19.1-38.4) in LD patients and 10.2 months (95% CI 8.4-11.9) in ED patients (Figure 1).

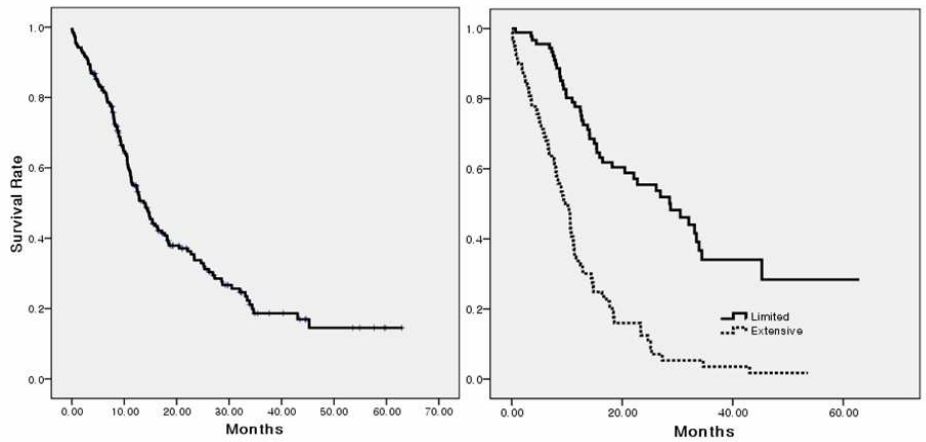

Figure 1-1. Overall survival curve

Figure 1-2. Overall survival curves for limited and extensive disease

Table 3 demonstrates the detailed results of the univariate analysis. In LD patients, no weight loss (p=0.011), normal CYFRA 21-1 level (p=0.023), and PCI (p<0.001) were identified as favorable prognostic factors. In ED patients, the following factors were identified as favorable prognostic factors: good performance status (p<0.001), no or single metastasis (p=0.008), liver metastasis (p<0.001), normal serum sodium level (p<0.001), normal albumin level (p=0.048), normal CEA level (p=0.044), and normal CYFRA 21-1 level (p=0.027).

Table 3. Univariate overall survival analysis (n=193)

Variables		MST(months)(95% CI)	*p*-value†
Extent of disease	Limited	28.7 (19.1-38.4)	<0.001
	Extensive	9.7 (7.9-11.5)	
Sex	Male	12.9 (10.2-15.7)	0.446
	Female	14.9 (9.6-20.3)	
Age	<70	14.8 (11.2-18.4)	0.012
	≥70	11.2 (8.7-13.7)	
Weight Loss	No	14.1 (11.1-17.2)	0.033
	Yes	11.4 (7.5-15.3)	
Performance status	ECOG 0-1	14.9 (11.4-18.5)	<0.001
	ECOG 2-4	5.7 (1.0-10.5)	
Smoking History	Never	23.4 (1.8-44.9)	0.085
	Smoker	13.7 (10.8-16.7)	
Distant Metastasis	No	23.3 (13.8-32.9)	<0.001
	Yes	9.2 (6.9-11.5)	
Number of Metastasis	0	23.3 (13.0-33.6)	<0.001
	1	10.7 (9.7-11.7)	
	≥2	6.7 (4.9-8.5)	
Pleural effusion	No	17.7 (10.2-25.3)	<0.001
	Yes	9.7 (7.1-12.3)	
Concurrent Thoracic RTx	No	10.2 (8.2-12.2)	<0.001
	Yes	28.6 (18.4-38.8)	
PCI	No	11.3 (9.7-12.9)	<0.001
	Yes	NR*	
1st line chemotherapy	Irinotecan	14.8 (11.9-17.7)	0.026
	Etoposide	9.2 (5.7-12.7)	
Sodium	≥135mmol/L	14.8 (10.9-18.7)	0.014
	<135mmol/L	8.9 (7.0-10.9)	
Albumin	≥3.3g/dL	14.8 (12.1-17.5)	<0.001
	<3.3g/dL	5.9 (1.4-10.4)	
LDH	≤455 IU/L	15.4 (10.0-20.8)	0.011
	>455 IU/L	9.2 (7.6-10.9)	
CRP	≤0.8mg/dL	23.4 (6.4-40.4)	0.012
	>0.8mg/dL	10.6 (8.7-12.5)	
CEA	≤5ng/dL	15.4 (11.9-18.9)	0.011
	>5ng/dL	9.8 (7.8-11.8)	
CYFRA 21-1	≤3.3ng/dL	22.7 (14.8-30.6)	<0.001
	>3.3ng/dL	9.7 (7.0-12.4)	

