Long-Term Survival Data of Patients With Limited-Disease Small-Cell Lung Cancer

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Abstract

Background. Long-term survival data of patients with limited-disease small-cell lung cancer (LD-SCLC) treated with concurrent chemoradiotherapy (CRT) have not been fully evaluated. Furthermore, the association between long-term prognosis and prognostic factors has not been sufficiently investigated.

Methods. The efficacy of concurrent CRT was retrospectively evaluated in 120 patients with LD-SCLC who were planned for curative CRT using concurrent accelerated hyperfractionated radiotherapy.

Results. The median patient age was 65.5 years. The majority of patients were males (73%) and had clinical stage III disease (80%). The median follow-up time for overall survival (OS) was 71.3 months. The median OS was 34.3 months; the 3- and 5-year OS rates were 52.4% and 41.8%, respectively. The median progression-free survival (PFS) was 12.2 months; the 3- and 5-year PFS rates were 37.6% and 33.6%, respectively. The 5-year OS rates of patients who achieved PFS at 12, 24, and 36 months were 70.9%, 83.6%, and 91.9%, respectively. The gradual increase in the 5-year OS rate following PFS extension and initial depression of Kaplan–Meier curves showed that disease progression frequently occurred in the first 2 years after concurrent CRT initiation. The Cox proportional hazards model revealed no significant factors that correlated with long-term survival through univariate and multivariate analyses.

Conclusions. Prognostic factors associated with long-term prognosis in LD-SCLC were not identified. Nonetheless, the 5-year OS rate was 41.8%, whereas the 5-year survival rate among patients without disease progression at 2 years was 83.6%. These data suggest that the prognosis of patients with LD-SCLC was improving.

Introduction

Lung cancer is the most common malignant tumor and the leading cause of cancer-related deaths worldwide [1]. Over recent years, deaths due to lung cancer have been increasing [2]. Small-cell lung cancer (SCLC) accounts for 10–15% of all newly diagnosed lung cancers [3–6]. Approximately 35–40% of SCLC cases are diagnosed with limited disease (LD), which is curable with multimodality treatment [7]. Clinically, SCLC is the most aggressive tumor, with a rapid doubling time and early development of distant metastasis; nonetheless, SCLC is highly responsive to chemotherapy and radiotherapy [7].

Meta-analyses have shown that the combination of chemotherapy and concurrent thoracic radiotherapy improves the overall survival (OS) in patients with LD-SCLC, as compared to chemotherapy alone [8–10]. The standard radiotherapy for LD-SCLC had been accelerated hyperfractionated radiotherapy (AHF-RT), and this was validated by a randomized controlled trial that compared it with conventional irradiation [11, 12]. Twenty years later, the standard treatment for LD-SCLC is still AHF-RT in combination with etoposide and platinum chemotherapy. Nonetheless, given the advances in radiotherapy techniques and diagnostic modalities, it remains unclear how chemoradiotherapy (CRT) affects the long-term prognosis of and prognostic factors for LD-SCLC. In particular, there have been a few studies evaluating the efficacy of concurrent CRT using AHF-RT in patients with LD-SCLC [13, 14]. Hence, the present study aimed to

evaluate the long-term survival of patients with LD-SCLC treated with concurrent CRT and to investigate the relationship between OS and progression-free survival (PFS).

Methods

Patient characteristics

We retrospectively evaluated the efficacy of CRT in patients with LD-SCLC at Shizuoka Cancer Center between September 2002 and February 2018. The patients were pathologically diagnosed with SCLC or combined SCLC. LD-SCLC was defined as a disease with lesions limited to the ipsilateral thorax, contralateral mediastinum, and contralateral supraclavicular fossa lymph nodes, without malignant pleural effusion or pericardial effusion. The distribution of the lesion was assessed using computed tomography (CT) from the chest to the abdomen or using positron emission tomography (PET), and the absence of brain metastases was confirmed by magnetic resonance imaging (MRI). This study included patients with LD-SCLC (including combined SCLC) who had a treatment plan of curative CRT with concurrent AHF-RT. Patients treated with late concurrent CRT (i.e., RT initiated after the start of the third course of chemotherapy) and sequential CRT were excluded. This retrospective study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and was approved by the Institutional Review Board of Shizuoka Cancer Center (J2021-35). We provided the patients with the opportunity to opt out of this study. Acquisition of informed consent from patients was waived owing to the retrospective nature of this study.

