

Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer and Interstitial Lung Abnormalities

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Abstract

Purpose: Patients with lung cancer and interstitial lung disease treated with radiotherapy have been reported to be at a risk of developing radiation pneumonitis. However, the association between interstitial lung abnormalities (ILA) and radiation pneumonitis in patients with limited-stage small cell lung cancer (LS-SCLC) remains unclear. Furthermore, the prognosis is unclear for patients with SCLC and ILA treated with chemoradiotherapy. We investigated the impact of ILA on radiation pneumonitis and assessed the prognosis of patients with LS-SCLC and ILA treated chemoradiotherapy.

Methods and materials: We retrospectively reviewed the medical records of 149 patients with LS-SCLC who received first-line treatment between January 2009 and December 2016.

Results: In a univariate analysis, the patients with ILA showed a higher incidence rate of radiation pneumonitis compared with those without ILA (64% vs. 10%); multivariate analysis confirmed that ILA was significantly associated with the incidence of radiation pneumonitis. In the univariate analysis, patients with ILA showed poorer overall survival than those without ILA (median, 18.9 vs. 67.9 months). Multivariate analysis showed that ILA was a significant independent negative prognostic factor. However, the 2-year and 5-year survival rates for the patients with ILA treated with chemoradiotherapy were 36% and 26%, respectively; for those treated with chemotherapy alone were 8% and 0%, respectively.

Conclusions: ILA was a predictive factor for radiation pneumonitis in patients with LS-SCLC treated with chemoradiotherapy. The prognosis of the patients with LS-SCLC and ILA was poor; however, some patients with ILA treated chemoradiotherapy achieved long-term survival.

Introduction

Standard treatment for patients with limited-stage small cell lung cancer (LS-SCLC) is concurrent chemoradiotherapy (CCRT) ¹⁻³. However, patients with lung cancer and interstitial lung disease (ILD) treated with radiotherapy have been reported to be at a risk of developing radiation pneumonitis (RP) ⁴. Therefore, we usually avoid prescribing radiotherapy to such patients.

Recently, slight concomitant interstitial lung changes have been detected in patients with having emphysema or lung cancer screening population ^{5,6} due to the expansion of chest computed tomography (CT) scans. These slight changes have been classified as interstitial lung abnormalities (ILA), defined as nondependent changes including reticular or ground-glass abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis ^{7,8}.

Our previous study showed that ILA was a risk factor for RP in patients with non-small cell lung cancer (NSCLC) treated with CCRT ⁹. However, the association between pre-existing radiological ILA and RP in patients with SCLC remains unclear. In addition, the prognosis for patients with SCLC and ILA treated with CCRT is unclear because the slight radiological findings of ILA are often missed. Therefore, in our study,

we aimed to investigate the association between ILA and RP in patients with LS-SCLC and ILA treated with CCRT at our institution, and to evaluate the prognosis of these patients.

Methods And Materials

The medical records of patients with LS-SCLC who underwent chemotherapy, radiotherapy, or surgery as first-line treatment at our institution, Japan, between January 2009 and December 2016 were reviewed retrospectively. The tumor, nodes; metastasis (TNM) stage was evaluated based on the 7th edition of the TNM classification of lung cancer¹⁰. Early concurrent CRT as the first-line treatment was defined as the administration of radiotherapy within 14 days after chemotherapy treatment.

The initial analysis included the patients with LS-SCLC treated with early concurrent CRT as the first-line treatment. We then compared the patients with LS-SCLC and ILA treated with concurrent or sequential CRT and chemotherapy alone as the first-line treatment. The comparison excluded patients with contralateral hilar lymph node metastasis treated with chemotherapy alone as the first-line treatment.

The patients who were previously received any chemotherapy or chest radiotherapy were excluded from this study. Also excluded were patients who were not followed up within 30 days after the final day of the first-line treatment.

The radiotherapy for the patients with LS-SCLC included in this study was performed early or late concurrently with the first cycle of chemotherapy or sequentially after four cycles of chemotherapy. In most cases, the total planned dose was 45 Gy in twice-daily fractions or 50 Gy in a once-daily fraction¹¹. The initial field for the patients who received the radiotherapy sequentially was based on the post-chemotherapy treatment tumor volume. The timing and prescribed dose of radiotherapy was determined by the physician in charge. All the patients were required to undergo a chest CT to facilitate treatment planning. The gross tumor volume (GTV) of the primary tumor (primary GTV) was delineated in the pulmonary windows; the nodal involvement (nodal GTV) was delineated in the mediastinal windows. The clinical target volume (CTV) initially included the primary and nodal GTVs, the ipsilateral hilum, and the elective mediastinum, for which the lower border was 3.0 cm below the carina. The dose was up to 40 Gy in a once-daily fraction of 2 Gy per fraction or 30 Gy in twice-daily fractions of 1.5 Gy per fraction. Thereafter, the CTV included only the primary GTV and nodal GTV. The planning target volume was the CTV plus a margin that ensured that the planned dose was actually delivered to the CTV. After the radiotherapy, prophylactic cranial irradiation was administered to patients with a complete or near-complete response, represented by a scar-like shadow on chest CT, if the physician in charge judged the patient would benefit from this. The prophylactic cranial irradiation consisted of 25 Gy in 10 fractions¹².

