

Title: Effect of sequential chemoradiotherapy in patients with limited-disease small-cell lung cancer who were ineligible for concurrent therapy: A retrospective study at two institutions

Authors: Sayaka Ohara^{1,2} (first author), Shintaro Kanda¹ (corresponding author), Hitomi Okuma¹, Yasushi Goto¹, Hidehito Horinouchi¹, Yutaka Fujiwara¹, Hiroshi Nokihara¹, Yoshinori Ito³, Noboru Yamamoto¹, Kazuhiro Usui⁴, Sakae Homma², Yuichiro Ohe¹(last author)

1 Department of Thoracic Oncology, National Cancer Center Hospital,

5-1-1 Tsukiji Chuo-ku Tokyo, Japan;

2 Department of Respiratory Medicine, Toho University Graduate School of Medicine,

6-11-1 Omori-Nishi Ota-ku Tokyo, Japan;

3 Department of Radiation Oncology, National Cancer Center Hospital,

4 Division of Respiriology, NTT Medical Center Tokyo,

5-9-22 Higashi-Gotanta Shinagawa-ku Tokyo, Japan;

Corresponding author: Shintaro Kanda¹ email: skanda@ncc.go.jp

TEL +81-3-3542-2511 FAX +81-3542-3815, 5-1-1 Tsukiji Chuo-ku Tokyo, Japan

Running title: Sequential chemoradiotherapy in LD-SCLC

Abstract

Background: The standard treatment for limited-disease small-cell lung cancer (LD-SCLC) is a combination of chemotherapy and concurrent thoracic radiotherapy. In selected cases, sequential radiotherapy is preferred because of the need for a large irradiation field, patient age, comorbidities, or performance status. Nevertheless, the efficacy of sequential chemoradiotherapy in patients in whom concurrent chemoradiotherapy is contraindicated is not well known.

Methods: We retrospectively analyzed 286 patients with LD-SCLC at two institutions in Japan between 2000 and 2014. We compared the clinical characteristics and treatment outcomes of patients undergoing sequential radiotherapy with those undergoing concurrent radiotherapy.

Results: One hundred and seventy-five patients received concurrent chemoradiotherapy, 33 received sequential chemoradiotherapy, and 46 received chemotherapy only. The median patient age was 64 years (range, 18-82 years) for the concurrent group and 71 years (49-82 years) for the sequential group. Conventional radiotherapy was selected more frequently than accelerated hyperfractionated radiotherapy (27 patients [82%] with conventional radiotherapy, and 6 patients [18%] with hyperfractionated radiotherapy). The major reasons for the selection of sequential radiotherapy were advanced age (12 patients) and a

large irradiation field (11 patients). The median overall survival time was 41.1 months for the sequential group and 38.1 months for the concurrent group. The 5-year survival rates were 36.0% for the sequential group and 41.6% for the concurrent group.

Conclusions: In clinical situation, since the treatment outcomes for patients with sequential radiotherapy were comparable to those receiving concurrent radiotherapy, sequential chemoradiotherapy can be a choice for the treatment of patients who are not candidates for concurrent chemoradiotherapy.

Mini abstracts

In some LD-SCLC, sequential chemoradiotherapy rather than concurrent chemoradiotherapy is preferred. We retrospectively compared treatment outcomes of sequential chemoradiotherapy and concurrent chemoradiotherapy and found comparable outcomes of sequential therapy.

Keywords

LD-SCLC, chemoradiotherapy, sequential

1.Introduction

Small cell lung cancer (SCLC) accounts for 10%-15% of all lung cancers and is characterized as a rapidly progressive disease(1). The standard care for limited-disease SCLC (LD-SCLC) is a combination of cisplatin-plus-etoposide chemotherapy and thoracic radiotherapy(2). Several randomized controlled trials and meta-analyses conducted to estimate the optimal timing of radiotherapy have demonstrated that better survival benefits were obtained if the radiotherapy was conducted concurrently with the chemotherapy, rather than sequentially(3, 4). An earlier timing for radiotherapy provides a greater survival benefit, compared with a later timing for radiotherapy(3, 5-9). In clinical practice, however, some cases are not suitable for concurrent treatment because of an advanced age, the need for a large irradiation field, or other reasons, and sequential chemoradiotherapy is recommended for such patients. Sequential chemoradiotherapy, rather than chemotherapy only, is considered in these cases, because of the sensitivity of SCLC to radiotherapy(2). However, the treatment outcome of patients who are not candidates for concurrent chemoradiotherapy but who are able to receive sequential chemoradiotherapy is not well known.

Consequently, we conducted a retrospective analysis of patients with LD-SCLC who received sequential chemoradiotherapy to determine the treatment outcomes of those patients. In the present study, we compared the treatment outcomes of LD-SCLC patients who received concurrent chemoradiotherapy and those who received sequential chemoradiotherapy. We also analyzed LD-SCLC patients who did not receive radiotherapy but who received chemotherapy only to better understand the benefits of radiotherapy.