Data collection

The following patient data at the start of CRT were obtained from medical records: age, sex, Eastern Cooperative Oncology Group (ECOG)-performance status (PS), smoking history, clinical stage according to the Union for International Cancer Control TNM Classification 8th edition, chemotherapy regimen, timing of thoracic radiotherapy, gross tumor volume (GTV), best response to CRT, date of death or any recurrences detected with any imaging modality or the last visit, site of recurrence, and treatment after disease progression. The best response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1.

The GTV was delineated in the planning CT, which was obtained before the start of radiotherapy, by a radiation oncologist using a commercial RT planning system (Pinnacle, Philips Radiation Oncology Systems, Milpitas, CA). The GTV included the primary tumor and positive regional lymph nodes, which were defined as nodes with a short-axis diameter of no less than 1 cm on CT scan, with high fluorodeoxyglucose uptake on PET scan, or pathological approval by endobronchial ultrasound-transbronchial needle aspiration.

Treatment

The patients received CRT with etoposide (ETP) plus cisplatin (CDDP) or carboplatin (CBDCA). All patients received chemotherapy with platinum-based regimens: CDDP (60 or 80 mg/m² on day 1) and ETP (80 or 100 mg/m² on days 1–3), or CBDCA (AUC=5 on day 1) and ETP (80 mg/m² on days 1–3) for up to four courses. Radiotherapy was performed concurrently with chemotherapy, and the planned dose of radiotherapy was AHF-RT with 45 Gy in 30 fractions twice a day for 15 days. Patients who started AHF-RT at the start of the third course of chemotherapy or later were excluded from this study due to the validity of considering the GTV baseline.

Statistical analysis

Univariate and multivariate analyses of OS and PFS were performed for all collected data on prognostic factors for LD-SCLC (Cox proportional hazards regression analysis). Differences between proportions were examined using Fisher's exact test. OS was assessed from the first day of chemotherapy until death or at the time of evaluation. PFS was assessed from the first day of treatment with chemotherapy to the earliest date of disease progression, as determined by CT or MRI using the RECIST criteria, or death from any cause. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards model was used for the univariate and multivariate analyses. All *P*-values were derived from two-sided significance tests. Statistical analyses were performed using JMP version 14.0 (SAS Institute, Cary, NC, USA), with statistical significance set at *P*<0.05.

Results

Patient characteristics

A total of 168 patients with LD-SCLC were eligible for concurrent CRT. Of these patients, 48 were excluded from this study because they received sequential radiotherapy (*n*=40), late concurrent radiotherapy (*n*=4), or conventional radiotherapy (*n*=4) (Fig. 1). In total, 120 patients with LD-SCLC were included in this study. The patients' characteristics are shown in Table 1. The median patient age was 65.5 years (range: 34–76 years), and 89 (74.2%) patients were males. The values of ECOG-PS 0 and 1 were 65 (54.2%) and 55 (45.8%), respectively. Stage III accounted for 96 (80.0%) patients, 48 (40.0%) patients had T3-4 disease, and 85 (70.8%) had N2-3 disease. The median GTV for all patients was 113 mL (range: –7.5–655.2 mL).

Treatment

Supplementary Table S1 summarizes the details of CRT. Overall, 114 (95.0%) patients received CDDP plus ETP, whereas the rest received CBDCA+ETP. A total of 109 (90.8%) patients completed the four planned courses. All patients underwent concurrent CRT, and the median time to complete radiotherapy was 23 days (range: 13–82 days). A total of 105 (87.5%) patients completed radiotherapy within 30 days. The majority of patients (90.8%) completed 4 cycles of ETP plus CDDP. The overall response was evaluated after the CRT completion. Twenty-three patients (19.2%) showed complete response (CR),

whereas 97 (80.8%) exhibited partial response (PR). Prophylactic cranial irradiation was performed in 61 patients, including 20 (87.0%) out of 23 patients with CR and 41 (42.2%) out of 91 patients with PR.