ILA was defined as nondependent changes including reticular or ground-glass abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis^{7,8}. However, infectious lung disease or drug-induced pneumonia were excluded. ILA existence of the chest CT scans acquired before the treatment was evaluated by one radiologist and two pulmonologists

blinded to knowledge of the patient outcomes. The area of ILA as a proportion of the area of a lung zone was measured every 5% by visual evaluation.

The development of RP or the acute exacerbation of ILA within 1 year after the last day of irradiation was counted as an event of “radiation-related pneumonitis (RRP).” The definition of RRP included any acute respiratory event characterized by new bilateral ground-glass opacification or consolidation not completely explained by an infectious disease, cardiac failure, or fluid overload¹³. A RRP event was counted from grade 2 with steroid administration to grade 5 for pneumonitis, based on the National Cancer Institute Common Terminology Criteria version 4.0¹⁴. If a patient treated with intravenous steroid pulse therapy died within 45 days after the last day of irradiation, the death was considered to have been caused by RRP.

In the data analysis, categorical variables were analyzed using the Fisher’s exact test; the Cox proportional hazards approach was used in univariate and multivariate analyzes of the incidence of RRP, progression-free survival (PFS), and overall survival (OS). OS was defined as the time from the start of the platinum-based chemotherapy as first-line treatment to death; PFS was calculated from the start of the platinum-based chemotherapy as first-line treatment to the date of disease progression or death from any cause. The end date for the survival analyses was defined as February 25, 2019. In addition, 2- and 5-year survival rates were estimated from Kaplan–Meier survival probabilities and the event times were estimated using the Kaplan–Meier method. The log-rank test was used to compare the cumulative survival between groups. All *P* values were two-sided, with values < 0.05 considered statistically significant. The statistical analyses were performed using the JMP® 11.2.0 software (SAS Institute, Cary, NC, USA).

The study protocol was approved by the institutional review board of the Shizuoka Cancer Center (IRB No. J2019-29-2019-1-3).

Results

Patient characteristics

During the defined study period, a total of 149 patients diagnosed with LS-SCLC underwent first-line treatment, including CRT (*n* = 107), operation (*n* = 10), chemotherapy alone (*n* = 31), and radiotherapy alone (*n* = 1) (Fig. 1A). Of these, 56 patients (38%) had concomitant ILA. The 107 patients treated with CRT were divided into early CCRT (*n* = 73) and late CCRT or sequential radiotherapy (*n* = 34) (Fig. 1B).

The characteristics of the 73 patients treated with early CCRT are shown in Table 1. Of the 73 patients, 11 (15%) had concomitant ILA. The ILA accounted for 5% of the area of a lung zone in seven (64%) and 10% in the other four (36%). There was no difference in LS-SCLC patient characteristics between ILA and non-ILA (Supplementary Table S1).

Table 1

Baseline characteristics of patients with LS-SCLC treated with early concurrent chemoradiotherapy (n = 73)

Variable	
Age, median (range), years	66 (34–77)
≥ 70/<70 years	19/54
Sex, male/female	55/18
ECOG-PS, 0/1/2	42/28/3
Clinical stage, I/II/III ^a	0/15/58
Brinkmann index, ≥ 400/<400	71/2
Pre-existence of ILA, Yes/No	11/62
V ₂₀ , median (range), %	24 (13–36) (n = 72)
Number receiving AHF	72
Number receiving PCI	45
Chemotherapy regimen, CDDP/CBDCA	72/1
^a The clinical staging was according to the 7th edition of the TNM classification.	
LS-SCLC, limited-stage small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; ILA, interstitial lung abnormality; V ₂₀ , volume that received at least 20 Gy; AHF, accelerated hyperfractionation; PCI, prophylactic cranial irradiation; CDDP, cisplatin; CBDCA, carboplatin	

Table 2A. Univariate analysis of progression-free survival in patients with LS-SCLC treated with early concurrent chemoradiotherapy (n = 73)

Variable	Univariate analysis		
	Relative risk	95% CI	<i>P</i> -value
Sex male	1.37	0.69–3.02	0.3983
Age ≥70 years	0.80	0.39–1.53	0.5190
ECOG-PS = 0	0.81	0.45–1.48	0.4867
Clinical stage III	1.22	0.61–2.69	0.5967
Pre-existing ILA	1.55	0.67–3.16	0.2579