2. Methods

2.1 Patients

We retrospectively analyzed 286 patients with LD-SCLC who were treated at the National Cancer Center Hospital and the NTT Medical Center in Japan between January 2000 and December 2014. Patients were histologically or cytologically confirmed to have SCLC. In our study, the definition of LD was a disease confined to one hemithorax, mediastinum, or bilateral supraclavicular fossae. A small amount of pleural effusion insufficient for the diagnosis of a malignancy in the ipsilateral hemithorax was included in the definition for LD(10).

2.2 Study design

We compared the clinical characteristics and treatment outcomes of patients who received sequential chemoradiotherapy (sequential group) with those who received concurrent chemoradiotherapy (concurrent group). Concurrent radiotherapy was defined as radiotherapy that was started during the chemotherapy period. Sequential radiotherapy was defined as radiotherapy that was started after the chemotherapy had been completed. Radiotherapy beginning during or after the third cycle of chemotherapy was included in the concurrent group but was considered as a late concurrent treatment. Although standard radiotherapy modality and dose were accelerated hyperfractionated radiotherapy with 45 Gy in 1.5 fractions twice a day for 15 days, they were varied because of timing and each person's background and general conditions. For those with pleural effusion, planning of radiotherapy was decided like other patients without pleural effusion. We excluded patients who had received radiotherapy as palliative therapy, patients who had received radiotherapy at a different institution, and patients who were treated with a modality other than accelerated hyperfractionated radiotherapy and conventional radiotherapy. We also retrospectively examined LD-SCLC patients who were unable to receive thoracic radiotherapy and who received chemotherapy only (chemotherapy only

group), since knowledge of the outcomes of patients treated only with chemotherapy was expected to provide information regarding the role of radiotherapy. We also analyzed the reasons for not conducting concurrent chemoradiotherapy, the response rates, and the modes of recurrence. Tumor response was assessed by each clinician at the completion of the treatment. Consequently, the patient response was not assessed at the same time in all the patients. Thus, for the concurrent group and the chemotherapy only group, the assessment was performed after the chemotherapy had been completed; for the sequential group, however, the assessment was performed after radiotherapy. As to the modes of recurrence, local recurrence was defined as a recurrence within the irradiation field, while distant recurrence was defined as a recurrence occurring outside of the irradiation field. Toxicities were defined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.

The subjects' medical records were reviewed to obtain clinical and demographic data, including sex, age, radiological findings, comorbidities, treatment and survival. The study protocol was approved by the Ethics Committee of the National Cancer Center Hospital (approval number 2015-355) and NTT Medical Center Tokyo (approval number 16-321).

2.3 Statistical Analysis

The primary endpoint was overall survival (OS). OS was measured from the date of the first day of the first treatment intervention to the date of death. The secondary end points were progression-free survival (PFS) and safety. PFS was measured from the date of the first day of the first treatment intervention to the date of the first observation of disease progression or death. OS and PFS were analyzed according to the Kaplan-Meier method using the log-rank test. Categorical variables were expressed as percentages.

All the statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

3. Results

3.1 Patients characteristics

Two hundred and eighty-six LD-SCLC patients (222 from the National Cancer Center Hospital and 64 from NTT Medical Center Tokyo) were categorized into

three groups, as shown in Figure 1. Two hundred and fifty-four patients received treatment including chemotherapy, 208 patients (73%) received chemoradiotherapy, and 46 patients (16%) received chemotherapy only. Among the 46 patients who received chemotherapy only, 5 patients were scheduled to receive radiotherapy after chemotherapy but were unable to do so. Thirty-two patients (11%) received treatments other than the three treatments mentioned above: 12 patients underwent surgery, 9 patients received palliative radiotherapy, 6 patients received chemoradiotherapy at another hospital, 3 patients did not have enough information included in their medical records, 1 patient received proton therapy, and 1 patient received best-supportive care without chemotherapy. Among those who received chemoradiotherapy, 175 patients (61%) received concurrent chemoradiotherapy and 34 patients (12%) received sequential chemoradiotherapy. Within the concurrent group, 160 patients started radiotherapy within the first two cycles of chemotherapy (early concurrent), while 15 patients started receiving radiotherapy at some time after the first two cycles (late concurrent). The median follow-up time was 25.8 months for the sequential group, 29.7 months for the concurrent group, and 13.6 months for the chemotherapy only group.

