Clinical outcomes and prognostic factors of limited-stage small cell lung cancer patients treated with chemoradiotherapy: a single-institutional study

Toyokazu Hayakawa,[1] Kazushige Hayakawa,[1,2] Itaru Soda,[1] Akane Sekiguchi,[1]
Shogo Kawakami,[1] Jiichiro Sasaki,[3] Katsuhiko Naoki,[3] Hiromichi Ishiyama[1]

[1] Department of Radiation Oncology, Kitasato University School of Medicine
[2] Department of Radiation Oncology, National Hospital Organization Disaster Medical Center, Tachikawa, Tokyo
[3] Department of Respiratory Medicine, Kitasato University School of Medicine

Objectives: The aim of this study was to report clinical outcomes and prognostic factors in limited-stage small cell lung cancer (LD-SCLC) patients treated with chemoradiotherapy (CRT) based on the clinical practice guidelines.
Methods: Medical records of 106 LD-SCLC patients who received concurrent CRT with once- or twice-daily fractions or sequential CRT with once-daily fractions were analyzed retrospectively. Prognostic factors were estimated using univariate and multivariate analyses.
Results: The 2-year overall survival and median survival time were 64.3% and 38.3 months, respectively. The 2-year and median progression-free survival were 44.4% and 16.5 months, respectively. In univariate and multivariate analysis, no clinical factors were detected as significant prognostic factors.
Conclusions: There were no significant prognostic factors for survival. However, the clinical outcomes of LD-SCLC patients based on the Japanese clinical practice guidelines were excellent.

Key words: limited-stage small cell lung cancer, chemoradiotherapy, prognostic factors, clinical practice guidelines

Introduction

Lung cancer continues to be the leading cause of the increasing cancer deaths in Japan, and in 2016 there were over 73,500 deaths annually from this disease.[1] Lung cancer will likely remain a major cause of worldwide cancer death in the 21st century. The biology and treatment of lung cancer are generally classified into two major groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

SCLC makes up about 15% of all lung cancers in Japan. At the time of diagnosis, 30% of patients with SCLC present with a limited stage of disease (LD), which is now called I-IIIC (the 8th edition of the TNM Classification for Lung Cancer, published by the UICC [Union for International Cancer Control]). The standard treatment of LD-SCLC is thoracic radiation therapy (TRT) concurrently combined with platinum-based chemotherapy in the Japanese practice guidelines. And prophylactic cranial irradiation (PCI) is also recommended for patients evaluated as complete remission after the initial chemoradiotherapy (CRT). However, the outcomes of recent studies remain poor, with a median survival of 19 to 27 months using current treatments, and only 16%−26% were long-term survivors.[2-3] For the past several years, the issues of the radiation therapy (RT) dose, volume, fractionation, TRT timing in adjuvant chemotherapy, and PCI have been important points for discussion to improve the overall survival of LD-SCLC.[2-15] We therefore analyzed the LD-SCLC patients in the present study who were being treated with CRT and estimated which is the most important RT factor among those above.

Materials and Methods

This retrospective study was approved and the requirement for informed patient consent was waived by the institutional review board of Kitasato University School of Medicine (B16-116).

Patients' selection and data collection

A total of 106 consecutive patients who had been diagnosed with LD-SCLC and treated with CRT at our department in Kitasato University Hospital between September 2000 and March 2017 were enrolled in this study. Limited stage of disease was defined as disease confined to a hemithorax, including nodal disease limited to ipsilateral hilum, bilateral mediastinum and/or supraclavicular fossae. Patients with pleural or pericardial dissemination (M1a) were excluded.

The diagnostic methods included physical examination, bronchoscopy, sputum cytology, chest radiography, computed tomography (CT), brain magnetic resonance imaging (MRI), bone scintigraphy, and positron emission tomography/CT with 2-deoxy-2-[fluorine-18]fluorodeoxyglucose (18F-FDG PET/CT). We decided the patients' diagnosis including staging evaluation and treatment strategy with multidisciplinary discussion.

Treatment

All patients received concurrent TRT (CCRT) or sequential TRT (SCRT) in combination with chemotherapy. In the CCRT group, PE (cisplatin 80 mg/m^2 intravenously (i.v.) on day 1 and etoposide 100 mg/m^2 i.v. on days 1－3) or CE (carboplatin (AUC = 5) i.v. on day 1 and etoposide 100 mg/m^2 i.v. on days 1－3) was chosen as the chemotherapy regimen in the all cases. In the SCRT Group, besides these regimens, AMR (amrubicin 45 mg/m^2 i.v. on days 1－3), or PI (cisplatin 60 mg/m^2 i.v. on day 1 and irinotecan 60 mg/m^2 i.v. on days 1, 8, and 15) was chosen.