LS-SCLC, limited-stage small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; ILA, interstitial lung abnormality; CI, confidence interval

Table 2B. Univariate and multivariate analyses of overall survival in patients with LS-SCLC treated with early concurrent chemoradiotherapy (n = 73)

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	<i>P</i> -value	Relative risk	95% CI	<i>P</i> -value
Sex male	1.77	0.79–4.71	0.1933			
Age ≥70 years	2.28	1.18–4.20	0.8471	0.88	0.39–1.84	0.7511
ECOG-PS = 0	0.86	0.45–1.67	0.6398	0.83	0.42–1.64	0.5840
Clinical stage III	0.95	0.45–2.23	0.8988	0.74	0.32–1.85	0.5002
Pre-existing ILA	2.29	0.97–4.78	0.0338	2.51	1.02–5.62	0.0460

LS-SCLC, limited-stage small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance score; ILA, interstitial lung abnormality; CI, confidence interval

The median follow-up duration for the censored cases was 60.4 months (range, 12.4–120.6 months). One ILA patient treated with early CCRT could not be administered the prescribed dose to cure because of the development of RRP.

Prognosis

The median PFS at the first-line treatment for all the patients with LS-SCLC treated with early CCRT was 16.8 months (Fig. 2A). There were no significant differences between categorical variables shown in Table 2A in which the preexistence of ILA was included (median PFS, 17.2 vs. 7.3 months, $P = 0.2579$, Fig. 2B).

For all the patients treated with early CCRT, the 2-year and 5-year survival rates at the first-line treatment were 52% and 48%, respectively; the median OS was 52.0 months (Fig. 3A). Table 2B summarizes the results of the univariate and multivariate analyzes of OS for these patients. In the univariate analysis, OS was poorer for the patients with pre-existing ILA than for those without ILA (median OS, 18.9 vs. 67.9 months, $P = 0.0338$; Fig. 3B). The multivariate analysis showed that pre-existing ILA was a significant independent negative prognostic factor, with a hazard ratio (HR) of 2.51 (95% confidence interval [CI], 1.02–5.62; $P = 0.0460$). The 2-year and 5-year survival rates for the patients with ILA were 35% and 27%, respectively, whereas those for the patients without ILA were 78% and 52%. None of the patients died because of RRP.

Incidence of radiation-related pneumonitis

Of the 73 patients with LS-SCLC treated with early CCRT, 13 (18%; 95% CI, 11–28%) suffered RRP worse than grade 2 that required steroid treatment within 1 year after the final irradiation. The numbers of patients with RRP of grades 2 and 3 were 10 and 3, respectively; none had RRP at a higher grade than this. Table 3 summarizes the univariate and multivariate analyses for the incidence of RRP. In univariate analyses, the patients with pre-existing ILA showed a higher incidence rate of RRP compared to those without ILA (64% vs. 10%, $P < 0.001$). The multivariate analysis showed that pre-existing ILA was significantly associated with the incidence of RRP (HR, 27.7; 95% CI, 3.73–105; $P < 0.001$). Among the 11 patients with ILA, 5 (45%) experienced grade 2 RRP and 2 (18%) experienced grade 3. In contrast, in the 62 patients without ILA, only 5 (8%) and 1 (2%) experienced RRP of grades 2 and 3, respectively.

Table 3

Univariate and multivariate analyses of radiation-related pneumonitis in patients with LS-SCLC treated with early concurrent chemoradiotherapy (n = 73)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> -value	HR	95% CI	<i>P</i> -value
Sex male	4.74	0.83–89.7	0.0850	5.29	0.68–123	0.1221
Age ≥ 70 years	1.33	0.32–4.77	0.6717			
ECOG-PS = 0	1.22	0.36–4.46	0.7464			
V ₂₀ ≥ 25	2.03	0.61–7.42	0.2526	3.64	0.82–20.9	0.0900
Pre-existing ILA	16.3	3.88–80.3	0.0001	27.7	3.73–105	0.0002

LS-SCLC, limited-stage small cell lung cancer; ECOG-PS, Eastern Cooperative Oncology Group performance score; ILA, interstitial lung abnormality; HR, hazard ratio; CI, confidence interval

In some patients experienced RRP, the standard chemotherapy recommended by The Japanese Lung Cancer Society Guideline 2019¹⁵, such as amrubicin or weekly cisplatin plus etoposide plus irinotecan, were not chosen due to avoiding chemotherapy-induced pneumonitis.