*NR: not reached, † *p*-value: log rank test

Abbreviations: MST, Median Survival Time; PCI, Prophylactic Cranial Irradiation; LDH, Lactate Dehydrogenase; CRP, C-reactive protein; CEA, Carcinoembryonic Antigen; CYFRA 21-1, cytokeratin fragment 19

Table 4. Multivariate overall survival analysis (n=193)

Variables	*p*-value†	Hazard Ratio (95% CI)
Extent of disease	0.006	6.3 (1.7-23.1)
Performance status	0.002	17.8 (2.9-107.9)
Weight Loss	0.02	6.0 (1.3-27.3)
CYFRA 21-1	0.016	4.6 (1.3-15.6)
LDH	0.035	3.2 (1.1-9.6)

† *p*-value: multivariate analysis by Cox's regression analysis

A multivariate Cox regression model was created based on the results of the univariate analyses (Table 4). The selected model included disease extent (p=0.006), performance status (p=0.002), weight loss (p=0.02), LDH level (p=0.035), and CYFRA 21-1 (p=0.016) level.

The regression tree is shown in Figure 2. The first and most significant prognostic factor grouped the patients was extent of disease (LD vs. ED). Subsequent partitioning into internal nodes was based on CYFRA 21-1 level in LD patients and performance status in ED patients. The next splits in ED were weight loss and LDH level. Six terminal nodes were made in this regression tree, creating four prognostic classes (A~D) (Table 5). The statistical comparisons among the terminal subgroups or combination of terminal subgroups used to form final subgroups with similar survival are detailed in Figure 2. Groups II, III, and IV were combined into one class because they showed similar survival and there were no significant differences among the subgroups (p=0.406; among groups I, II, and III; p=0.196 between groups II and III, p=0.924 between groups III and IV, and p=0.314 between groups II and IV). The median survival times for groups A,

B, C, and D were 32.03, 12.43, 8.00 and 3.47 months, respectively (p <0.001). Survival curves for patients in the four prognostic subgroups are shown in Figure 3. The most favorable class was defined by LD and normal CYFRA 21-1 levels. The poorest survival was defined by ED and poor performance status (ECOG 2-4).