The patients' characteristics are shown in Table 1. The median age was younger in the concurrent group than in the sequential and chemotherapy only group (64 years for concurrent group, 71 years for sequential and chemotherapy only group). There was a significant difference in age between the concurrent group and the sequential group ($P < 0.05$). The numbers of elderly patients over 70 years of age were 37 (27%) for the concurrent group, 18 (55%) for the sequential group, and 36 (78%) for the chemotherapy only group. Men were more frequent than women in all the groups. There was a significant difference in the type of radiotherapy used in the two chemoradiotherapy groups. The concurrent group had more patients who had received accelerated hyperfractionated radiotherapy (152 patients, 87%) than conventional radiotherapy (7 patients, 21%). For the accelerated hyperfractionated radiotherapy, all the patients received a total of 45 Gy in 1.5 fractions twice a day for 15 days. For conventional radiotherapy, 20 out of 23 patients in the concurrent group received a total of 50 Gy in 25 fractions, while the remaining 3 patients received 60 Gy in 30 fractions. In the sequential group, 24 patients received 50 Gy in 25 fractions of conventional radiotherapy, while two patients were scheduled to receive 50 Gy but only received 48 Gy in 24 fractions and

44Gy in 22 fractions because of radiation pneumonitis. And another one received 40 Gy in 20 fractions because of previous history of thoracic radiotherapy. Concerning prophylactic cranial irradiation, in both groups, no more than half of patients received prophylactic cranial irradiation after chemoradiotherapy (88patients (50%) in concurrent group, 10 patients(30%) in sequential group). As to the chemotherapy regimen, in the concurrent group, 122 patients (70%) received cisplatin plus etoposide, 11 patients (6%) received carboplatin plus etoposide, 12 patients (7%) received cisplatin plus etoposide followed by cisplatin, vincristine, doxorubicin, and etoposide as a clinical trial, and 11 patients (6%) received one cycle of cisplatin plus etoposide followed by cisplatin plus irinotecan as a clinical trial. In the sequential group, 13 patients (39%) received carboplatin plus etoposide, 10 patients (30%) received cisplatin plus irinotecan, and 8 patients (24%) received cisplatin plus etoposide. In the chemotherapy only group, 34 patients (74%) received carboplatin plus etoposide, 9 patients (20%) received cisplatin plus etoposide, and 2 patients (4%) received cisplatin plus irinotecan.

Since the standard treatment for LD-SCLC is concurrent chemoradiotherapy, the reasons for choosing chemotherapy only, rather than

concurrent chemoradiotherapy, are shown in Table. 2. An advanced age (12 patients, 36%) was the most frequent reason for choosing sequential chemoradiotherapy. The second most-frequent reason was a large irradiation field (11 patients, 33%). Other reasons were extra-pulmonary comorbidities such as a combination of stomach cancer and chronic kidney disease, chronic heart failure, and diabetes mellitus (4 patients, 12%), low pulmonary function because of chronic obstructive pulmonary disease (COPD) (4 patients, 12%), small amounts of pleural effusion (4 patients, 12%), lung cancer-related obstructive pneumonitis, or atelectasis (3 patients, 9%), or a poor performance status (2 patients, 6%). Some patients received sequential chemoradiotherapy for a combination of the above reasons. For the chemotherapy only group, interstitial pneumonitis was the major reason for not delivering radiotherapy. An advanced age, large irradiation field, and low pulmonary function because of COPD were other reasons for the decision not to perform radiotherapy the chemotherapy only group. Extra-pulmonary comorbidities such as diabetes mellitus, pulmonary comorbidities such as bronchial asthma and sarcoidosis, a suspicion of carcinomatous meningitis, a suspicion of double cancer, and patient choice were other reasons why chemotherapy only was selected.

3.2 Treatment outcomes

The response rates are shown in Table 3. In the concurrent group, a complete response was seen in 62 patients (35%), a partial response was seen in 105 patients (60%), stable disease was seen in 4 patients (2%), and progressive disease was seen in 3 patients (2%). The response in two patients was unknown because these patients were transferred to another hospital before their response was assessed. In the sequential group, 6 patients (18%) had a complete response, and 27 patients (82%) had a partial response, none of the patients had stable disease or progressive disease. In the sequential group, the response after chemotherapy but before radiotherapy was a complete response for 6 patients (18%), a partial response for 23 patients (70%), and stable disease for 4 patients (12%).

The median PFS was 16.8 months (95% confidence interval [CI], 7.5-58.3 months) for the sequential group, 12.1 months (95% CI, 10.4-14.3 months) for the concurrent group, and 5.7 months (95% CI, 5.1-8.0 months) for the chemotherapy only group (Figure 2a). The comparison of PFS between concurrent group and sequential group was $P=0.717$. The hazard ratio for the sequential group compared with the on concurrent group was 0.92 (95% CI,

0.59-1.45; $P = 0.72$). The 5-year progression-free survival rates were 31.2% for the sequential group, 27.1% for the concurrent group, and 11.6% for the chemotherapy only group. When the PFS analysis was limited to patients ≥ 70 years old, the median PFS was 9.2 months (95% CI, 7.5-NA) for the sequential group, 11.3 months (95% CI, 9.1-16.9) for the concurrent group, and 6.1 months (95% CI, 4.7-8.6) for the chemotherapy only group. The 5-year PFS rates were 30.0%, 16.0%, and 15.0% for the sequential, concurrent, and chemotherapy only groups, respectively.