All patients underwent planning CT for three-dimensional conformal TRT. Gross tumor volume (GTV) included the primary tumor and positive lymph nodes >1 cm in the short diameter or had a positive accumulation of 18F-FDG PET/CT. The clinical target volume (CTV) included GTV with appropriate margin expansion and positive lymph node stations. Although initial CTV always covered ipsilateral hilar and mediastinal lymph nodes, elective nodal irradiation to clinically uninvolved lymph node stations was omitted as a general rule.

TRT was given with 10 MV linear accelerator and a 1.5 Gy twice-daily schedule with a total dose of 45－48

Gy (accelerated hyperfractionation, AHF) or 1.8－2 Gy once-daily fractionation with a total dose of 45－61.2 Gy (conventional fractionation, CF). After a radiation dose of 30－36 Gy in AHF or 40 Gy in CF, planning CT was performed for boost treatment. Boost RT was administered to GTV seen on pretreatment CT. Doses of CF-RT were delivered to patients ineligible for AHF or to those who received SCRT.

PCI (25 Gy in 10 fractions) was given to patients who achieved complete response (CR) and consented to receiving PCI.

Follow-up and statistical analyses

All patients were followed up until death or for at least 2 years, although 9 patients were lost to follow-up within 5 years after the treatment. Tumor progression was defined as radiographic, symptomatic, bronchoscopic, or pathologic evidence that was thought to be consistent with recurrent tumor rather than radiation-related change or other benign abnormalities. Local failure was defined as increased size of primary lesion within or around radiation field. Regional failure was defined as increased size of mediastinal lymph nodes or regrowth of involved lymph nodes. When imaging findings were indeterminate, failure was determined by subsequent imaging studies and not recorded as recurrence until definite progression. Distant metastases was defined as metastases in sites other than those mentioned. Complications were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

The overall survival (OS) and progression free survival (PFS) curves were calculated, using the Kaplan-Meier method, from the first day of treatment with either chemotherapy or radiotherapy. Patient, tumor, and treatment variables were tested for potential prognostic impact on OS and PFS by univariate and multivariate analysis using Cox's proportional hazard model. The parameters evaluated in the univariate analysis were: age, gender, ECOG (Eastern Cooperative Oncology Group) performance status, clinical stage, primary site, total radiation dose, fractionation (AHF or CF), timing of RT (CCRT or SCRT), PCI (received or not received), and severity of radiation pneumonitis and hematologic toxicity. A P value of <0.05 was considered as statistically significant. In multivariate analysis, parameters with a P value of <0.2 in univariate analysis were selected as predictor variables.

Results

The patients' characteristics are summarized in Table 1.

The majority of patients were male (73.6%) and the patients' median age was 66 years (range, 42－85 years). Among the 106 patients, 74 patients (69.8%) received CCRT and 32 patients (30.2%) received SCRT. In the CCRT group, 52 patients (70.3%) received AHF-RT, and 22 patients (29.7%) received CF-RT. In the CCRT group, 65 patients received PE, and 9 patients received CE. The chemotherapy cycles ranged from 1－4 (median, 4). Fifty-six patients began TRT simultaneously with the first cycle of chemotherapy, 14 from the second, and 3 patients from the third cycle. One patient received 4 cycles of chemotherapy before receiving CCRT, and 33 patients received SCRT. The median of total dose was 54 Gy (range, 45－61.2 Gy).

Median follow-up time was 29.7 months (range, 5.5－148.5 months). The 2-year and median OS were 64.3%, 38.3 months (95%CI 28.6－84.8), respectively (Figure 1). The 2-year and median PFS were 44.4% and 16.5 months (95%CI 12.3－32.7), respectively. Univariate and multivariate analyses are summarized in Table 2A,B. No clinical factors were detected as significant prognostic factors. Sixty-six of 106 patients had disease relapse, and 32 of those 66 patients received salvage chemotherapy. Salvage chemotherapy did not significantly prolong the OS (hazard ratio 1.18; 95%CI 0.67－2.07; P = 0.573).

A total of 23 patients had brain metastases. Seven of 35 patients who received PCI developed brain metastases, and 16 of 71 patients who did not receive PCI developed brain metastases (Table 3). There was no statistical difference in the frequency of brain metastases between the patients who received and those who did not receive PCI.