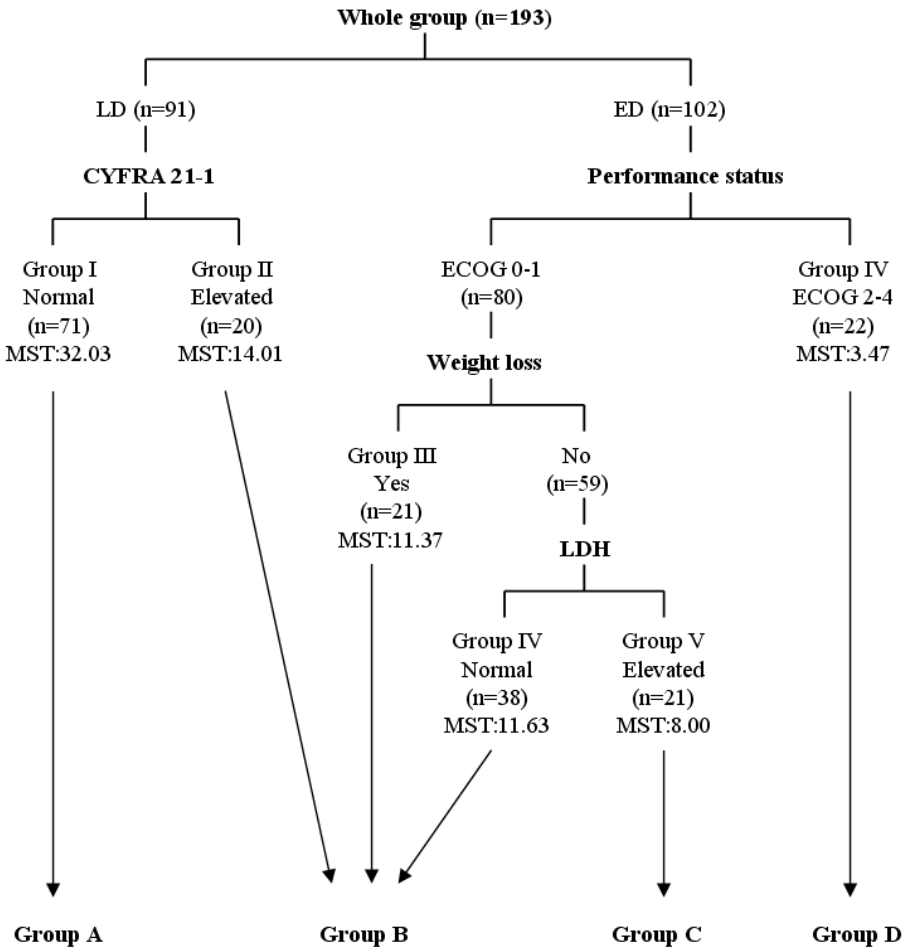

Figure 2. Classification and regression trees

Table 5. Summary of prognostic groups

Group (n=193)	Description	MST (months) (95% CI)
A (n=71)	LD, normal CYFRA 21-1	32.03 (25.48-38.59)
B (n=79)	LD, elevated CYFRA 21-1	
	ED, good PS, weight loss+	12.43 (9.72-15.14)
	ED, good PS, no weight loss, normal LDH	
C (n=21)	ED, good PS, no weight loss, elevated LDH	8.00 (5.18-10.82)
D (n=22)	ED, poor PS	3.47 (1.78-5.12)

MST, Median Survival Time; LD, limited disease; ED, extensive disease; PS, performance status

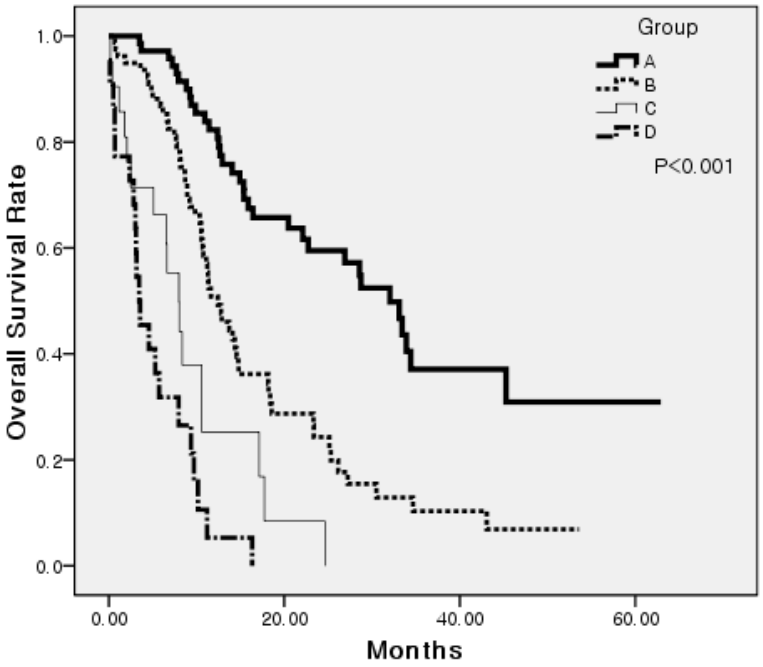

Figure 3. Kaplan-Meier survival curves of the four proposed prognostic groups

4. Progression-free survival

Median PFS time was 8.7 months (95% CI, 7.3-10.0) in all patients, 14.5 months (95% CI, 4.0-24.9) in LD patients, and 6.2 months (95% CI, 5.4-6.9) in ED patients.