Impact of radiation therapy

We explored the impact of adding radiation therapy to chemotherapy for the patients with LS-SCLC and ILA. A total of 56 patients diagnosed with LS-SCLC and ILA underwent first-line treatment, among whom 25 received CRT, including early or late concurrent or sequential radiation therapy, whereas the 24 patients without contralateral hilar lymph node (N3) involvement received chemotherapy alone (Fig. 1A). The characteristics of these patients are summarized in Table 4. There was no difference in age, sex, PS status, clinical stage, or smoking status between these two groups. However, compared with the patients treated with chemotherapy alone as the first-line treatment, the ILA of those treated with CRT tended to cover a lower proportion of the area of any lung zone ($P = 0.0106$).

Table 4
Baseline characteristics of patients with LS-Small and ILA in this study

First-line treatment: Variable	Chemoradiotherapy (n = 25)	Chemotherapy (n = 24)	P
Age, ≥ 70/<70 years	16/9	18/6	0.5380
Sex, male/female	21/4	20/4	1.0000
PS, 0/1/2 (0 vs 1 or 2)	15/10/0	10/11/3	0.2578
Clinical stage ^a , I/II/III (I vs II/III)	1/1/23	1/5/18	1.0000
Brinkmann index, ≥ 400/<400	24/1	23/1	1.0000
Proportion of ILA area of any lung zone, 5%/10%/15–30%/30–50% (5%/10% vs 15–30%/30–50%)	13/11/1/0	9/7/7/1	0.0106
V ₂₀ , median (range)	22 (10–32)		
Variable	ILA (n = 11)	Non-ILA (n = 62)	P
Age, ≥ 70/<70 years	4/7	15/47	0.4611
Sex, male/female	10/1	45/17	0.2729
PS, 0/1/2 (0 vs 1 or 2)	7/4/0	35/24/3	1.0000
Clinical stage ^a , I/II/III (I vs II/III)	0/0/11	35/24/3	0.1054
Brinkmann index, ≥ 400/<400	11/0	60/2	1.0000
V ₂₀ , median (range)	24 (15–32)	24 (13–36)	0.6435
^a Clinical staging was done according to the 7th edition of the TNM classification			
LS-SCLC, limited-stage small cell lung cancer; PS, Performance Status; ILA, interstitial lung abnormality; CT, computed tomography			

The median OS at the first-line treatment was 17.5 months for the patients treated with CRT and 14.4 months for those treated with chemotherapy alone (Fig. 4). The 2-year and 5-year survival rates for the patients treated with CRT were 36% and 26%, respectively; for those treated with chemotherapy alone were 8% and 0%, respectively.

Discussion

The results of this study showed that pre-existing radiological ILA was risk factor for RRP in patients with LS-SCLC, and that the patients with LS-SCLC treated with early CCRT who had ILA had a poorer prognosis than those without ILA. However, some patients with LS-SCLC and ILA treated CRT could achieve long-term survival.

We retrospectively reviewed the records of 73 patients with LS-SCLC treated with early CCRT, of which 11 (15%) had ILA. Pre-existing ILA was significantly associated with the incidence of RRP. This suggests that a finding of ILA could be a predictive factor for RRP in patients with LS-SCLC treated with CCRT. The frequency of RRP was similar to that in our previous study of patients with NSCLC and ILA treated with CRT⁹. ILA may be of similar importance as ILD in predicting RRP because a part of ILA was reported to proceed as ILD¹⁶. Although previous studies reported unfavorable impact of ILA on RP in patients with lung cancer receiving thoracic radiotherapy, their study cohorts were heterogeneous population with tumor stage, total radiation dose, chemotherapy regimen or timing of radiotherapy^{17,18}. In contrast in this study, most patients received treatment were etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy which is standard treatment recommended by The Japanese

Lung Cancer Society Guideline 2019¹⁵. Few studies focus on the risk of RRP for patients with LS-SCLC treated with radiotherapy. Therefore, the findings of our study are important to understand the risk of RRP before patients with LS-SCLC and ILA receive CRT.

We analyzed the prognosis of the patients with LS-SCLC treated with early CCRT. There was no difference in PFS between the patients with ILA and those without ILA. On the other hand, the analysis showed that pre-existing ILA was a significant independent negative prognostic factor for OS. There was no difference between the patients with and without ILA in the rate of second-line chemotherapy given at the time of relapse of SCLC. However, because of RRP, fewer of the patients with ILA were able to receive the regimen recommended by the Japanese guidelines. It has also previously been reported that patients with ILA without cancer have a poor prognosis^{16,19}. Therefore, ILA can result in increased all-cause mortality other than SCLC in this population.