The median OS was 41.1 months (95% CI, 16.0-75.4 months) for the sequential group, 38.1 months (95% CI, 30.3-52.0 months) for the concurrent group, and 15.6 months (95% CI, 11.7-19.7 months) for the chemotherapy only group (Figure 2b). The comparison of OS between concurrent group and sequential group was $P=0.464$. The hazard ratio for the sequential group compared with the concurrent group was 1.20 (95% CI, 0.74-1.93; $P = 0.46$). The 5-year survival rate for the concurrent group was 36.0% for the sequential group, 41.6% for the concurrent group, and 15.4% for the chemotherapy only group. For elderly patients ≥ 70 years old, the median OS periods were 23.5 months (95% CI, 9.76-NA) for the sequential group, 34.0 months (95% CI,

16.7-96.7) for the concurrent group, and 15.0 months (95% CI, 10.9-25.7) for the chemotherapy only group. The 5-year survival rates for elderly patients were 23.5%, 42.5%, and 19.5% for the sequential, concurrent, and chemotherapy only groups, respectively.

The sites of first progression were similar in the concurrent and sequential groups (Table 3). Local recurrences were less common than distant recurrences in both groups. Among the 4 patients with small amounts of pleural effusion at the time of diagnosis in the sequential group, 2 patients did not develop recurrences, while the other 2 patients developed recurrences but not in the pleural effusion.

After recurrence, amrubicin was the most frequent chemotherapy regimen used in both groups, with 67 patients in the concurrent group and 10 patients in the sequential group. The second most frequent regimen used was irinotecan monotherapy, with 31 patients in the concurrent group and 2 patients in the sequential group. Irinotecan, cisplatin and etoposide, known as PEI, were used in 29 patients in the concurrent group and one patient in the sequential group. Topotecan was used for 17 patients in the concurrent group and 2 patients in the sequential group. Other regimens, such as the platinum-plus-etoposide regimen,

the platinum-plus-irinotecan regimen, and the paclitaxel regimen, were also seen.

3.3 Toxicities

A higher rate of febrile neutropenia of more than grade 3 was seen in the concurrent group than in the sequential group (52 patients [30%] in the concurrent group, 4 patients [12%] in the sequential group). Pneumonitis of more than grade 3 were experienced in 8 patients (5%) in the concurrent group and 5 patients (15%) in the sequential group. In all the patients with pneumonitis more than grade 3, pneumonitis were radiation pneumonitis rather than chemotherapy-induced radiotherapy. Pneumonitis occurred more than one month later than last chemotherapy treatment and accorded with irradiation field indicating radiation pneumonitis rather than chemotherapy-induced pneumonitis. Treatment-related deaths occurred in 2 patients (6%) in the sequential group because of pneumonitis.

4. Discussion

We retrospectively analyzed LD-SCLC patients who received chemoradiotherapy at two institutions in Japan. Our retrospective study was the

first study to demonstrate that sequential chemoradiotherapy resulted in relatively good outcomes among patients who were not candidates for concurrent chemoradiotherapy for the treatment of LD-SCLC. Concurrent chemoradiotherapy was associated with a longer PFS and OS than sequential chemoradiotherapy, but the sequential group had outcomes that were comparable to those of the concurrent group. Our results showing a longer PFS and OS for concurrent chemoradiotherapy were similar to those of other previous studies(3, 5-9). Unlike previous studies, however, the sequential group in our study was comprised of a group of patients who could not receive concurrent radiotherapy or who were thought to have a high risk of an adverse outcome if they received concurrent radiotherapy but were able to receive sequential chemotherapy. The sequential group in previous prospective studies, on the other hand, was comprised of patients who were also candidates for concurrent chemoradiotherapy. Thus, the backgrounds of the patients in the sequential group in our study differed from those in the sequential groups in the previous studies. No study has ever focused on patients who could not receive radiotherapy concurrently. Our study provides a possible choice to conduct radiotherapy sequentially in cases where concurrent radiotherapy is inadvisable.

For example, among the patients who did not receive radiotherapy because of a small amount of pleural effusion and suspected malignancy, none of the presently reported patients experienced an increase in pleural effusion and some of them did not even experience a relapse after sequential chemoradiotherapy, unlike a previous study in which minimal pleural effusion was correlated with a poor survival outcome(11). For the treatment of cases in which physicians might hesitate to use concurrent radiotherapy, the choice of sequential radiotherapy might enable a better outcome than the avoidance of radiotherapy altogether.