In the multivariate analysis, extent of disease (p<0.001), performance status (p<0.001), CRP level (p=0.033), and CYFRA 21-1 level (p=0.014) predicted a longer PFS. In LD patients, those who received palliative radiation therapy (p=0.026) and PCI (p=0.046) and who had no weight loss (p=0.047) had longer PFS. In ED patients, good performance status (p<0.001), normal LDH (p=0.007) and no leukocytosis (p=0.01) were independent predictor for a longer PFS.

5. Long-term survival

Forty patients (20.7%) were identified as long-term survivors, including 33 (36.3%) LD patients and 7 (6.9%) ED patients. Most long-term survivors experienced a complete response (15%) or partial response (72.5%). Among them, 17 patients are currently dead, and 23 patients are alive at the time of this report. Median survival time for long-term survivor was 45.3 months (95% CI, 27.5-63.1). The survival curve appeared to plateau after 45 months of further survival duration (Figure 4). Predictive factors for long-term survival in the univariate analysis were extent of disease, number of metastatic sites, thoracic radiation, PCI, and response to chemotherapy (Table 6). LD (HR=8.13, 95% CI, 1.43-46.38; p =0.018) and PCI (HR=2.94, 95% CI,

1.20-7.24; *p*=0.019) were found in the multivariate analysis to be independent prognostic factors.

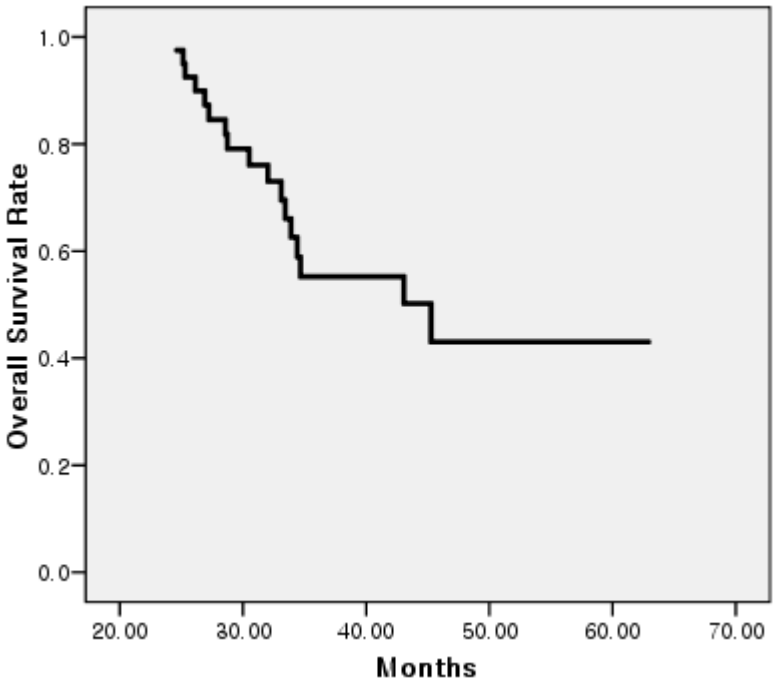

Figure 4. Overall survival in long-term survivors

Table 6. Characteristics of long-term survivors

Variables	Number	%	*p*-value†
Extent of disease			<0.001
Limited	33	82.5	
Extensive	7	17.5	
Age			0.084
<70	33	82.5	
≥70	7	17.5	
Sex			0.258
Male	31	77.5	
Female	9	22.5	
Weight loss			0.915
No	30	75	
Yes	10	25	
Performance status			0.083
ECOG 0-1	37	92.5	
ECOG2-4	3	7.5	
Smoking history			0.252
Never	7	17.5	
Former	9	22.5	
Current	24	60	
Number of Metastasis			<0.001
0	37	92.5	
1	2	5	
≥2	1	2.5	
Thoracic radiation			
No	9	22.5	<0.001
Yes	31	77.5	
Palliative radiation			0.436
No	29	72.5	
Yes	11	27.5	
PCI			<0.001
No	24	60	
Yes	16	40	
Chemotherapy			0.078
Irinotecan	38	95	
Etoposide	2	5	
Maximal response			0.024
CR	6	15	
PR	29	72.5	
SD	3	7.5	
PD	1	2.5	
not-evaluated	1	2.5	

†*p*-value: Chi-square test

IV. DISCUSSION

In the last two decades, several models and prognostic indices have been described for defining risk groups of SCLC patients. In this study, we attempted to reproduce the results obtained in previous reports.