This study included a total of 149 patients diagnosed with LS-SCLC who underwent first-line treatment, of whom 56 (38%) had concomitant ILA. It has previously been reported that concomitant ILA was observed in about 10–20% of the patients included in trials concerning chronic obstructive pulmonary disease (the COPDGene study^{5,8}, ECLIPSE Study²⁰, and AGES-Reykjavik Study²¹), a study of screening for lung cancer using low-dose helical CT scans (the National Lung Screening Trial^{6,22}), and a study to identify common factors or characteristics that contribute to cardiovascular disease (Framingham Heart Study)^{7,16,19}. The proportion of patients with concomitant ILA in our study was substantially greater than in those previous studies. This may be because of the strong association between SCLC and a history of heavy cigarette smoking, which is also associated with the development of ILA⁸.

Finally, we explored the impact of adding radiation therapy to chemotherapy for patients with LS-SCLC and ILA. OS was similar between the two therapies, but the 2-year and 5-year survival rates were considerably higher for the patients treated with CRT. This suggests that, although there are selection bias and risk of RRP for the patients with SCLC and ILA treated with CRT, radiation therapy is probably needed to achieve long-term survival.

Several limitations of this study should be considered. First, the patients with LS-SCLC treated with early CCRT had milder ILA, in which lower proportion of the area of any lung zone was observed, compared with those with chemotherapy alone. Second, this was a retrospective, nonrandomized study conducted at a single center.

Conclusions

A substantial proportion of patients with LS-SCLC had concomitant ILA that was a predictive factor for RRP in patients with LS-SCLC treated with CCRT; the prognosis of patients with LS-SCLC and ILA treated with CCRT was poor. Radiation therapy is probably needed to achieve long-term survival in patients with LS-SCLC and ILA treated with CRT, although there is a risk of RRP.

In future, it is important to be able to identify patients with LS-SCLC and ILA treated with CRT who are at high risk for RRP. This would allow many patients with LS-SCLC and ILA to safely receive CRT and achieve long-term survival.

Abbreviations

LS-SCLC, limited-stage small cell lung cancer

CCRT, concurrent chemoradiotherapy

ILD, interstitial lung disease

RP, radiation pneumonitis

ILA, interstitial lung abnormalities

NSCLC, non-small cell lung cancer

RRP, radiation-related pneumonitis

PFS, progression-free survival

OS, overall survival

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The end date for the analyses was defined as February 25, 2019.

Competing interest:

HK reports personal fees from Eli Lilly K.K, personal fees from Taiho Pharmaceutical, outside the submitted work. KW reports personal fees from Chugai Pharmaceutical Co, Ltd., personal fees from Ono Pharmaceutical Co, Ltd. , personal fees from Boeringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Taiho Pharma, personal fees from AstraZeneca K.K., outside the submitted work. TN has nothing to disclose. NM reports grants from Boeringer Ingelheim,

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Authors' contributions:

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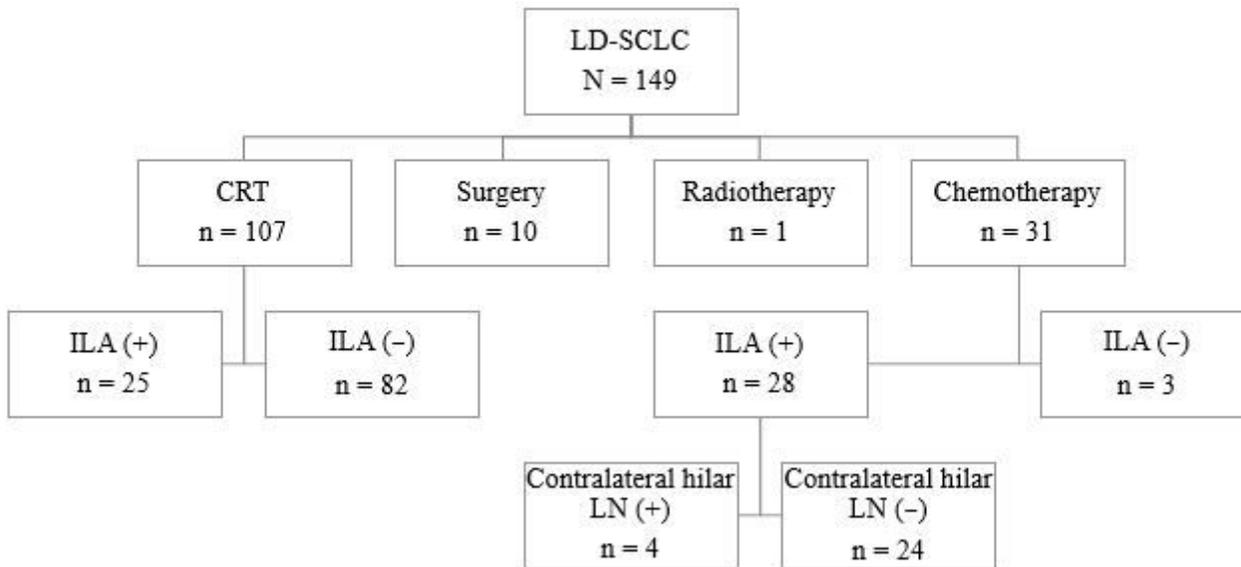
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Figures