Long-term survival and prognostic factors

In the analysis of OS, the median follow-up was 71.3 months (95% confidence interval [CI]: 86.6-61.6 months), and 42 out of 120 patients were considered as censored cases at the last confirmation of survival. The median OS was 34.3 months (95% CI: 28.6–46.0 months), with 3- and 5-year OS rates of 52.4% (95% CI: 43.3–61.4%) and 41.8% (95% CI: 32.9–51.2%), respectively. The median PFS was 12.2 months (95% CI: 10.1–23.1 months), with 3- and 5-year PFS rates of 37.6% (95% CI: 29.3–46.7%) and 33.6% (95% CI: 25.5–42.7%), respectively (Fig. 2a and c). The Kaplan–Meier curves for OS and PFS of all patients with LD-SCLC eligible for CRT are shown in Fig. 2c and d, with 3- and 5-year OS rates of 49.5% (95% CI: 41.1–41.1%) and 36.9% (95% CI: 29.6–44.8%), respectively. On the other hand, the 3- and 5-year PFS rates were 34.2% (95% CI: 27.3–41.8%) and 30.5% (95% CI: 23.8–38.1%), respectively. As shown in Table 2, univariate and multivariate analyses did not show any significant factors related to better OS or PFS.

Association of long-term OS and PFS at each point

As shown in Table 3 and Supplementary Fig. S1, the 5-year survival rates of those who were progression-free at each time point were 46.3% (95% CI: 36.5–56.3%) at 6 months, 57.5% (95% CI: 45.8–68.4%) at 9 months, 70.9% (95% CI: 57.5–81.4%) at 12 months, 72.6% (95% CI: 58.8–83.1%) at 15 months, 81.9% (95% CI: 67.8–90.7%) at 18 months, 81.7% (95% CI: 67.4–90.6%) at 21 months, 83.6% (95% CI: 69.4–92.0%) at 24 months, 85.7% (95% CI: 71.6–93.5%) at 27 months, 87.7% (95% CI: 73.5–94.8%) at 30 months, 87.7% (95% CI: 73.5–94.8%) at 33 months, 91.9% (95% CI: 77.7–97.4%) at 36 months, 91.9% (95% CI: 77.7–97.4%) at 39 months, and 94.3% (95% CI: 80.0–98.6%) at 42 months.

Discussion

This study revealed that the 3- and 5-year OS rates were 52.4% and 41.8%, respectively, in patients with LD-SCLC receiving concurrent CRT using AHF-RT. The combination of CDDP and ETP has already been a standard chemotherapy regimen in LD-SCLC since the 1980s, and the combination of chemotherapy with thoracic irradiation has been investigated since the 1990s [15, 16]. Chemotherapy regimens have made little progress in LD-SCLC treatment, with minor advances in irradiation methods [11, 12, 17]. From the 1990s to the 2000s, the 5-year OS of patients with LD-SCLC who underwent CRT was reported to be at 15–20% [12, 16, 17]. In addition to poor progression of treatment efficacy, the 5-year OS of patients with LD-SCLC treated with CRT was 34% in the CONVERT study and 40% in this study [11]. In a report from the ACS in 2021, the 2-year survival rate in patients with extensive disease SCLC (ED-SCLC) showed little improvement from 7–8%; In contrast, the 2-year survival rate for LD-SCLC improved from 36–46%, which may be due to progress in radiotherapy [11, 12, 14] and accurate clinical disease diagnosis [18]. Since 70% of patients underwent PET-CT before treatment in this study, accurate staging might also contribute to these improvements. In patients with ED-SCLC, the combination therapy of immune checkpoint

inhibitors and chemotherapy showed a significant survival benefit compared with chemotherapy alone [19, 20]. Since a randomized phase III study of the addition of durvalumab to concurrent CRT is now ongoing, these data can be helpful as historical data [21].

To the best of our knowledge, this is the first study to evaluate the relationship between PFS and long-term OS in patients with LD-SCLC treated with concurrent CRT. The Kaplan–Meier curves for PFS and 5-year survival rate of patients who were progression-free at each time point revealed that disease progression was frequently observed within two years after the initiation of chemotherapy, particularly in the first year. Akamatsu et al. reported that patients with locally advanced non-SCLC who maintained progression-free intervals longer than 24 months had a 5-year survival rate of approximately 90%. These data suggest that most disease progression occurred in the first 2 years after CRT initiation [22]. Patients with LD-SCLC treated with CRT tended to show earlier progression than patients with locally advanced non-small-cell lung cancer. These data may be due to the cytological characteristics of SCLC, such as rapid proliferation or extended metastasis of cancer cells [22, 23].