Disease extent and performance status are almost always consistently found to be the most important clinical factors in SCLC outcome in previous studies.[1, 14, 16-21] We confirmed that dividing patients based on LD and ED had dominant prognostic implications for both overall survival and PFS. The median survival of LD patients in our cohort was 28.7 months, which was longer than that previously reported. It seems that most of the LD patients (93.4%) received both chemotherapy and radiation therapy, and had good performance status (89%). The median survival of ED patients was 10.2 months, which was shorter than in the JCOG trial (12.8 months),[7] but slightly longer than other studies. The longer survival outcome may be explained by the fact that the majority of patients in this study had IP chemotherapy, which was superior to EP in the JCOG trial. Although this difference in treatment efficacy was not confirmed by the SWOG trial or our findings in this study, it remains possible that IP chemotherapy is superior to EP in Asian patients because of pharmacogenomic differences between western and Asian populations.

Good performance status was also a major independent prognostic parameter for overall survival, PFS and overall response. Weight loss was related only to

overall survival. Even though age and sex have been identified as prognostic factors in previous reports,[14, 22, 23] there was no significant correlation with outcomes in this study.[18] Unlike our expectations,[24] smoking history also did not significantly affect the outcomes of SCLC.[25] Even so, we do not conclude that smoking history has nothing to do with SCLC, because this study relied on a retrospective review.

Our observation of a relationship between survival and performance status, weight loss, and serum LDH level confirmed previous observations.[1, 3, 19, 26] In addition, the negative influence of an elevated level of CYFRA 21-1 has been reported in SCLC patients.[27] Generally, it has been shown that elevated levels of CYFRA 21-1 are related to NSCLC, especially squamous cell carcinoma, and that it correlates with tumor extension.[28, 29]

We divided 193 SCLC patients into four subgroups with different survival potentials by evaluating the extent of disease, performance status, pretreatment weight loss, LDH level, and CYFRA 21-1 level. The purpose of the tree analysis was to derive a classification rule that used pre-treatment variables to group patients with similar prognoses. This classification approach could potentially be applied to the treatment of individual patients as well as clinical trials after validation with further prospective applications.

We placed the defining the threshold for long-term survival higher than the two years that is often reported. A 2-year survival rate does not necessarily represent a cure, because disease continues to recur and patients still die from their lung cancer.[14] In the present study, only disease extent and PCI history

were associated with the likelihood that a patient would be a long-term survivor. Several studies assert the prognostic significance of disease extent and performance status for long-term survival.[14, 30] Because most of the patients in this study had good performance status, there was no significant difference in the multivariate analysis. It was confirmed the association of PCI with overall survival, a higher rate of disease-free survival, and a lower cumulative incidence of brain metastasis in prior study.[11] In addition, the recent EORTC trial reported that PCI significantly reduced the risk for symptomatic brain metastasis and significantly improved both disease-free survival and overall survival in ED patients with any response to chemotherapy.[31]

Due to the single center retrospective study design, some factors currently known to have influence on prognosis were not examined (e.g., alkaline phosphatase, uric acid, and neuron specific enolase, etc.). Different prognostic factors such as molecular biomarkers may also provide valuable information to further improve the prognostic index proposed by this study.

The analysis of prognostic factors could be useful both for patient stratification in future randomized trials and decision-making in individual patients. Variables other than extent of disease or performance status, LDH level, weight loss, and CYFRA 21-1 level, should be taken into account when designing future clinical trials and should be used to stratify randomized clinical trials. A prospective analysis or meta-analysis is needed to obtain a consensus for prognostic factors. Further studies can also determine how to

best treat high-risk patients to reduce treatment-related mortality and provide the best palliation and prolongation of life.