There are several possible reasons for the good outcome of the sequential radiotherapy group in our study. The first possible reason is that the sequential group in our study was comprised of patients who were able to undergo radiotherapy sequentially, meaning that the chemotherapy prior to the radiotherapy had been effective, enabling them to undergo radiotherapy. Patients who were scheduled to undergo radiotherapy sequentially but could not complete radiotherapy because of disease progression were not included in the sequential treatment group. There were five such cases in the chemotherapy only group. Secondly a survival benefit might have been seen because the

previous prospective studies were mostly conducted in the early 2000s, and new chemotherapy agents and regimens, such as amrubicin, topotecan, and the PEI regimen, have since been developed for patients with recurrences. Amrubicin is known to be an active agent in patients with relapse(12). In our study, amrubicin was widely used for the treatment of relapses in both the concurrent group and the sequential group. Thus, patients who experience a relapse now have more chemotherapy options than before. These are some of the possible reasons for the relatively good outcome in the sequential radiotherapy group.

Our study revealed that age is an important factor when deciding on appropriate treatment strategies in clinical situations, and it also suggested that sequential chemoradiotherapy might be suitable for elderly patients, in terms of toxicities. The age of the sequential group was, indeed, significantly older than that of the concurrent group. Although no clinical trials limited to elderly patients have been conducted, a subgroup analysis in one study, showed that the response rate and the survival rate of for elderly patients over 70 years old were similar to those of younger patients, but that the incidence of hematologic toxicity was greater (13, 14). When we limited our analysis to elderly patient, the OS of the sequential group was shorter than that of the concurrent group but longer

than that of the chemotherapy only group. Nevertheless, a lower incidence of febrile neutropenia in the sequential group supports the possible choice of sequential radiotherapy in elderly patients.

Our study revealed less patients with PCI in boths group especially in sequential group. The reason for less percentage of patients with PCI is related to less patients with complete response. The current evidence about PCI is that it gives clinical benefit for those with (nearly) complete response(15). And the decision of persecuting PCI is greatly dependent on each patient's situation and background for those with partial response. And there were even less PCI population in the sequential group, the reason might be that patients in the sequential group included those with higher age, with comorbidities, which tended to choose observation rather than persecuting PCI fearing adverse events or lowering quality of life. As to outcomes, there were differences in two groups with percentage of PCI, we speculate that PCI did not affected to outcomes, because the OS of both groups did not differ significantly.

A limitation of our study is its retrospective nature, with all data based on medical records. As a result, some information that might have influenced the decision not to perform concurrent chemoradiotherapy might have been missed.

Another limitation is that the patients in the sequential group had risk factors that prevented them from being candidates for concurrent radiotherapy. Therefore, the treatment outcomes were probably greatly influenced by these risk factors, and assessments of the treatment outcomes based on the treatment timings were difficult. Despite these limitations, our study was valuable in that being a retrospective study, it can provide possible answers to clinical questions that are actually encountered in clinical situations.

5. Conclusion

The treatment outcomes of patients who could not receive concurrent radiotherapy but were able to complete sequential radiotherapy were comparable to those of patients who received concurrent radiotherapy. Although it is limited to patients with good response to chemotherapy and not applicable to all the patients who were ineligible to concurrent radiotherapy, for patients in whom concurrent chemoradiotherapy is not indicated, sequential chemoradiotherapy should be considered as a treatment choice.

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Table 1. Patients characteristics

		Concurrent n = 175	Sequential n = 33	CT only n = 46
Age	Median (range) ≤70 years old	64 (18-81) 37 (21%)	71 (49-82) 18 (55%)	71 (56-86) 36 (78%)
Sex	Female Male	42 (24%) 133 (76%)	10 (30%) 23 (70%)	6 (13%) 40 (87%)
PS	0-1 2-3	171 (98%) 4 (2%)	31 (94%) 2 (6%)	43 (93%) 3 (7%)
Clinical Stage	I II III	2 (1%) 24 (14%) 149 (85%)	2 (6%) 3 (9%) 28 (85%)	5 (11%) 10 (22%) 31 (67%)
Radiotherapy	Hyperfractionated Conventional	152 (87%) 23 (13%)	6 (18%) 27 (82%)	-
Prophylactic cranial irradiation		88 (50%)	10 (30%)	-
Chemotherapy Regimen	CDDP+ETP CBDCA+ETP CDDP+ETP→CDBCA+ETP CDDP+CPT CDDP+CPT→CDDP+ETP CDDP+ETP→CDDP+CPT*1 CDDP+ETP→CDDP+AMR*2 CDDP+ETP→CODE*2 CBDCA+AMR*3	122 (70%) 11 (6%) 5 (3%) 0 (0%) 6 (3%) 11 (6%) 8 (5%) 12 (7%) 0 (0%)	8 (24%) 13 (39%) 0 (0%) 10 (30%) 1 (3%) 0 (0%) 0 (0%) 0 (0%) 1 (2%)	9 (20%) 34 (74%) 0 (0%) 2 (4%) 0 (0%) 0 (0%) 0 (0%) 0 (0%) 1 (2%)