A



B

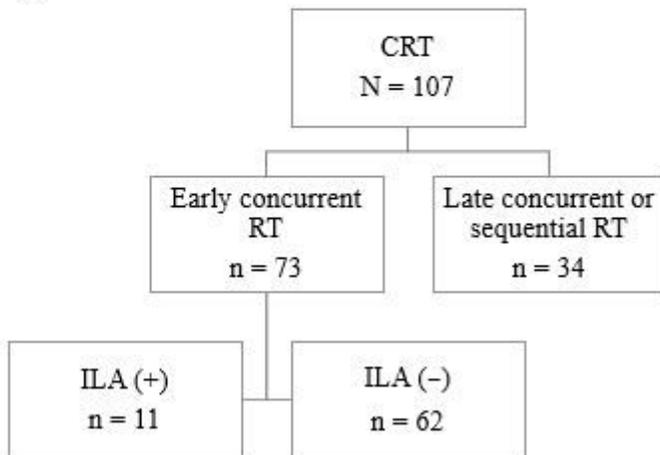


Figure 1

(A) Consort diagram of all the patients with LS-SCLC included in the study. (B) Consort diagram of the patients with LS-SCLC treated with CRT. LS-SCLC, limited-stage small cell lung cancer; CRT, chemoradiotherapy; ILA, interstitial lung abnormalities; RT, radiotherapy; LN, lymph nodes