V. CONCLUSION

We confirmed the well-known prognostic values of disease extent and performance status, but also identified weight loss, LDH level, and CYFRA 21-1 level as independent prognostic factors. A prognostic model was proposed with four classifications of SCLC based on these variables. This model needs to be validated through a prospective study in the future. The independent prognostic potential of the level of CYFRA 21-1 should be also be validated by further studies.

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< ABSTRACT(IN KOREAN)>

소세포폐암 환자에서 예후인자의 분석 및 지표

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홍수정

소세포폐암은 전체 폐암의 약 20%를 차지하며, 비소세포폐암에 비해 예후가 불량한 것으로 알려져 있다. 본 연구에서는 전체생존, 무진행 생존, 항암치료에 따른 반응에 대하여 예후인자를 찾아, 예상되는 생존에 따라 환자들을 분류하는데 목적을 두었다. 또한 진단 이후 2년 이상 생존하는 장기 생존자의 특성들을 분석하고자 하였다.

2002년 1월부터 2007년 9월까지 세브란스병원에서 진단받은 소세포폐암 환자 193명을 대상으로 후향적 연구를 진행하였다. 환자들의 치료 전 임상지표, 종양 관련인자들, 치료에 관련된 인자들을 조사하였다.

총 193명의 환자 중 제한병기가 91명 (47.2%), 확장병기가 102명 (52.8%) 이었다. 전체 환자의 반응률은 74.3%였으며, 중앙 생존기간은 14.1개월 (95% CI 11.3-16.8) 이었다. 제한병기에서의 중앙 생존 기간은 28.7개월 (95% CI, 19.1-38.4), 확장병기에서는 10.2개월

(95% CI, 8.4-11.9) 이었다. 다변량 분석에서 전체 생존에 영향을 미치는 예후인자로 병기, 수행능력, 체중감소, LDH, CYFRA 21-1등이 통계적으로 유의하였다. 위의 다섯 가지 인자로 classification and regression trees (CART) 분석 방법을 이용하여, 전체 환자를 비슷한 생존기간을 가지는 네 군으로 분류하였다. A군은 제한병기이면서 CYFRA 21-1값이 정상인 군, B군은 제한병기이면서 CYRFA 21-1값이 정상 수치 이상이거나, 확장병기이고 수행능력이 좋으면서 체중감소가 있거나, 확장병기이고 수행능력이 좋고, 체중감소가 없으면서 정상 LDH값을 가지는 환자들이 여기에 속했다. C군은 확장병기이면서, 수행능력이 좋고 체중감소가 없지만 LDH가 정상수치 이상인 환자들이었으며, D군은 확장병기 이면서 수행능력이 나쁜 환자들로 구성되었다. 네 군의 각각 중앙 생존기간은 각각 32.0, 12.8, 8.0, 3.5개월 (p<0.001) 이었다. 전체 환자에서 무 진행 생존은 8.7개월 (95% CI, 7.3-10.0) 이었으며, 제한병기 및 확장병기 에서는 각각 14.5개월 (95% CI, 4.0-24.9), 6.2개월 (95% CI, 5.4-6.9) 이었다. 다변량 분석에서는 병기, 수행능력, CRP, CYFRA 21-1등이 통계적으로 유의한 무진행 생존의 예측인자였다. 전체 환자 중 40명(20.7%) 이 2년 이상 장기 생존자로 관찰되었고, 이들의 중앙 생존기간은 45.3개월이었다. 장기 생존을 예측하는 인자는 병기와 예방적 두부 방사선 치료 여부가 통계적으로 의미 있었다.

본 연구에서는 종전의 연구에서 소세포폐암의 예후인자로 잘

알려진 병기와 수행능력의 중요성을 확인할 수 있었으며, 치료 전 체중감소, LDH, CYFRA 21-1 수치도 예후인자로써 통계적으로 유의하였다. 또한 CART분석 방법을 사용하여 환자 군을 예후에 따라 네 군으로 분류하였다. 향후 전향적인 연구로 환자 분류 모델의 타당성 평가가 필요할 것으로 생각된다.

핵심되는 말 : 소세포폐암, 예후인자, 생존