The vast majority of patients (79.2%) experienced radiation pneumonitis (Figure 2). However, most of the patients (75.5%) had grade 1 or 2 radiation pneumonitis. Only 3 patients had grade 3 radiation pneumonitis and 1 patient had grade 5.

Table 1. Patients' characteristics

Variable	Factor	N (%)
Sex	Female	28 (26.4)
	Male	78 (73.6)
Age: Median, Range	66 years	42－85 years
Performance status	0－1	96 (90.6)
	≥2	8 (7.5)
	Unknown	2 (1.9)
T factor	1	27 (25.5)
	2	27 (25.5)
	3	15 (14.1)
	4	34 (32.1)
	Unknown	3 (2.8)
N factor	0	6 (5.7)
	1	18 (17.0)
	2	52 (49.0)
	3	30 (28.3)
Primary site	Lower lobe	36 (34.0)
	Other	70 (66.0)
CRT timing	Concurrent	74 (69.8)
	Sequential	32 (30.2)
Fractionation	AHF	52 (49.1)
	Conventional	54 (50.1)
Total dose: Median, Range	54 Gy	45－61.2 Gy
PCI	Yes	35 (33.0)
	No	71 (67.0)

CRT, chemoradiotherapy; AHF, accelerated hyperfractionation; PCI, prophylactic cranial irradiation
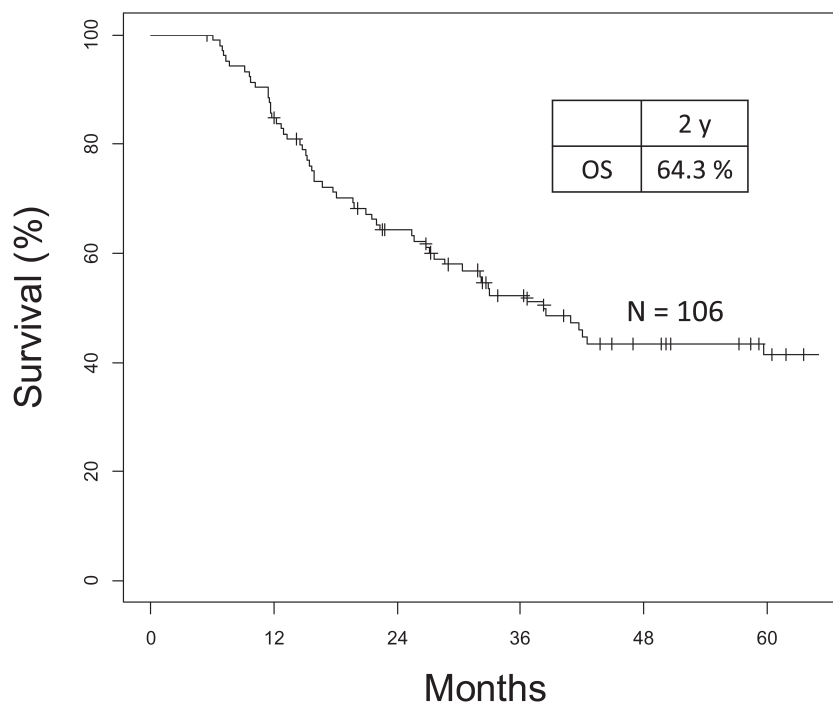
Figure 1. Kaplan-Meier curves for overall survival (OS)

Table 2A. Univariate and multivariate analysis (OS)

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Sex[a]	1.24	0.68－2.26	0.483	—	—	—
Age	1.02	0.99－1.05	0.307	—	—	—
PS	1.45	0.97－2.16	0.071	0.91	0.51－1.62	0.744
T factor	1.13	0.91－1.41	0.260	—	—	—
N factor	1.25	0.91－1.73	0.167	1.25	0.85－1.85	0.252
Primary site[b]	0.66	0.39－1.11	0.117	0.69	0.36－1.30	0.249
CRT[c] timing	1.62	0.93－2.82	0.089	2.31	0.84－6.35	0.104
Fractionation[d]	1.43	0.85－2.38	0.175	0.66	0.26－1.71	0.396
Total dose	1.00	0.96－1.05	0.891	—	—	—
PCI	0.65	0.37－1.13	0.125	0.93	0.45－1.90	0.841
RP grade	1.47	0.98－2.22	0.065	1.34	0.90－2.01	0.153
HT score[e]	1.14	0.83－1.55	0.413	—	—	—