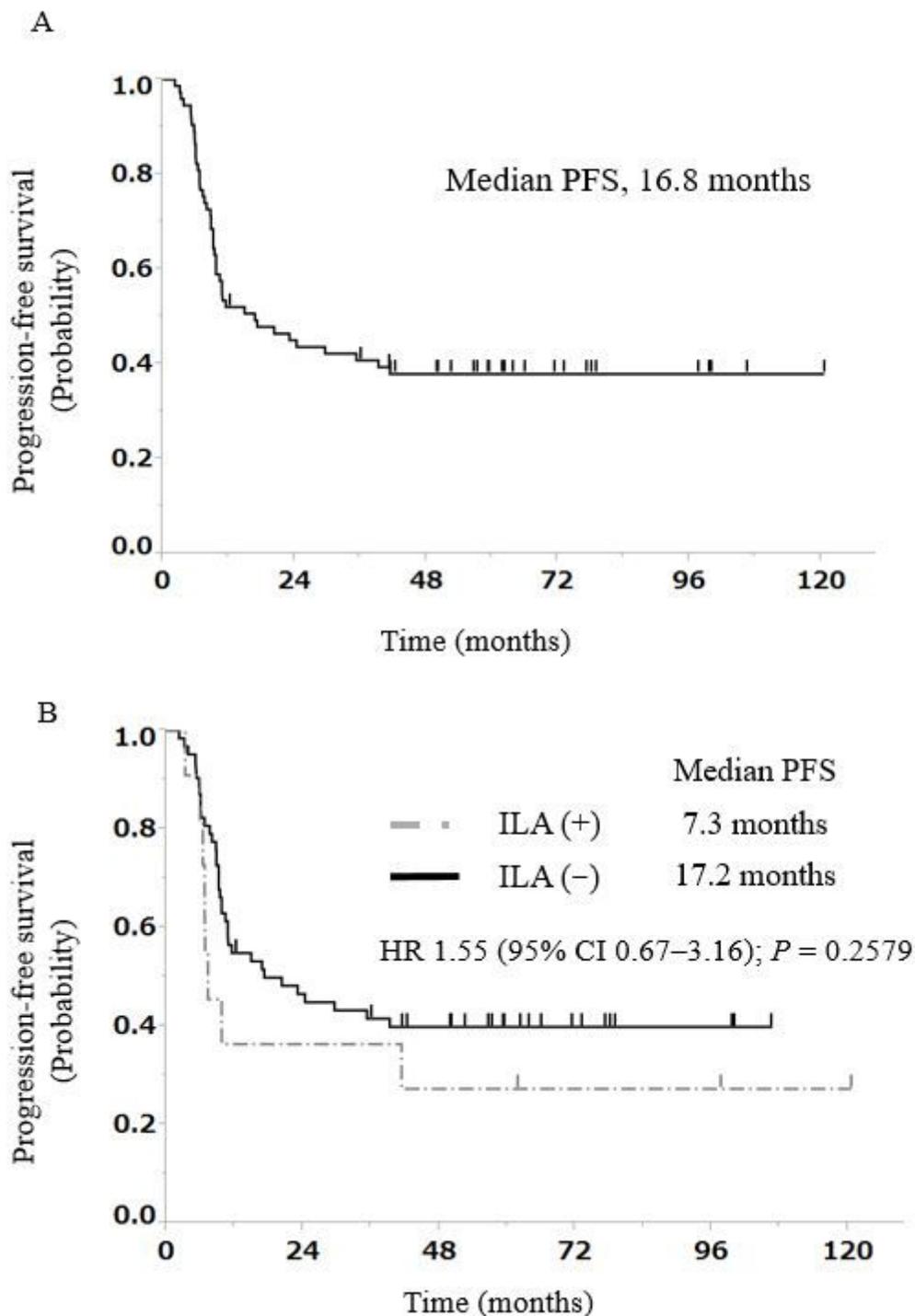


Figure 2

(A) Progression-free survival (PFS) curve for the 73 patients with LS-SCLC treated with early concurrent CRT. (B) PFS curves for the 11 of these patients with ILA and the 62 patients without ILA. LS-SCLC, limited-stage small cell lung cancer; CRT, chemoradiotherapy; ILA, interstitial lung abnormalities; HR, hazard ratio; CI, confidence interval

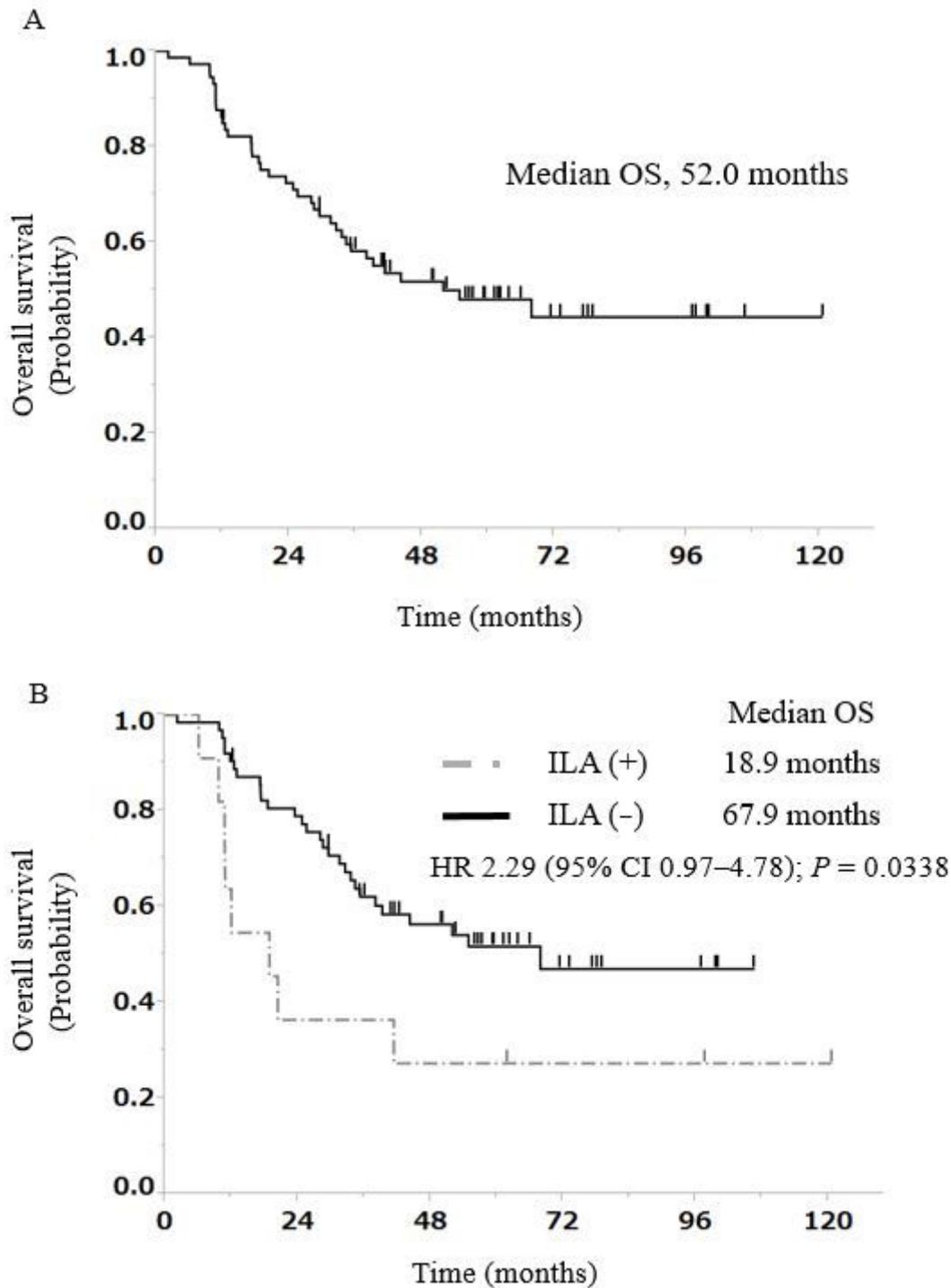


Figure 3

(A) Overall survival (OS) curve for 73 patients with LS-SCLC treated with early concurrent CRT. (B) OS curves for the 11 of these patients ILA and the 62 patients without ILA. LS-SCLC, limited-stage small cell lung cancer; CRT, chemoradiotherapy; ILA, interstitial lung abnormalities; HR, hazard ratio; CI, confidence interval