Abbreviations

CT, chemotherapy; PS, performance status as defined by the Eastern Cooperative Oncology Group; CDDP, cisplatin; CBDCA, carboplatin; ETP, etoposide; AMR, amrubicin; CPT, irinotecan; CODE, cisplatin+vincristine+doxorubicin+etoposide

- *1 clinical trial (JCOG0202)[16]
- *2 clinical trial (JCOG1011)[17]
- *3 clinical trial[18]

Table 2. Reasons for choosing sequential CRT and chemotherapy only

	Sequential n = 33	CT only n = 46
Advanced age	12 (36%)	14 (30%)
Large irradiation field	11 (33%)	9 (20%)
Pleural effusion	4 (12%)	1 (2%)
Low pulmonary function (COPD)	4 (12%)	5 (11%)
Interstitial pneumonitis	0 (0%)	15 (33%)
Pulmonary comorbidities	0 (0%)	2 (4%)
Obstructive pneumonitis, Atelectasis	3 (9%)	0 (0%)
Poor performance status	2 (6%)	4 (9%)
Extra-pulmonary comorbidities	4 (12%)	2 (4%)
Patients' choice	0 (0%)	2 (4%)
Others*	0 (0%)	2 (4%)

Abbreviation

CRT, chemoradiotherapy; CT, chemotherapy; COPD, chronic obstructive pulmonary disease

*Others: one patient suspected of having double cancer, and one patient suspected of having carcinomatous meningitis

Table 3. Responses and recurrences

	Concurrent* n = 175	Sequential n = 33	CT only* n = 46
Tumor response			
Response Rate	95%	100%	83%
Complete Response	62 (35%)	6 (18%)	5 (11%)
Partial Response	105 (60%)	27 (82%)	33 (72%)
Stable Disease	4 (2%)	0 (0%)	3 (7%)
Progressive Disease	3 (2%)	0 (0%)	4 (9%)
Recurrence	126 (72%)	21 (64%)	3 (7%)
Local	46 (27%)	6 (18%)	
Only local	37 (21%)	4 (12%)	
Local and distant	9 (6%)	2 (6%)	
Only Distant	78 (45%)	14 (42%)	
Recurrence site unknown	2	0	
Chemotherapy regimens used after recurrence			
AMR	67 (38%)	10 (30%)	16 (35%)
CPT	31 (18%)	2 (6%)	6 (13%)
PEI	29 (17%)	1 (3%)	3 (7%)
Topotecan	17 (10%)	2 (6%)	3 (7%)
CDDP/CBDCA+ETP	9 (5%)	1 (3%)	3 (7%)
CDDP/CBDCA+CPT	10 (6%)	1 (3%)	3 (7%)
Others	11 (6%)	0 (0%)	3 (7%)

*One patient in the concurrent group and one patient in the CT only group had an unknown response.

CT only, only chemotherapy; Local, recurrence site within the irradiation field; Distant, recurrence site outside of the irradiation field; AMR, amrubicin; CPT, irinotecan; PEI, Irinotecan, Cisplatin and Etoposide; CDDP, cisplatin; CBDCA, carboplatin; ETP, etoposide

Others: regimens such as carboplatin+paclitaxel, paclitaxel monotherapy, cisplatin+ vincristine+doxorubicin+etoposide, tegafur/gimeracil/oteracil, oral etoposide, investigational new drugs

Table 4. Major adverse events in two groups

	Concurrent n = 175	Sequential n = 33
Febrile Neutropenia Grade 3-	52 (30%)	4 (12%)
Pneumonitis Grade 3	7 (4%)	3 (9%)
Grade 4	1 (1%)	0 (0%)
Grade 5	0 (0%)	2 (6%)

Grading is based on the CACTAE version 4.0

References

1. van Meerbeeck JP, Fennell DA, De Ruysscher DKM. Small-cell lung cancer. *Lancet*. 2011;378(9804):1741-55.
2. Pignon JP, Arriagada R, Ihde DC et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992;327(23):1618-24.
3. Takada M, Fukuoka M, Kawahara M et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol*. 2002;20(14):3054-60.
4. Fried DB, Morris DE, Poole C et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol*. 2004;22(23):4837-45.
5. Murray N, Coy P, Pater JL et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1993;11(2):336-44.
6. Perry MC, Eaton WL, Propert KJ et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. *N Engl J Med*.

1987;316(15):912-8.

7. Sun JM, Ahn YC, Choi EK et al. Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer. *Ann Oncol*. 2013;24(8):2088-92.

8. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. *J Clin Oncol*. 1997;15(3):893-900.

9. De Ruysscher D, Lueza B, Le Pechoux C et al. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. *Ann Oncol*. 2016;27(10):1818-28.

10. Niho S, Kubota K, Yoh K et al. Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis. *J Thorac Oncol*. 6(4):796-800.