HR, hazard ratio; CI, confidence interval; PS, performance status; CRT, chemoradiotherapy; PCI, prophylactic cranial irradiation; RP, radiation pneumonitis; HT, hematologic toxicity; [a]female, favorable; [b]lower lobe, not favorable; [c]CCRT, favorable; [d]AHF, favorable; [e]HT score, number of grade ≥3 anemia, neutropenia, and thrombocytopenia toxicities

Table 2B. Univariate and multivariate analysis (progression free survival)

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Sex[a]	1.06	0.62－1.83	0.829	－	－	－
Age	1.00	0.97－1.03	0.930	－	－	－
PS	1.29	0.89－1.87	0.174	1.28	0.88－1.87	0.285
T factor	1.02	0.83－1.26	0.839	－	－	－
N factor	1.21	0.90－1.63	0.207	－	－	－
Primary site[b]	0.61	0.37－1.00	0.050	0.62	0.38－1.02	0.062
CRT[c] timing	1.18	0.70－2.01	0.539	－	－	－
Fractionation[d]	1.14	0.70－1.85	0.592	－	－	－
Total dose	1.00	0.95－1.04	0.889	－	－	－
PCI	0.76	0.45－1.27	0.290	－	－	－
RP grade	0.90	0.60－1.36	0.626	－	－	－
HT score[e]	1.08	0.80－1.47	0.603	－	－	－
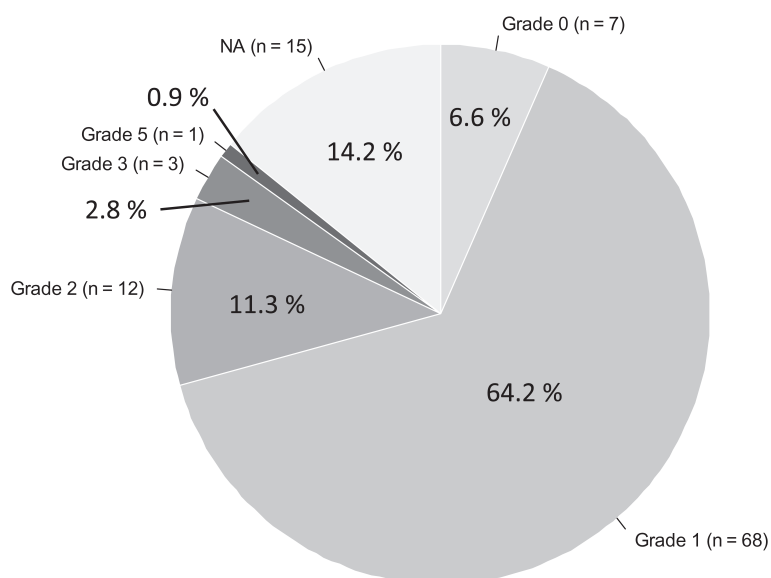
Figure 2. Frequencies of radiation pneumonitis

Table 3. Incidence of brain metastasis

Variable	n	Brain metastasis n (%)	No brain metastasis n (%)	P value
PCI	35	7 (20.0)	28 (80.0)	1.00
No PCI	71	16 (22.5)	55 (77.5)	

Table 4. Hematologic toxicity

| Toxicity | CTCAE grade, version 4.0 | | | | | | Grade 3－4 (%) |
	0	1	2	3	4	UK	
Anemia	2	29	40	29	1	5	28.3
Neutropenia	0	1	12	35	53	5	83.0
Thrombocytopenia	6	47	21	18	9	5	25.5

CTCAE, the Common Terminology Criteria for Adverse Events; UK, unknown

Hematologic toxicity is shown in Table 4. The most common grade 3－4 adverse event was neutropenia (83%).

Discussion

In the clinical practice guidelines for LD-SCLC, the concurrent use of TRT with platinum-based chemotherapy has been recommended since several years ago[14,16] because combined modality therapy reduced intrathoracic failure as the first progression site to approximately half, compared with that after chemotherapy alone. But optimal planning of TRT combined with chemotherapy remains controversial after a relatively long period of time.