In this study, identified prognostic factors (poor PS, sex, age, and GTV) [24–29] were not significantly correlated with long-term survival. Patients with poor PS (ECOG-PS 2) were excluded from this study. Furthermore, there is only small number of patients with ECOG-PS 2 thus, ECOG-PS was not considered as a prognostic factor in this study. Foster et al. reported that younger patients with LD-SCLC have a better prognosis [25, 29]. However in this study, age was not a significant factor even after undergoing univariate analysis as a continuous variable. Therefore, our study focused on patients treated with concurrent CRT, which differs from the results of the overall LD-SCLC population [29]. Although sex was reported as a prognostic factor in several studies [24, 25, 28], this study did not show sex as a prognostic factor. These results may have been influenced by the small number of women included in this analysis. Reymen et al. reported GTV as an independent prognostic factor in patients with LD-SCLC [27]. In the said study, 86% of patients showed intervals of more than 30 days between the start of any treatment and the end of radiation therapy (SER). In our study, 12.5% of the patients also showed an SER of more than 30 days; however, GTV was not a significant prognostic factor. In patients with short SER, the prognostic impact of GTV in patients with LD-SCLC might be small. Several studies reported GTV as a predictive factor for non-small-cell lung cancer [30–32]; however, the results of this study suggest that early concurrent CRT provided therapeutic benefit, regardless of tumor size, due to the high responsivity of SCLC to CRT.

This study had some limitations. First, this was a single-center study with only a small number of enrolled patients. Second, although the induction chemotherapy regimen was standardized as platinum plus ETP, dose reduction and change in regimen were carried out based on the physician's decisions. Third, because of its retrospective nature, the timing of imaging evaluation was dependent on the clinical physicians. Further analysis through a prospective or retrospective study with a large sample size may be warranted to confirm these results.

In conclusion, although prognostic factors associated with long-term prognosis in LD-SCLC were not identified, the 5-year survival rate was approximately 40% in patients with LD-SCLC who received concurrent CRT in real-world settings. In this study, the 5-year survival rate among patients without disease progression at 2 years was 84%. These data might be helpful as a historical control in randomized controlled trials in future clinical trials for patients with LD-SCLC.

Declarations

Funding

Conflicts of interest The authors declare no conflict of interest.

Availability of data and material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions

Ethics approval This retrospective study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and was approved by the Institutional Review Board of Shizuoka Cancer Center (J2021-35).

Consent to participate Acquisition of informed consent from patients was waived owing to the retrospective nature of this study.

Consent for publication Not applicable.

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Tables

Table 1 Patient background

All patients (n=120)	Number of patients (n)	Percentage (%)
Age (years)		
Median (range)	65.5 years (34-76)	
<65 years	53	44.2
≥65 years	67	55.8
Sex		
Male	89	74.2
Female	31	25.8
ECOG performance status		
0	65	54.2
1	55	45.8
Pathological diagnosis		
Small cell carcinoma	114	95.0
Combined SCLC with LCNEC	4	3.3
Combined SCLC with adenocarcinoma	1	0.8
Combined SCLC with squamous cell carcinoma	1	0.8
Clinical stage (UICC-TNM 8 th)		
IIB	24	20.0
IIIA	45	37.5
IIIB	36	30.0
IIIC	15	12.5
T stage		
Tx	3	2.5
T1	31	25.8
T2	38	31.7
T3	16	13.3
T4	32	26.7
N stage		
N0	7	5.8
N1	28	23.3
N2	52	43.3
N3	33	27.5
GTV (mL)		
Median (range)	113.1 (7.5-655.2) mL	
<113 mL	60	50.0
≥113 mL	60	50.0
PET-CT		
Performed	84	70.0
Not performed	36	30.0

Abbreviations:

ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung carcinoma; LCNEC, large cell neuroendocrine carcinoma; UICC-TNM 8th, Union International for Cancer Control-TNM 8th edition; GTV, gross tumor volume; PET, positron emission tomography.