11. Ryu JS, Lim JH, Lee JM et al. Minimal Pleural Effusion in Small Cell Lung Cancer: Proportion, Mechanisms, and Prognostic Effect. *Radiology*. 2016;278(2):593-600.

12. Mitsuoka S, Kudoh S, Kimura T et al. Clinical outcome of amrubicin

therapy according to the prior chemotherapy sensitivities of extensive small cell lung cancer. Osaka City Med J. 2011;57(2):59-66.

13. Schild SE, Stella PJ, Geyer SM et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. J Clin Oncol. 2003;21(17):3201-6.

14. Yuen AR, Zou G, Turrisi AT et al. Similar outcome of elderly patients in intergroup trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer. 2000;89(9):1953-60.

15. Auperin A, Arriagada R, Pignon JP et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7):476-84.

16. Kubota K, Hida T, Ishikura S et al. Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study. Lancet Oncol. 2014;15(1):106-13.

17. Sekine I, Harada H, Yamamoto N et al. Randomized phase II trial of weekly dose-intensive chemotherapy or amrubicin plus cisplatin chemotherapy following induction chemoradiotherapy for limited-disease small cell lung cancer (JCOG1011). *Lung cancer*. 2017;108:232-7.
18. Inoue A, Ishimoto O, Fukumoto S et al. A phase II study of amrubicin combined with carboplatin for elderly patients with small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0405. *Ann Oncol*. 2010;21(4):800-3.

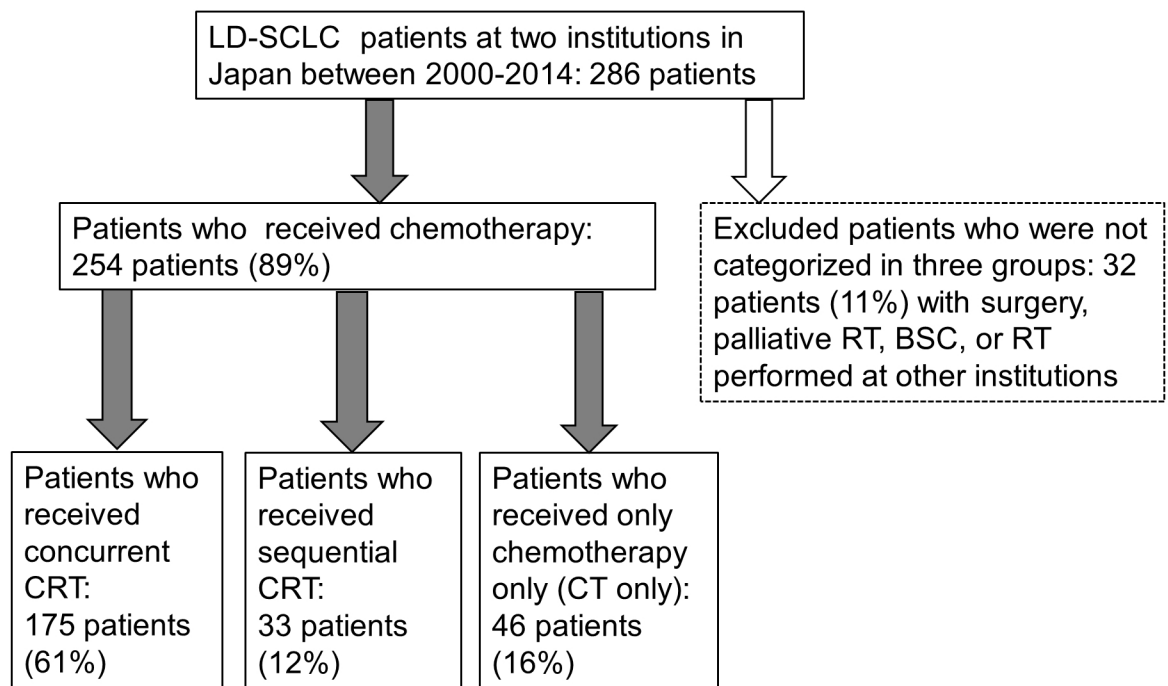
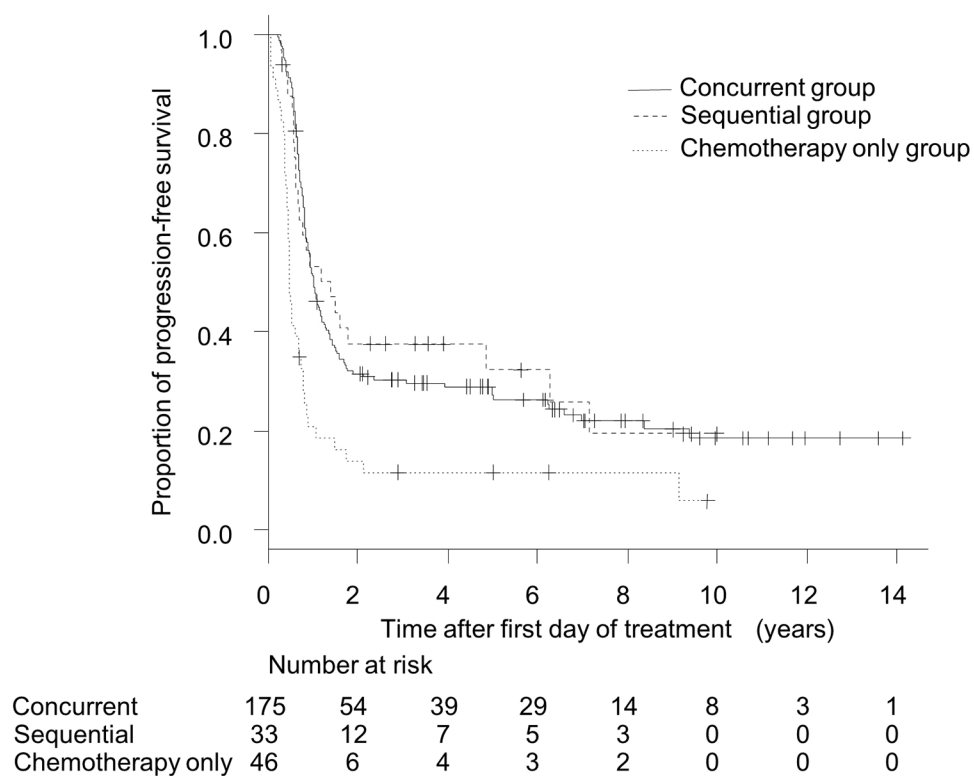