For TRT, the optimal dose, fractionation, treatment volume, and timing with chemotherapy remain important issues. Recent treatment results have indicated that a positive effect for combined modality therapy employed thoracic irradiation early in the course of treatment, concurrently with chemotherapy.[8,13] The variables of radiation dose, fractionation, and treatment volume seem to be important in the successful management of LD-SCLC. A randomized trial by the JCOG (Japanese Cooperative Oncology Group) assessed sequential versus concurrent TRT combined with PE for LD-SCLC patients, and they reported that patients treated with concurrent TRT lived longer than did those treated with sequential radiotherapy.[3] Another randomized phase III trial by the National Cancer Institute of Canada compared radiotherapy beginning with either cycle 2 or 6 of chemotherapy; they demonstrated that early radiotherapy was associated with improved local and systemic control and with longer survival.[2] A systematic review on the timing of thoracic radiotherapy in LD-SCLC determined that early concurrent TRT results in a small, but significant, improvement in overall survival when compared to late concurrent or sequential TRT.[13]

Dose escalation over moderate dose levels (45－50 Gy) does not increase local chest control regardless of timing of TRT, probably due to treatment-related toxicities and distant failure. Reducing treatment volumes may permit increasing doses without enhancing normal tissue damage. Also, a 1.5 Gy twice-daily schedule may increase the dose intensity of the TRT and result in a high response rate and increased survival.[14,16] Currently, a 1.5 Gy twice-daily fractionation of a total dose of 45 Gy is a standard dose for LD-SCLC. However, the once-daily standard fractionation was not delivered at its maximum tolerated dose, so it remains unclear if hyperfractionation is superior to once daily chest radiotherapy given at a biologically equivalent dose. For LD-SCLC, the NCCN (National Comprehensive Cancer Network) guidelines recommend that radiation should be delivered concurrently with chemotherapy and should start with the first or second cycle (category 1) at a dose of either 1.5 Gy twice daily for a total dose of 45 Gy, or 1.8－2.0 Gy/day for a total dose of 60－70 Gy. Recently the CONVERT trial,[17] which was an open-label, phase 3, randomized, superiority trial comparing 45 Gy radiotherapy in 30 twice daily fractions of 1.5 Gy with 66 Gy in 33 once-daily fractions of 2 Gy, revealed that survival outcomes did not differ between twice-daily and once-daily concurrent CRT in patients with LD-SCLC. The results in the present study revealed that there were no significant differences in survival between once-a-day TRT for a total dose of 45－61.2 Gy with concurrent PE or CE and twice-a-day TRT for a total dose of 45－48 Gy with concurrent PE or CE.

Furthermore, these results revealed that there was no significant difference between the sequential use of TRT following chemotherapy and the concurrent use of TRT with chemotherapy regarding the patients' prognoses. In the present study, 35 patients (33%) were ≥70 years old. Yuen et al.[19] reported that elderly patients with LD-SCLC treated with CCRT had similar survival rates compared with those <70 years old. However, they also reported that treatment toxicity was greater among the elderly. The Japanese practice guidelines recommend SCRT following CE as a curative treatment if administration of

PE is difficult due to advanced age and/or poor performance status, among other factors. In Kitasato University Hospital, we decide treatment strategies for each thoracic cancer patient according to ongoing multidisciplinary discussions. Therefore, we deliver the appropriate treatment to all patients including the elderly.

In other studies in the literature, especially prospective studies, treatment methods have been strictly regulated according to each treatment protocol and not allowed to be modified depending on each patient's individual condition. On the other hand, we can deliver the most optimal treatment to each patient. That is most likely the reason the clinical outcomes of LD-SCLC patients in our institute have been better than those reported in other studies.

Regarding PCI, a recent meta-analysis revealed that PCI improved both overall survival and disease-free survival among patients with SCLC in complete remission.[9] Establishing the optimal dose and timing of PCI to further reduce the incidence of brain metastases with minimal and acceptable toxicity should be the aim of future clinical trials. On the other hand, Mamesaya et al.[20] reported that PCI may not have a survival benefit in patients with LD-SCLC because they had no brain metastases after the initial therapy, even though patients achieved a good response to definitive CRT. In the present study, whether patients received PCI or not was not detected as a significant prognostic factor for OS or PFS. Furthermore, there were no statistical differences in the frequency of brain metastases between the patients who received and those who did not receive PCI. PCI may be omitted, especially for elderly LD-SCLC patients, to avoid late neurocognitive dysfunction due to PCI if careful follow-up observation of the patients' brain function can be adopted.

This study was limited by its single-institute, retrospective, nonrandomized design.

In conclusion, these results show that there were no significant prognostic factors for survival. However, the clinical outcomes of LD-SCLC patients based on the Japanese clinical practice guidelines were excellent and, to our knowledge, better than those of previous studies in the literature.

Conflicts of Interest: None

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