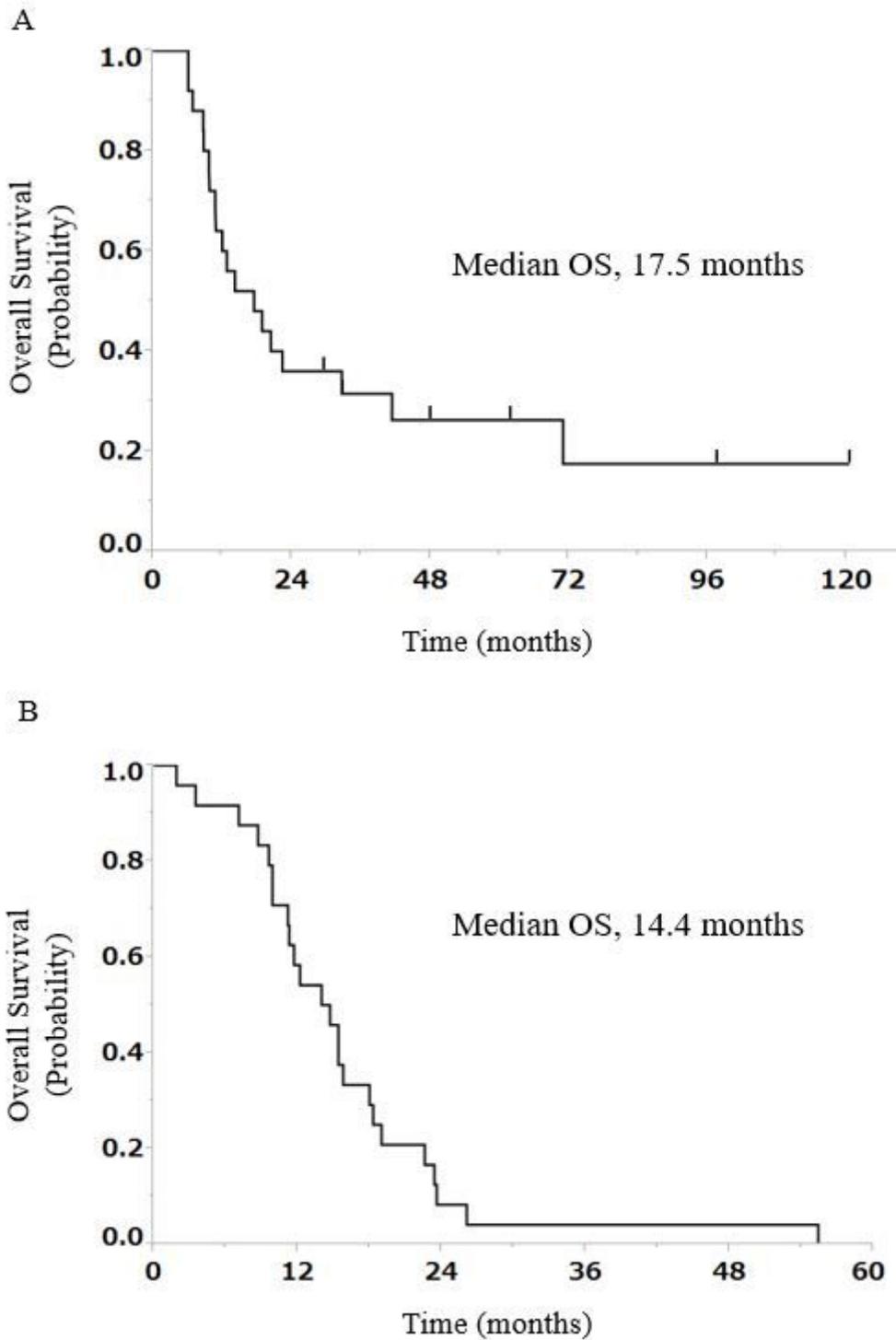


Figure 4

(A) Overall survival (OS) curve for 25 patients with LS-SCLC and ILA treated with CRT. (B) OS curve for 24 patients with LS-SCLC and ILA treated with chemotherapy alone. LS-SCLC, limited-stage small cell lung cancer; ILA, interstitial lung abnormalities; CRT, chemoradiotherapy

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