Figure 1

(a)



(b)

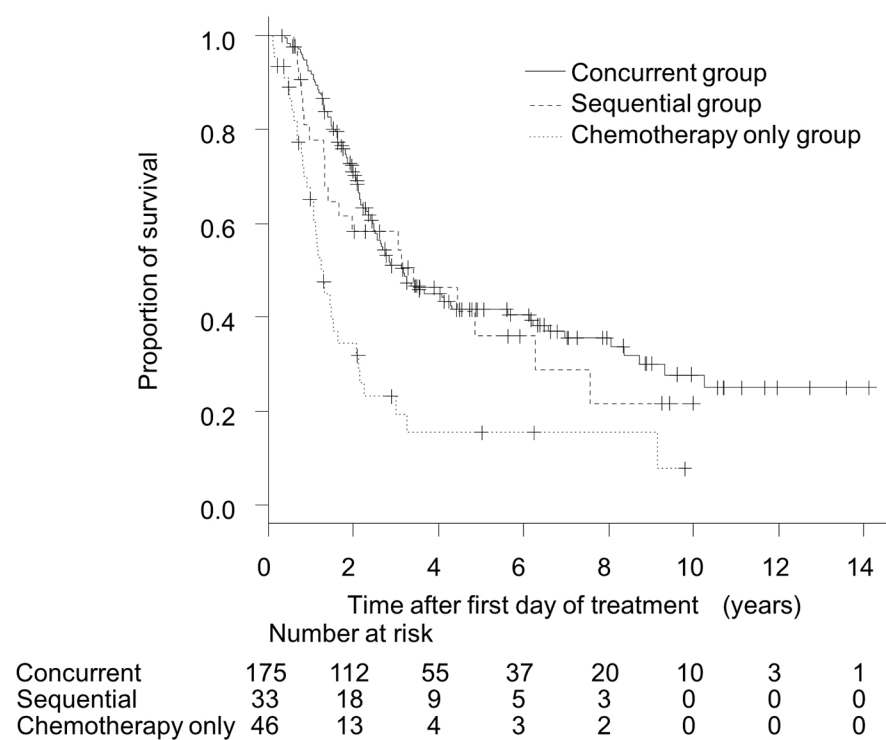


Figure 2

Figure legends

Figure 1. Participating patients.

LD-SCLC, limited-disease small-cell lung cancer; CRT, chemoradiotherapy; BSC, best-supportive care.

Figure 2. (a) Progression-free-survival (PFS) since the first day of treatment in the concurrent group, the sequential group and the chemotherapy only group.

Median PFS: 16.8 months (95% confidence interval [CI], 7.5-58.3 months) for the sequential group, 12.1 months (95% CI, 10.4-14.3 months) for the concurrent group, and 5.7 months (95% CI, 5.1-8.0 months) for the chemotherapy only group.

(b) Overall survival (OS) since the first day of treatment in the concurrent group, the sequential group, and the chemotherapy only group. Median OS: 41.1 months (95% CI, 16.0-75.4 months) for the sequential group, 38.1 months (95% CI, 30.3-52.0 months) for the concurrent group, and 15.6 months (95% CI, 11.7-19.7 months) for the chemotherapy only group.