Table 2 Univariate and multivariate analyses of progression-free survival and overall survival in limited-disease small cell lung cancer patients treated with chemoradiotherapy

	PFS analysis				OS analysis			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
≥65 years)	1.04 (0.67–1.59)	0.8708	0.90 (0.57–1.43)	0.6567	0.89 (0.57–1.40)	0.6209	0.76 (0.47–1.24)	0.2726
PS)	1.19 (0.72–1.94)	0.4973	1.37 (0.80–2.35)	0.2490	1.20 (0.71–2.01)	0.4950	1.45 (0.83–2.53)	0.1968
1)	0.68 (0.44–1.03)	0.0699	0.71 (0.45–1.13)	0.1486	0.70 (0.45–1.09)	0.1149	0.71 (0.44–1.15)	0.1657
2/3, 4)	0.88 (0.57–1.36)	0.5639	1.08 (0.67–1.75)	0.7445	1.00 (0.64–1.58)	0.9873	1.23 (0.75–2.03)	0.4070
1/2, 3)	1.00 (0.62–1.60)	0.9962	0.99 (0.58–1.68)	0.9686	0.91 (0.55–1.49)	0.6932	0.93 (0.54–1.60)	0.7867
by regimen	1.51 (0.55–4.12)	0.4232	1.51 (0.53–4.26)	0.4383	1.26 (0.46–3.45)	0.6581	1.27 (0.45–3.62)	0.6512
PL/≥113 mL)	0.70 (0.46–1.07)	0.0997	0.67 (0.39–1.15)	0.1481	0.71 (0.45–1.11)	0.1313	0.62 (0.35–1.08)	0.0887
formed/not	1.03 (0.65–1.62)	0.9102	1.22 (0.74–2.02)	0.4375	0.99 (0.62–1.60)	0.9797	1.19 (0.70–2.00)	0.5244
variable)	1.01 (0.98–1.03)	0.6924	–	–	1.01 (0.98–1.04)	0.4989	–	–

Abbreviations:

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PE, cisplatin and etoposide; CE, carboplatin and etoposide; GTV, gross tumor volume; PET-CT, positron emission tomography-computed tomography

Table 3 Association between 5-year survival rate and progression-free survival at each time point in limited-disease small cell lung cancer patients treated with chemoradiotherapy

n	5-year survival rate of patients who achieved progression-free survival at each time point	
	of	Progression-free survival at each time point
	120	41.8 (95% CI: 32.9–51.2)
	103	46.3 (95% CI: 36.5–56.3)
	78	57.5 (95% CI: 45.8–68.4)
IS	61	70.9 (95% CI: 57.5–81.4)
IS	56	72.6 (95% CI: 58.8–83.1)
IS	50	81.7 (95% CI: 67.4–90.6)
IS	49	81.9 (95% CI: 67.8–90.7)
IS	48	83.6 (95% CI: 69.4–92.0)
IS	47	85.7 (95% CI: 71.6–93.5)
IS	44	87.7 (95% CI: 73.5–94.8)
IS	43	87.7 (95% CI: 73.5–94.8)
IS	41	91.9 (95% CI: 77.7–97.4)
IS	40	91.9 (95% CI: 77.7–97.4)
IS	38	94.3 (95% CI: 80.0–98.6)

Abbreviation: 95% CI, 95% confidence interval.

Figures

Fig. 1

Figure 1

Flow chart of patient recruitment Abbreviations:LD-SCLC, limited disease small cell lung cancer; CRT, chemoradiotherapy; RT, radiotherapy; PS, performance status *Ceased both chemotherapy and radiotherapy

Fig. 2

Figure 2

Kaplan-Meier-estimated overall survival and progression-free curves in patients with LD-SCLC (A) Overall survival of patients with LD-SCLC treated with concurrent CRT (n=120); (B) Overall survival of all patients with LD-SCLC eligible for CRT (n=168); (C) Progression-free survival of patients with LD-SCLC treated with concurrent CRT (n=120); (D) Progression-free survival of all patients with LD-SCLC eligible for CRT (n=168). Abbreviations: LD-SCLC, limited disease small cell lung cancer; CRT, chemoradiotherapy; OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval.

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